Burkitt-like lymphoma with 11q aberration: a germinal center-derived lymphoma genetically unrelated to Burkitt lymphoma

Blanca Gonzalez-Farre,1,2,3* Joan Enric Ramis-Zaldivar,2,3* Julia Salmeron-Villalobos,2 Olga Balagüé,1,2,3 Verónica Celis,4 Jaime Verdu-Amoros,5 Ferran Nadeu,2,3 Constantino Sábado,6 Antonio Ferrández,7 Marta Garrido,6 Federico García-Bragado,9 María Dolores de la Maya,10 José Manuel Vagace,10 Carlos Manuel Panizo,11 Itziar Astigarraga,12 Mara Andrés,13 Elaine S. Jaffe,14 Elias Campo1,2,3* and Itziar Salaverria2,3*

1Hematopathology Unit, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain; 2Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; 3Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain; 4Pediatric Oncology Department, Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain; 5Pediatric Oncology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain; 6Pediatric Oncology Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 7Pathology Department, Hospital Clínic de Valencia, Valencia, Spain; 8Pathology Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 9Pathology Department, Complejo Hospitalario de Navarra, Pamplona, Spain; 10Pediatric Hematology Department, Hospital Materno Infantil de Badajoz, Badajoz, Spain; 11Department of Hematology, Clínica Universidad de Navarra and Instituto de Investigación Sanitaria de Navarra (IdISNA), Pamplona, Spain; 12Pediatrics Department, Hospital Universitario Cruces, IIS Biocruces Bizkaia, UPV/EHU, Barakaldo, Spain; 13Pediatric Oncology Department, Hospital La Fe, Valencia, Spain and 14Hematopathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

*BGF, JERZ, EC and IS contributed equally to this work.

©2019 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2018.207928

Received: October 5, 2018.
Accepted: February 7, 2019.
Pre-published: February 7, 2019.
Correspondence: ITZIAR SALAVERRIA - isalaver@clinic.cat
Supplementary Material

Burkitt-like lymphoma with 11q aberration: A germinal center derived lymphoma genetically unrelated to Burkitt lymphoma

Gonzalez-Farre & Ramis-Zaldivar et al
Supplementary Methods

Copy number analysis
DNAs were hybridized on Oncoscan FFPE or SNP array platform (ThermoFisher Scientific, Waltham, MA). Gains and losses and copy-number neutral loss of heterozygosity (CNN-LOH) regions were evaluated and visually inspected using Nexus Biodiscovery version 9.0 software (Biodiscovery, Hawthorne, CA). Human reference genome was GRCh37/hg19. The copy number alterations (CNAs) with minimum size of 100 kb and CNN-LOH larger than 5 Mb were considered informative. Physiological deletions of the immunoglobulin loci were excluded from the analysis. T-cell receptor locus deletions were also excluded, most probably representing physiological deletions of accompanying reactive T cells. Copy number data are deposited at GEO database GSE116527. Published CN data on MYC-positive BL1 were reanalyzed.

Library preparation SureSelect XT and Targeted sequencing approach
DNA and RNA were extracted using standard protocols from formalin fixed paraffin embedded material in 12 and frozen tissue in 3 cases (Qiagen, Hilden, Germany). A total of 100ng of genomic DNA was sheared using the Covaris S220 focused-ultra sonicator (Covaris, Woburn, MA) to a target peak size of 150–200 bp. Library preparation were performed using SureSelectXT Custom Capture Library baits as described in SureSelectXT Target Enrichment System protocol (Agilent Technologies, Santa Clara, CA). For amplification of the post capture libraries, 10 to 13 cycles were performed depending on the initial sample quality. The libraries were qualified using the Bioanalyzer HS (Agilent technologies), quantified with the KAPA Library Quantification Kit (Kapa Biosystems, Wilmington, Massachusetts) and sequenced in a MiSeq instrument (Illumina, San Diego, CA) in a paired-end run of 150 bp. The average sequencing coverage of 10 Burkitt-like lymphoma with 11q (BLL-11q) cases across
regions was 478x (range 97-1229) and over 93% of the targeted regions were covered by at least 100 reads. (Supplementary Figure S7).

FASTQ files were generated by MiSeq control software and quality control of the raw data was performed using the FastQC tool (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/). Sequencing reads were subsequently aligned to the human reference genome (GRCh37/hg19) using the Burrows-Wheeler Aligner–MEM algorithm. Variant calling was performed using two different variant callers: Somatic Variant Caller (Illumina) and annotated using the VariantStudio software v3.0 and Mutect2 (Genome Analysis Toolkit (GATK), version 4.0.3) and annotated by ANNOVAR. We used Somatic Variant Caller (Illumina) with the default settings to analyze sequencing results and to call the variants. Low quality or low coverage calls (total depth <20) were excluded. For Mutect2 variants, low quality variants were also excluded using FilterMutectCalls (GATK) with default thresholds. Only variants identified by both algorithms were considered. For further analysis we excluded all synonymous and intron variants outside splicing sites (not included in the panel, with exception of intron 1 of MYC) and known polymorphisms described in the Single Nucleotide Polymorphism Database (dbSNP138) or ExAC database (release 2015) with more than 0.1% frequency according to the corresponding ethnicity. Finally, each variant was also inspected with the Integrative Genomics Viewer (IGV, Broad Institute, version 2.3) software to exclude artifacts.

Prediction of mutation effect
Since there was no germline DNA available, in order to select somatic variants, potential driver mutations were predicted according to previously published criteria in which the 90% of the mutations classified as functional were demonstrated to be somatic (Supplementary Table S7). Inclusion criteria were: 1) any variant described previously as somatic or functional on previous reports or COSMIC, 2) All truncating variants (nonsense, frameshift, splice donor or acceptor mutations; and 3) the
remaining missense variants that were predicted to be functionally deleterious using Mutation Assessor\textsuperscript{6} and SIFT\textsuperscript{7} predictors. Other predictors as Polyphen-2 (Polymorphism Phenotyping-2)\textsuperscript{8} and CADD (Combined Annotation Dependent Depletion)\textsuperscript{9} were also used.

**Quantitative PCR**

Gene expression levels of \textit{MYC} and \textit{ETS1} of 10 BLL-11q with RNA available and 12 conventional \textit{MYC}-positive BL were investigated by real time quantitative PCR (qPCR) as described previously.\textsuperscript{10} Complementary DNA synthesis was carried out from 500 ng of total RNA and the product was amplified and quantified using TaqMan Universal PCR Master Mix no AmpErase UNG (Thermo Fisher Scientific Inc.), designed primer sets, and TaqMan Gene Expression Assays for \textit{MYC} (Hs00153408\_m1) and \textit{ETS1} (Hs00428293\_m1) (Thermo Fisher Scientific Inc.). DNA was analyzed using duplicates in a StepOne Plus Real-Time PCR System (Thermo Fisher Scientific Inc.). Relative quantification of gene expression was then analyzed with the $2^{\text{-\Delta\Delta C_{T}}}$ method using \textit{B2M} (Hs00939627\_m1), as the endogenous control gene, and Universal Human Reference RNA (Stratagene, Agilent Technologies, Santa Clara, CA, USA), composed of total RNA from 10 human cell lines, as the mathematical calibrator.

