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Haematologica 2019 [Epub ahead of print]

Citation: Carla Fuster, David Martín-García, Olga Balagué, Alba Navarro, Ferran Nadeu, Dolors Costa, Miriam Prieto, Itziar Salaverria, Blanca Espinet, Alfredo Rivas-Delgado, Maria José Terol, Eva Giné, Pilar Forcada, Margaret Ashton-Key, Xose S. Puente, Steven H. Swerdlow, Sílvia Beà, and Elias Campo. Cryptic insertions of the immunoglobulin light chain enhancer region near CCND1 in t(11;14)-negative mantle cell lymphoma.

Haematologica. 2019; 104:xxx

doi:10.3324/haematol.2019.237073

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Cryptic insertions of the immunoglobulin light chain enhancer region near *CCND1* in t(11;14)-negative mantle cell lymphoma

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Running Title: Cryptic *CCND1* rearrangements in MCL

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Words: 1474; **Figures:** 2; **Tables:** 1; **References:** 15; **Supplemental Files:** 1

Funding

This work was supported by research funding from Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III PI17/01061 (SB), Ministerio de Economía y Competitividad, SAF2015-64885-R (EC), SAF2017-87811-R (XSP) from Plan Nacional de I+D+I, the NIH grant