**Supplementary Results**

**Morphological features of 9 MYC-negative, 11q-negative lymphoma cases**

Among the 95 cases with an initial diagnosis of BL, atypical BL or high grade B-cell lymphoma, not otherwise specified (HGBCL,NOS) nine (9.5\%) were negative for \textit{MYC} rearrangements, using both the break-apart and the double fusion probes (only seven cases analyzed), and for the 11q alteration. After the morphological review three cases were better reclassified to diffuse large B-cell lymphoma (DLBCL). These cases were composed of a proliferation of centroblastic cells with starry sky pattern, germinal
center phenotype and very high proliferative index. One case was weakly positive for BCL2. The remaining 6 cases had HGBCL, NOS morphology, two of them with blastoid features. Four cases had a germinal center phenotype and BCL2 negativity and two cases had an activated phenotype with BCL2 positivity. All cases had a proliferative index close to 100%.

**Comparison of Copy number profile of BLL-11q with other lymphoma entities**

BLL-11q lymphoma had similar levels of genomic complexity as conventional MYC-positive BL with 7.1 vs. 6 alterations, respectively. However, gains of 5q21.3-q32 and losses of 6q12.1-q21 were virtually exclusive of BLL-11q whereas 1q gains were only seen in MYC-positive BL. In comparison to the two molecular DLBCL subtypes, BLL-11q cases displayed significantly lower levels of complexity than ABC and GCB-DLBCL (7.1 vs. 22 alterations in ABC and 19 alterations in GCB; both \( P<0.001 \)), had the specific 11q alterations and lacked gains of 2p16.1 and 7p and losses of 1p36.32 associated with GCB phenotype and losses of 6q23.3, 9p21.3 and 17p13.2 related to ABC-DLBCL.

To determine the specificity of the 11q-gain/loss pattern in BLL-11q in comparison to lymphoid neoplasms other than BL and DLBCL, we screened previously published data considering both patterns of prototypical pattern of gain followed by loss or only the presence of terminal 11q24.3-q25 loss. Frequencies observed were less than 1% in all the reviewed entities including follicular lymphoma,\(^\text{11}\) nodal marginal zone lymphoma,\(^\text{12}\) chronic lymphocytic leukemia\(^\text{13}\) or plasma cell myeloma\(^\text{14,15}\) with exception of transformed follicular lymphoma\(^\text{11}\) in which 16% cases, presented the 11q aberrations. These data suggest that this alteration is mainly absent in other recognized lymphoma entities and characterizes genetically BLL-11q tumors.
Supplementary Figures

Supplementary Figure S1. Diagram of the strategy used for the identification of Burkitt-like with 11q aberration in a cohort of (A) 60 patients <40 years old and (B) 35 patients ≥ 40 years old with a morphological diagnosis of Burkitt lymphoma (BL)/atypical BL and high grade B-cell lymphoma, not otherwise specified (HGBCL, NOS) according to the updated WHO Classification 2016. Seventeen out of nine cases negative for both MYC and 11q alterations with material available were tested by MYC/IGH double color double fusion probe, and all resulted to be negative for the fusion. Abbreviations: DLBCL, diffuse large B-cell lymphoma; DHL, double hit lymphoma; THL, triple hit lymphoma.

A

60 BL/atypical BL/HGBCL, NOS < 40 years old

MYC break status by FISH

46 BL MYC trans + (76.7%)

14 BL/atypical BL/ HGBCL, NOS MYC trans - (23.3%)

11q status by CN array

46 Burkitt Lymphoma

6 cases (10%) DLBCL (3)

HGBCL, NOS (3)

8 cases (13.3%) Burkitt-like lymphoma with 11q

+3 consultation cases

B

35 BL/atypical BL/HGBCL, NOS ≥ 40 years old

MYC break status by FISH

32 MYC trans + (91.4%)

3 MYC-negative HGBCL, NOS (8.6%)

11q status by FISH

21 BL (60%)

1 DLBCL (2.86%)

10 cases (28.6%) DHL (8)

THL (2)

3 cases (8.6%)
Supplementary Figure S2. Individual and integrative copy number plots of (A) eleven Burkitt-like with 11q and (B) six MYC-negative 11q-negative lymphoma cases. The vertical axis indicates frequency of the genomic aberration among the analyzed cases. Gains are depicted in blue, losses are depicted in red, and regions of CNN-LOH are represented in yellow.
Supplementary Figure S3. Representative 11q aberration by FISH. (A) FISH image of a representative case (#17) harboring 11q aberration using a custom probe combining CEP11 (Spectrum Aqua), RP11-414G21 (Spectrum Green) and R11-629A20 (Spectrum Red) bac clones. (B) Two blue signals are observed per cell corresponding to the two chr11 centromeres, (C) the presence of three green signals per cell indicates 11q gain and (D) the presence of only one red is indicative of the 11q terminal loss.
Supplementary Figure S4. *MYC* and *ETS1* RNA expression levels in BLL-11q. (A) Box plot of the percentage of *MYC* expression analyzed by qPCR in BLL-11q (n=9) vs. *MYC*-positive BL (n=9). (B) Box plot of the percentage of *ETS1* expression analyzed by qPCR in BLL-11q (n=10) vs. *MYC*-positive BL (n=12). The significance of difference was determined by t-test and Mann-Whitney test respectively.
Supplementary Figure S5. Ideogram of chromosome 11q arm of 11 MYC-negative cases harboring 11q aberration by CN array. Gains are represented in blue, red corresponds to losses and CNN-LOH are represented in yellow. Two minimal regions of gain (MRGs) and one minimal region of loss (MRL) are pointed with blue and red boxes, respectively, and the minimal region of amplification (MRA) is indicated with the green box.
Supplementary Figure S6. Comparative plot of copy number aberrations between Burkitt-like lymphoma with 11q aberration (n=11) and (A) conventional MYC-positive Burkitt Lymphoma (n=35), (B) GCB-Diffuse Large B-cell lymphoma (n=45) and (C) ABC-Diffuse Large B-cell lymphoma (n=49). X-axis depicts chromosome positions with dotted lines pointing centromeres. Y-axis indicates frequency of the genomic aberration among the analyzed cases. Significantly different regions of alterations among groups (Fisher test non-adjusted \( P \leq 0.01 \)) are labeled with corresponding color asterisks.
Supplementary Figure S7. (A) Comparative plot of copy number aberrations between Burkitt-like lymphoma with 11q aberration (n=11) and 6 MYC-negative 11q-negative cases (B) Mutational overview of 4 MYC-negative 11q negative cases in comparison with BLL with 11q aberration. The heat map shows the case specific pattern of driver mutations found by next generation sequencing. Each column represents a case and each row represents a gene. The right bar graph illustrates the mutation frequency of each gene.
Supplementary Figure S8. Mean coverage distribution per gene of the 10 BLL-11q cases analyzed by target NGS. Y-axis indicates the mean number of reads. The red line depicts the mean coverage of all 10 cases. DNA from #2, #4 and #7 BLL-11q cases were extracted from frozen tissue.
Supplementary Figure S9. NGS analysis pipeline followed to identify potential driver mutations in 10 BLL-11q samples. Two different variant callers were used: Somatic Variant Caller (Illumina) and Mutect2 (GATK version 4.0.3) and potential driver mutations were predicted according to previously published criteria. SIFT predictor was only used for mutations in which a definitive score was not provided by Mutation Assessor.
**Supplementary Tables**

**Supplementary Table S1.** Details of all antibodies used, source and conditions of use.

| Antibody | Clone | Source | Antigen retrieval/visualization | Dilution |
|----------|-------|--------|---------------------------------|----------|
| CD20     | L26   | DAKO, Copenhagen, Denmark       | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| CD79a    | JCB 117 | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| CD3      | Polyclonal | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| CD5      | 4C7   | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| CD10     | 56C6  | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| BCL6     | PG-B6p | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| BCL2     | 124   | DAKO | EDTA 1 mM pH 9/ ENVISION FLEX (DAKO) | RTU      |
| Ki67     | Mib-1 | DAKO | Citrate 10 mM pH 6/ ENVISION FLEX (DAKO) | RTU      |
| MUM1     | MRQ-43 | Ventana, Roche | CC1 solution / ultraView Universal DAB Detection Kit. Automated immunostainer (Benchmark XT; Ventana) | RTU      |
| MYC*     | Y69   | Ventana, Roche | CC1 solution / ultraView Universal DAB Detection Kit. Automated immunostainer (Benchmark XT; Ventana) | RTU      |
| LMO2*    | 1A9-1 | Ventana, Roche, Tucson, AZ, USA | CC1 solution / ultraView Universal DAB Detection Kit. Automated immunostainer (Benchmark XT; Ventana) | RTU      |

RTU, ready to use.

*LMO2 was considered positive when >30% of the cells were positive and MYC was considered positive when more than 40% of positive tumor cells were observed, following the criteria of Colomo et al\(^\text{17}\) and Johnson et al\(^\text{18}\) respectively.*
**Supplementary Table S2.** Ninety-six genes sequenced using Target NGS panel including references for inclusion in the mutational analysis and mean coverage by gene and amplicon.

*Provided in excel format*
**Supplementary Table S3.** Primers used for the verification of variants in MYC, BTG2, ETS1 and TP53 and the re-analysis of ID3, TCF3 (exon 17) and CCND3 (exon 5).

### Primers ETS1

| Primer | Sequence (5’-3’) | PCR product length (bp) | Case/Mutation | Variant | Mutation position (hg19) |
|--------|------------------|-------------------------|---------------|---------|--------------------------|
| ETS1_1 F | CTGCAGGTCACACACAAAGC | 157 | BLL2 | T>T/C | 128332392 |
| ETS1_1 R | TAAATTCAGTGGCCAGGA | | BLL7 | C>C/T | 128332410 |
| ETS1_5 F | CCACGGCTCAGTTTCATA | 168 | BLL2 | A>A/T | 128332477 |
| ETS1_5 R | GGGTCACTGAATGGGTAT | | | | |
| ETS1_3 F | TTTGAATTCCACGCCCATCTC | 167 | BLL14 | G>G/A | 128333508 |
| ETS1_3 F | GTGGGGATTAGCTGCGTAGA | | | | |
| ETS1_E1F | GAAAGGGGGAAGAAGTCAGAG | 200 | Exon 1 of transcript | | |
| ETS1_E1R | CAAAACGTACCACACCTCCTA | | | | |

### Primers BTG2

| Primer | Sequence (5’-3’) | PCR product length (bp) | Case/Mutation | Variant | Mutation position (hg19) |
|--------|------------------|-------------------------|---------------|---------|--------------------------|
| BTG2_1F | GACATGAGCCACACGGAAG | 228 | BLL1 | C>C/T | 203274858 |
| BTG2_1R | CTGCCGCAGGAGTGAGAA | | BLL2 | G>G/A | 203274867 |
| | | | BLL7 | del | 203274878 |

### Primers MYC

| Primer | Sequence (5’-3’) | PCR product length (bp) | Case/Mutation | Variant | Mutation position (hg19) |
|--------|------------------|-------------------------|---------------|---------|--------------------------|
| MYC_2 F | GAGCTGCTGGGAGGAGACAT | 150 | BLL7 | T>T/G | 128750921 |
| MYC_2 R | CTGGTAGGAGGCCAGCTTCT | | | | |
| MYC_4 F | CTCTTGCGAAAAGGTCAGAG | 158 | BLL1 | C>C/G | 128752800 |
| MYC_4 R | CCTTTGGGAGGCAGAGTAGT | | | | |

### Primers TP53

| Primer | Sequence (5’-3’) | PCR product length (bp) | Case/Mutation | Variant | Mutation position (hg19) |
|--------|------------------|-------------------------|---------------|---------|--------------------------|
| TP53_2 F | CCAGTGATGTGATGGTGAG | 163 | BLL4 | C>C/T | 7577538 |
| TP53_2 R | CCTGCTTGGCACAGGTTCT | | | | |
| Primer   | Sequence (5´-3´)                  | PCR product length (bp) | Reference          |
|----------|----------------------------------|-------------------------|--------------------|
| ID3-FZ-F | TCCAGGCAGGCTCTATAAGTG CCAGTGAGTGGAATTTT | 694                     | Rohde, et al19     |
| ID3-FZ-R | TCCAGGCAGGCTCTATAAGTG CCAGTGAGTGGAATTTT | 694                     | Rohde, et al19     |
| ID3-PE-F | GCTTACCTGGATGGGAAGGT             | 204                     |                    |
| ID3-PE-R | GAGGAGGCCGGAGTGAGTTG            |                         |                    |

| Primer   | Sequence (5´-3´)                  | PCR product length (bp) | Reference          |
|----------|----------------------------------|-------------------------|--------------------|
| TCF3-FZ-F | TGCTGTGCCAACCACATGTAAG CCATG GTGGAGGCTTTGAAAGAAGAG | 609                     | Rohde, et al19     |
| TCF3-FZ-R | TGCTGTGCCAACCACATGTAAG CCATG GTGGAGGCTTTGAAAGAAGAG | 609                     | Rohde, et al19     |
| TCF3-PE-F | CAGGATGACGAGCTTGCTTCT           | 180                     |                    |
| TCF3-PE-R | CAGGATGACGAGCTTGCTTCT           | 180                     |                    |

| Primer   | Sequence (5´-3´)                  | PCR product length (bp) | Reference          |
|----------|----------------------------------|-------------------------|--------------------|
| CCND3-FZ-F | CCATGTGTTGGGAGCTGTC             | 328                     | Rohde, et al19     |
| CCND3-FZ-R | CCATGTGTTGGGAGCTGTC             | 328                     | Rohde, et al19     |
| CCND3-PE-F | GCCCCTCCTCTCTGGCTTAGT            | 198                     |                    |
| CCND3-PE-R | GCCCCTCCTCTCTGGCTTAGT            | 198                     |                    |

Bp: base pairs; F: forward, R: reverse
**Supplementary Table S4.** Taqman assays used for qPCR analyses. (Applied Biosystems inc)

| Gene Symbol | Assay ID             | Amplicon size (bp) | Reference sequence |
|-------------|----------------------|--------------------|--------------------|
| *ETS1*      | Hs00428293_m1        | 99                 | NM_005238          |
| *MYC*       | Hs00153408_m1        | 107                | NM_002467          |
| *B2M*       | Hs00984230_m1        | 81                 | NM_004048          |
**Supplementary Table S5.** Summary of copy number findings and FISH pattern constellation of the 11q aberration in the current series of BLL-11q.

| Case | CN array | 11q FISH (CEP11 [D11Z1] + RP11-414G21+RP11-629A20) | 11q FISH result |
|------|----------|--------------------------------------------------|-----------------|
|      | Pattern of chr11 | Number of alterations | 11q FISH constellation pattern<sup>20</sup> |                  |
| #1   | Only terminal loss | 2 CNA | nuc ish (D11Z1x2,RP11-414G21x2,RP11-629A20x1) | Only terminal loss |
| #2   | Gain/terminal loss | 3 CNA | nuc ish (D11Z1x2,RP11-414G21x2,RP11-629A20x1) | Only terminal loss |
| #3   | Gain/terminal loss | 6 CNA, 1 CNN-LOH | nuc ish (D11Z1x2,RP11-414G21x2-3,RP11-629A20x1) | Gain*/terminal loss |
| #4   | Gain/amplification/CNN-LOH | 15 CNA+1CNN-LOH | nuc ish (D11Z1x2,RP11-414G21x2-5,RP11-629A20x2) | Amplification |
| #5   | Gain/amplification/terminal loss | 4 CNA | nuc ish (D11Z1x2,RP11-414G21x4-5,RP11-629A20x1) | Amplification/terminal loss |
| #6   | Only terminal loss | 6 CNA+11 CNN-LOH | nuc ish (D11Z1x2,RP11-414G21x2,RP11-629A20x1) | Only terminal loss |
| #7   | Gain/terminal loss | 8 CNA | nuc ish (D11Z1x2,RP11-414G21x3,RP11-629A20x1) | Gain/terminal loss |
| #14  | Gain/terminal loss | 4 CNA | nuc ish (D11Z1x2,RP11-414G21x2,RP11-629A20x1) | Only terminal loss |
| #15  | Gain/terminal loss | 12 CNA+1CNN-LOH | Not done |                  |
| #16  | Gain/amplification/terminal loss | 4 CNA | nuc ish (D11Z1x2,RP11-414G21x3,RP11-629A20x1) | Gain/terminal loss |
| #17  | Gain/amplification/terminal loss | 14 CNA+3CNN-LOH | nuc ish (D11Z1x2,RP11-414G21x3-4,RP11-629A20x1) | Amplification*/terminal loss |

CNA: copy number alteration. CNN-LOH: copy number neutral loss of heterozygosity. *Only observed in a few cells. CN and FISH results were not concordant in cases #2, and #14 most likely due to the fact that gained region covered by BAC RP11-414G21 was most likely inverted and then both copies were very narrow to be clearly distinguished as independent signals in the FISH constellation.
**Supplementary Table S6.** Global table of copy number and copy number neutral of heterozygosity (CNN-LOH) alterations of the 11 BLL-11q aberration and the 6 MYC-negative 11q-negative cases.

| Case | Array | Chromosome Region (Hg19) | Event | Length (bp) | Cytoband |
|------|-------|--------------------------|-------|-------------|-----------|
| #1   |       |                          |       |             |           |
|      | Oncoscan | chr6:67,759,432-110,118,776 | CN Loss | 42359345 | q12 - q21 |
|      | Oncoscan | chr11:124,440,617-132,877,670 | CN Loss | 8437054 | q24.2 - q25 |
| #2   |       |                          |       |             |           |
|      | Cytoscan | chr6:302,273-3,157,193 | CN Gain | 2854921 | p25.3 - p25.2 |
|      | Cytoscan | chr11:66,015,813-120,252,657 | CN Gain | 54236845 | q13.2 - q23.3 |
|      | Cytoscan | chr11:120,253,875-135,006,516 | CN Loss | 14752642 | q23.3 - q25 |
| #3   |       |                          |       |             |           |
|      | Oncoscan | chr5:1-180,915,260 | CN Gain | 180915260 | p15.33 - q35.3 |
|      | Oncoscan | chr11:103,326,831-111,737,912 | CN Gain | 8411082 | q22.3 - q23.1 |
|      | Oncoscan | chr11:111,747,297-113,562,039 | CN Loss | 1814743 | q23.1 - q23.2 |
|      | Oncoscan | chr11:114,767,237-116,764,582 | CN Gain | 1997346 | q23.3 |
|      | Oncoscan | chr11:127,681,132-132,020,453 | CN Loss | 4339322 | q24.2 - q25 |
|      | Oncoscan | chr17:40,114,049-81,195,210 | CNN-LOH | 41081162 | q21.2 - q25.3 |
|      | Oncoscan | chr11:11,747,297-113,562,039 | CN Loss | 1814743 | q23.1 - q23.2 |
| #4   |       |                          |       |             |           |
|      | SNP6   | chr1:148,377,370-198,022,430 | CN Gain | 49645061 | q24 - q29 |
|      | SNP6   | chr3:151,106,726-151,889,624 | CN Loss | 782899 | q31.3 |
|      | SNP6   | chr3:62,787,661-63,773,155 | CN Loss | 985495 | q11.1 - q12 |
|      | SNP6   | chr3:66,607,178-136,034,966 | CN Loss | 69227789 | q12 - q23.3 |
|      | SNP6   | chr6:137,582,049-168,332,407 | CN Loss | 30750359 | q23.3 - q27 |
|      | SNP6   | chr6:168,596,580-171,115,067 | CN Loss | 2518488 | q27 |
|      | SNP6   | chr8:118,905,307-134,171,629 | CN Gain | 15266323 | q24.11 - q24.22 |
|      | SNP6   | chr11:77,429,089-117,851,837 | CN Gain | 40422749 | q14.1 - q23.3 |
|      | SNP6   | chr11:117,851,837-120,155,799 | High Copy Gain | 2303963 | q23.3 |
|      | SNP6   | chr11:120,155,799-135,006,516 | CNN-LOH | 14850718 | q23.3 - q25 |
|      | SNP6   | chr12:40,494,911-93,085,645 | CN Gain | 52590735 | q12 - q22 |
|      | SNP6   | chr12:93,085,646-95,374,851 | CN Loss | 2289206 | q22 |
|      | SNP6   | chr12:95,374,851-96,373,225 | CN Gain | 998375 | q22 - q23.1 |
|      | SNP6   | chr18:29,031,540-56,749,287 | CN Gain | 27717748 | q12.1 - q21.32 |
|      | SNP6   | chr18:56,749,288-78,077,248 | CN Loss | 21327961 | q21.32 - q23 |
|      | SNP6   | chr19:6,700,469-6,935,092 | CN Loss | 234624 | p13.3 - p13.2 |
| Case | Array | Chromosome Region (Hg19) | Event            | Length (bp) | Cytoband       |
|------|-------|--------------------------|------------------|-------------|----------------|
|      | Oncoscan | chr6:78,975,348-114,942,024 | CN Loss | 35966677 | q14.1 - q22.1 |
|      | Oncoscan | chr11:83,088,730-117,240,357 | CN Gain | 34151628 | q14.1 - q23.3 |
|      | Oncoscan | chr11:117,242,677-120,392,430 | High Copy Gain | 3149754 | q23.3 |
|      | Oncoscan | chr11:120,398,613-134,938,847 | CN Loss | 14540235 | q23.3 - q25 |
| #5   | Oncoscan | chr1:150,029,936-151,599,267 | High Copy Gain | 1569332 | q21.2 - q21.3 |
|      | Oncoscan | chr1:151,744,168-249,212,878 | CNN-LOH | 97468711 | q21.3 - q44 |
|      | Oncoscan | chr3:117,248,700-124,701,188 | CNN-LOH | 7452489 | q13.31 - q21.2 |
|      | Oncoscan | chr3:177,647,728-197,852,564 | CN Gain | 20204837 | q26.32 - q29 |
|      | Oncoscan | chr4:124,989,820-147,017,448 | CNN-LOH | 22027629 | q28.1 - q31.22 |
|      | Oncoscan | chr5:38,139-5,124,613 | CNN-LOH | 5086475 | p15.33 - p15.32 |
|      | Oncoscan | chr5:76,061,256-96,465,623 | CNN-LOH | 20404368 | q13.3 - q15 |
|      | Oncoscan | chr5:171,201,195-180,698,312 | CNN-LOH | 9497118 | q35.1 - q35.3 |
|      | Oncoscan | chr8:79,796,337-94,671,697 | CNN-LOH | 14875361 | q21.12 - q22.1 |
|      | Oncoscan | chr9:204,738-10,275,857 | CNN-LOH | 10071120 | p24.3 - p23 |
|      | Oncoscan | chr11:70,045,922-106,288,554 | CNN-LOH | 36242633 | q13.3 - q22.3 |
|      | Oncoscan | chr11:128,214,400-134,938,847 | CN Loss | 6724448 | q24.3 - q25 |
|      | Oncoscan | chr12:189,400-133,818,115 | CN Gain | 133628716 | p13.33 - q24.33 |
|      | Oncoscan | chr13:91,639,578-92,147,712 | CN Gain | 508135 | p31.3 |
|      | Oncoscan | chr14:54,084,642-76,110,632 | CNN-LOH | 22025991 | q22.1 - q24.3 |
|      | Oncoscan | chr18:54,084,642-76,110,632 | CN Gain | 2527795 | q21.33 - q22.1 |
|      | Oncoscan | chr18:55,902,055-66,218,776 | CNN-LOH | 10316722 | q21.31 - q22.1 |
| #6   | Oncoscan | chr1:5,195,097-7,019,203 | CN Loss | 1824107 | p36.32 - p36.31 |
|      | Cytoscan | chr3:60,388,322-60,712,277 | CN Loss | 323956 | p14.2 |
|      | Cytoscan | chr5:104,762,975-174,135,222 | CN Gain | 69372248 | q21.3 - q35.2 |
|      | Cytoscan | chr5:178,688,093-180,719,789 | CN Gain | 2031697 | q35.3 |
|      | Cytoscan | chr11:72,390,640-72,717,317 | High Copy Gain | 326678 | q13.4 |
|      | Cytoscan | chr11:72,717,332-119,682,209 | CN Gain | 46964878 | q13.4 - q23.3 |
|      | Cytoscan | chr11:119,682,255-134,938,470 | CN Loss | 15256216 | q23.3 - q25 |
|      | Cytoscan | chr12:1-133,851,895 | CN Gain | 133851895 | p13.33 - q24.33 |
| Case | Array | Chromosome Region (Hg19) | Event | Length (bp) | Cytoband |
|------|-------|--------------------------|-------|-------------|----------|
| #8   | Oncoscan | chr1:23,506,625-23,985,309 | CN Loss | 478685 | p36.12 - p36.11 |
|      | Oncoscan | chr1:116,776,586-118,300,350 | CN Loss | 1523765 | p13.1 - p12 |
|      | Oncoscan | chr1:189,763,755-200,583,380 | CN Gain | 10819626 | q31.1 - q32.1 |
|      | Oncoscan | chr2:180,790,820-198,749,269 | CN Gain | 17958450 | q31.3 - q33.1 |
|      | Oncoscan | chr6:204,909-57,305,822 | CN Gain | 57100914 | p25.3 - p11.2 |
|      | Oncoscan | chr6:57,329,886-58,055,927 | CN Loss | 726042 | p11.2 |
|      | Oncoscan | chr6:58,213,475-58,770,502 | CN Gain | 557028 | p11.2 - p11.1 |
|      | Oncoscan | chr6:61,886,393-170,913,051 | CN Loss | 109026659 | q11.1 - q27 |
|      | Oncoscan | chr7:1-159,138,663 | CN Gain | 159138663 | p22.3 - q36.3 |
|      | Oncoscan | chr7:1-159,138,663 | CNN-LOH | 159138663 | p22.3 - q36.3 |
|      | Oncoscan | chr8:55,457,188-71,067,368 | CN Loss | 15610181 | q11.23 - q13.3 |
|      | Oncoscan | chr9:204,738-35,809,328 | CNN-LOH | 35604591 | p24.3 - p13.3 |
|      | Oncoscan | chr9:21,901,263-22,056,499 | Homozygous Copy Loss | 155237 | p21.3 |
|      | Oncoscan | chr11:45,810,652-46,460,038 | CN Loss | 649387 | p11.2 |
|      | Oncoscan | chr12:189,400-8,447,618 | CN Loss | 8258219 | p13.33 - p13.31 |
|      | Oncoscan | chr12:19,557,354-21,282,570 | CN Loss | 1725217 | p12.3 - p12.2 |
|      | Oncoscan | chr12:21,295,612-29,285,577 | CN Gain | 7989966 | p12.2 - p11.22 |
|      | Oncoscan | chr12:30,814,259-33,886,138 | CN Gain | 3071880 | p11.21 - p11.1 |
|      | Oncoscan | chr12:39,204,714-70,880,468 | CN Gain | 31675755 | q12 - q15 |
|      | Oncoscan | chr12:74,309,125-77,911,802 | CN Gain | 3602678 | q21.1 - q21.2 |
|      | Oncoscan | chr12:79,610,263-82,677,229 | CN Gain | 3066967 | q21.2 - q21.31 |
|      | Oncoscan | chr12:84,462,140-89,275,759 | CN Loss | 4813620 | q21.31 - q21.33 |
|      | Oncoscan | chr12:91,825,095-94,371,476 | CN Loss | 2546382 | q21.33 - q22 |
|      | Oncoscan | chr12:98,498,625-115,061,325 | CN Gain | 16562701 | q23.1 - q24.21 |
|      | Oncoscan | chr12:128,397,472-133,818,115 | CN Gain | 5420644 | q24.32 - q24.33 |
|      | Oncoscan | chr13:45,901,876-53,198,648 | CN Loss | 7296773 | q14.13 - q14.3 |
|      | Oncoscan | chr13:58,291,792-69,716,364 | CN Gain | 11424573 | q21.1 - q21.33 |
|      | Oncoscan | chr20:29,519,156-40,272,376 | CN Loss | 10753221 | q11.21 - q12 |
|      | Oncoscan | chrX:1-155,270,560 | CN Loss | 155270560 | p22.33 - q28 |
| #9   | Oncoscan | chr5:1-180,915,260 | CN Gain | 180915260 | p15.33 - q35.3 |
|      | Oncoscan | chr6:204,909-52,036,300 | CNN-LOH | 51831392 | p25.3 - p12.2 |
|      | Oncoscan | chr6:32,100,302-32,998,152 | High Copy Gain | 897851 | p21.32 |
|      | Oncoscan | chr7:41,421-159,118,443 | CN Gain | 159077023 | p22.3 - q36.3 |
|      | Oncoscan | chr12:1-133,851,895 | CN Gain | 133851895 | p13.33 - q24.33 |
|      | Oncoscan | chr17:40,424,255-80,263,427 | CNN-LOH | 39839173 | q21.2 - q25.3 |
|      | Oncoscan | chr17:62,949,100-63,165,077 | Homozygous Copy Loss | 215978 | q24.1 |
|      | Oncoscan | chr21:14,375,361-48,045,085 | CN Gain | 33669725 | q11.2 - q22.3 |
| Case | Array | Chromosome Region (Hg19) | Event | Length (bp) | Cytoband |
|------|-------|--------------------------|-------|-------------|----------|
| #10  | Oncoscan chr17:400,959-12,159,990 | CNN-LOH | 11759032 | p13.3 - p12 |
| #11  | SNP6 chr1:73,100,845-74,442,581 | CN Gain | 1341737 | p31.1 |
|      | SNP6 chr1:149,962,792-152,551,299 | CN Gain | 2588508 | q21.2 - q21.3 |
|      | SNP6 chr6:40,083,170-42,855,926 | CN Gain | 2772757 | p21.2 - p21.1 |
|      | SNP6 chr6:78,166,644-117,921,913 | CN Loss | 39755270 | q14.1 - q22.1 |
|      | SNP6 chr8:106,741,322-107,876,319 | CN Gain | 1134998 | q23.1 |
|      | SNP6 chr8:128,951,273-129,358,847 | CN Gain | 407575 | q24.21 |
|      | SNP6 chr9:223,542-3,003,015 | CN Gain | 2779474 | p24.3 - p24.2 |
|      | SNP6 chr12:0-133,851,896 | CN Gain | 133851896 | p13.33 - q24.33 |
|      | SNP6 chr13:56,118,024-57,280,068 | CN Gain | 1162045 | q21.1 |
|      | SNP6 chr13:91,986,235-92,361,312 | CN Gain | 375078 | q21.3 |
|      | SNP6 chr17:49,745,106-81,195,210 | CNN-LOH | 31450105 | q21.33 - q25.3 |
|      | SNP6 chr17:400,959-19,497,890 | CNN-LOH | 19096932 | p13.3 - p11.2 |
|      | SNP6 chr19:37,006,258-37,414,445 | CN Gain | 408188 | q13.12 |
|      | SNP6 chr21:14,369,207-48,129,895 | CN Gain | 33760689 | q11.2 - q22.3 |
| #12  | Oncoscan chr1:144,790,037-193,932,788 | CN Gain | 49142752 | q21.1 - q31.3 |
|      | Oncoscan chr2:134,242,471-139,641,542 | CN Gain | 5399072 | q21.2 - q22.1 |
|      | Oncoscan chr2:212,437,072-215,227,024 | CN Gain | 2789953 | q34 |
|      | Oncoscan chr3:63,411-60,777,554 | CNN-LOH | 60714144 | p26.3 - p14.2 |
|      | Oncoscan chr3:116,120,738-117,045,461 | CN Loss | 924724 | q13.31 |
|      | Oncoscan chr4:181,713,895-190,915,650 | CN Loss | 9201756 | q34.3 - q35.2 |
|      | Oncoscan chr5:38,139-1,985,845 | CN Gain | 1947707 | p15.33 |
|      | Oncoscan chr6:85,053,988-92,677,362 | CN Gain | 7623375 | q14.3 - q15 |
|      | Oncoscan chr7:88,362,639-94,444,750 | CN Gain | 6082112 | q21.13 - q21.3 |
|      | Oncoscan chr8:128,651,315-128,766,080 | CN Gain | 114766 | q24.21 |
|      | Oncoscan chr8:128,767,004-128,840,276 | CN Loss | 73273 | q24.21 |
|      | Oncoscan chr13:64,574,575-69,315,335 | CN Gain | 4740861 | q21.31 - q21.33 |
|      | Oncoscan chr17:400,959-19,497,890 | CNN-LOH | 19096932 | p13.3 - p11.2 |
|      | Oncoscan chr19:247,232-3,093,163 | CN Gain | 2845932 | p13.3 |
|      | Oncoscan chr22:42,109,917-51,213,826 | CN Loss | 9103910 | q13.2 - q13.33 |
| Case | Array | Chromosome Region (Hg19) | Event | Length (bp) | Cytoband |
|------|-------|--------------------------|-------|-------------|----------|
| #13  | Oncoscan | chr7:41,421-24,971,213 | CN Gain | 24929793 | p22.3 - p15.3 |
|      | Oncoscan | chrX:25,296,129-58,470,802 | CN Gain | 33174674 | p21.3 - p11.1 |
|      | Oncoscan | chr10:567,325-135,434,303 | CN Gain | 134866979 | p15.3 - q26.3 |
|      | Oncoscan | chr4:91,749,811-91,794,821 | CN Gain | 45011 | q22.1 |
|      | Oncoscan | chr1:104,446,681-110,195,901 | CN Gain | 5749221 | p21.1 - p13.3 |
|      | Oncoscan | chr1:110,200,360-110,240,929 | CN Gain | 40570 | p13.3 |
|      | Oncoscan | chr12:189,400-133,818,115 | CN Gain | 133628716 | p13.3 - q24.3 |
|      | Oncoscan | chr2:32,757,598-37,578,208 | CN Gain | 4820611 | p22.3 - p22.2 |
|      | Oncoscan | chr2:121,588,532-129,317,105 | CN Loss | 7728574 | q14.2 - q14.3 |
|      | Oncoscan | chr2:137,910,175-151,016,074 | CN Loss | 13105900 | q22.1 - q23.3 |
|      | Oncoscan | chr2:153,153,555-160,994,348 | CN Loss | 7840794 | q23.3 - q24.2 |
|      | Oncoscan | chr19:247,232-11,674,294 | CN Loss | 11427063 | p13.3 - p13.2 |
|      | Oncoscan | chr19:6,528,235-7,104,673 | Homozygous Copy Loss | 576439 | p13.3 - p13.2 |
| #14  | Oncoscan | chr7:74,132,398-159,118,443 | CN Gain | 84986046 | q11.23 - q36.3 |
|      | Oncoscan | chr11:1-60,760,530 | CN Gain | 60760530 | p15.5 - q12.2 |
|      | Oncoscan | chr11:91,274,842-118,350,945 | CN Gain | 27076104 | q14.3 - q23.3 |
|      | Oncoscan | chr11:18,352,769-134,938,847 | CN Loss | 16586079 | q23.3 - q25 |
| #15  | Oncoscan | chr5:99,257,992-146,632,594 | CN Gain | 47374603 | q21.1 - q32 |
|      | Oncoscan | chr6:63,365,565-123,492,278 | CN Loss | 60126714 | q11.2 - q22.31 |
|      | Oncoscan | chr10:122,564,306-135,434,303 | CN Gain | 12869998 | q26.12 - q26.3 |
|      | Oncoscan | chr11:93,515,058-120,717,000 | CN Gain | 27201949 | q21 - q23.3 |
|      | Oncoscan | chr11:120,732,508-135,006,516 | CN Loss | 14274009 | q23.3 - q25 |
|      | Oncoscan | chr12:189,400-1,896,996 | CN Gain | 1707557 | p13.33 |
|      | Oncoscan | chr12:22,812,766-28,466,571 | High Copy Gain | 5653806 | p12.1 - p11.22 |
|      | Oncoscan | chr12:28,476,847-64,720,693 | CN Gain | 36243847 | p11.22 - q14.2 |
|      | Oncoscan | chr12:64,720,694-73,671,118 | High Copy Gain | 8950425 | q14.2 - q21.1 |
|      | Oncoscan | chr13:85,803,897-99,955,533 | CN Gain | 14151637 | q31.1 - q32.3 |
|      | Oncoscan | chr13:99,967,798-115,103,150 | CN Loss | 15135353 | q32.3 - q34 |
|      | Oncoscan | chr16:58,143,392-90,195,538 | CN Gain | 32052147 | q21 - q24.3 |
|      | Oncoscan | chr17:59,315,145-80,263,427 | CNN-LOH | 20948283 | q23.2 - q25.3 |
| #16  | Oncoscan | chr6:83,574,391-120,108,162 | CN Loss | 36533772 | q14.1 - q22.31 |
|      | Oncoscan | chr11:73,228,685-113,724,673 | CN Gain | 40495989 | q13.4 - q23.2 |
|      | Oncoscan | chr11:113,733,111-120,176,979 | High Copy Gain | 6443869 | q23.2 - q23.3 |
|      | Oncoscan | chr11:120,187,433-134,938,847 | CN Loss | 14751415 | q23.3 - q25 |
| Case | Array | Chromosome Region (Hg19) | Event | Length (bp) | Cytoband |
|------|-------|--------------------------|-------|-------------|----------|
| #17  | | chr3:149,230,137-197,852,564 | CN Gain | 48622428 | q25.1 - q29 |
|      | | chr4:77,277,624-107,631,213 | CN Gain | 30353590 | q21.1 - q24 |
|      | | chr7:111,092,478-159,118,443 | CN Loss | 48025966 | q31.1 - q36.3 |
|      | | chr8:172,417-33,010,693 | CNN-LOH | 32838277 | p23.3 - p12 |
|      | | chr8:1-146,364,022 | CN Gain | 146364022 | p23.3 - q24.3 |
|      | | chr8:58,406,216-146,292,734 | CNN-LOH | 87886519 | q12.1 - q24.3 |
|      | | chr11:70,719,897-118,343,378 | CN Gain | 47623482 | q13.4 - q23.3 |
|      | | chr11:118,347,020-121,053,084 | High Copy Gain | 2706065 | q23.3 |
|      | | chr11:121,062,860-134,906,706 | CN Loss | 13843847 | q23.3 - q25 |
|      | | chr13:79,420,211-83,071,814 | High Copy Gain | 3651604 | q31.1 |
|      | | chr13:83,098,518-94,240,082 | CN Gain | 11141565 | q31.1 - q31.3 |
|      | | chr13:94,251,808-115,103,150 | CN Loss | 20851343 | q31.3 - q34 |
|      | | chr15:74,343,354-102,397,317 | CN Gain | 28053964 | q24.1 - q26.3 |
|      | | chr17:7,536,527-7,619,668 | CN Loss | 83142 | p13.1 |
|      | | chr18:33,243,441-55,865,613 | CN Gain | 22622173 | q12.2 - q21.31 |
|      | | chr18:55,893,217-78,007,784 | CN Loss | 22114568 | q21.31 - q23 |
|      | | chr20:32,385,089-62,912,463 | CNN-LOH | 30527375 | q11.22 - q13.33 |
**Supplementary Table S7.** List of somatic mutations in BLL-11q including prediction of amino acid changes that affect protein function (MA, SIFT, Polyphen2, CADD).

*Provided in excel format.*
**Supplementary Table S8.** Mutational patterns across different germinal center derived lymphoma subgroups including BL, DLBCL, DH/TH, and HGBCL, NOS with or without MYC rearrangement. The BL pattern includes mutations in BL-associated genes and the GCB-DLBCL pattern includes mutations associated with GCB phenotype according to literature. BLL-11q mutational pattern includes genes mutated in more than 2 BLL-11q cases, not included in the other two signatures.

| Mutational patterns | Gene   | BLL-11q current series | GCB-DLBCL n=83 | HGBCL DH/TH n=44 | HGBCL with or without MYC-R n=9 | BL n=32 |
|---------------------|--------|------------------------|----------------|-----------------|-------------------------------|---------|
|                     |        | n=10 (%)               | (%)           | (%)             | (%)                          | (%)     |
| BLL-11q             | BTG2   | 40                     | 4.8*          | -               | -                            | 0*      |
|                     | ETS1   | 30                     | 1.2*          | -               | -                            | 0*      |
|                     | EP300  | 30                     | 6*            | 6.8             | 0                            | 0*      |
| Burkitt Lymphoma    | ID3    | 0                      | 0             | 25              | 88.9*                        | 59.4*   |
|                     | TCF3   | 0                      | 0             | 4.5             | 0                            | 31.3    |
|                     | CCND3  | 0                      | 3.6           | 29.2*           | 22.2                         | 9.4     |
|                     | MYC    | 20                     | 2.4           | 43.2            | 44.4                         | 71.9*   |
|                     | DDX3X  | 30                     | 0*            | -               | -                            | 31.3    |
| GCB-DLBCL           | KMT2D  | 20                     | 32.5          | 60*             | -                            | 6.3     |
|                     | CREBBP | 20                     | 25.3          | 50              | 44.4                         | 6.3     |
|                     | TNFRSF14 | 0                     | 20.5          | 20*             | -                            | 0       |
|                     | B2M    | 0                      | 20.5          | 10*             | -                            | 0       |
|                     | EZH2   | 10                     | 21.7          | 27.3            | 0                            | 0       |
|                     | GNA13  | 30                     | 21.7          | 15*             | -                            | 9.4     |
|                     | FOXO1  | 10                     | 13.3          | 30*             | -                            | 6.3     |
|                     | ACTB   | 0                      | 13.3          | -               | -                            | 0       |
|                     | SOCS1  | 0                      | 15.7          | 30*             | -                            | 0       |

* Significant differences of mutated gene prevalence between BLL-11q series and the other germinal center entities (P<0.05).

a Only in Morin et al series n=23. b Only in Momose et al. n=24. c Only in Evrard et al. n=20.
Supplementary References

1. Scholtysek R, Kreuz M, Klappler W et al. Detection of genomic aberrations in molecularly defined Burkitt's lymphoma by array-based, high resolution, single nucleotide polymorphism analysis. Haematologica. 2010;95(12):2047-2055.

2. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009;25(14):1754-1760.

3. McKenna A, Hanna M, Banks E et al. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. 2010;20(9):1297-1303.

4. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010;38(16):e164.

5. Karube K, Enjuanes A, Dlouhy I et al. Integrating genomic alterations in diffuse large B-cell lymphoma identifies new relevant pathways and potential therapeutic targets. Leukemia. 2018;32(3):675-684.

6. Reva B, Antipin Y, Sander C. Predicting the functional impact of protein mutations: application to cancer genomics. Nucleic Acids Res. 2011;39(17):e118.

7. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc. 2009;4(7):1073-1081.

8. Adzhubei IA, Schmidt S, Peshkin L et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7(4):248-249.

9. Kircher M, Witten DM, Jain P et al. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014;46(3):310-315.

10. Salaverria I, Royo C, Carvajal-Cuenca A et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(−) mantle cell lymphoma. Blood. 2013;121(8):1394-1402.

11. Bouska A, McKeithan TW, Deffenbacher KE et al. Genome-wide copy-number analyses reveal genomic abnormalities involved in transformation of follicular lymphoma. Blood. 2014;123(11):1681-1690.

12. Spina V, Khiabanian H, Messina M et al. The genetics of nodal marginal zone lymphoma. Blood. 2016;128(10):1362-1373.

13. Puente XS, Bea S, Valdes-Mas R et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. Nature. 2015;526(7574):519-24.

14. Lopez-Corral L, Sarasquete ME, Bea S et al. SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies, from MGUS to myeloma status. Leukemia. 2012;26(12):2521-2529.

15. Paiva B, Mateos MV, Sanchez-Abarca LI et al. Immune status of high-risk smoldering multiple myeloma patients and its therapeutic modulation under LenDex: a longitudinal analysis. Blood. 2016;127(9):1151-1162.

16. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (Eds) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. (Revised 4th edition) IARC: Lyon 2017.

17. Colomo L, Vazquez I, Papaleo N et al. LMO2-negative Expression Predicts the Presence of MYC Translocations in Aggressive B-Cell Lymphomas. Am J Surg Pathol. 2017;41(7):877-886.
18. Johnson NA, Slack GW, Savage KJ et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3452-3459.

19. Rohde M, Bonn BR, Zimmermann M et al. Relevance of ID3-TCF3-CCND3 pathway mutations in pediatric aggressive B-cell lymphoma treated according to the non-Hodgkin Lymphoma Berlin-Frankfurt-Munster protocols. Haematologica. 2017;102(6):1091-1098.

20. ISCN 2013: an international system for human cytogenetic nomenclature (2013). In: Shaffer Lisa G., McGowan-Jordan J, Schmid M, eds.: Karger; 2013.

21. Schmitz R, Young RM, Ceribelli M et al. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature. 2012;490(7418):116-120.

22. Richter J, Schlesner M, Hoffmann S et al. Recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. Nat Genet. 2012;44(12):1316-1320.

23. Morin RD, Mungall K, Pleasance E et al. Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing. Blood. 2013;122(7):1256-1265.

24. Evrard SM, Pericart S, Grand D et al. Targeted next generation sequencing reveals high mutation frequency of CREBBP, BCL2 and KMT2D in high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Haematologica. 2018

25. Momose S, Weissbach S, Pischimarov J et al. The diagnostic gray zone between Burkitt lymphoma and diffuse large B-cell lymphoma is also a gray zone of the mutational spectrum. Leukemia. 2015;29(8):1789-1791.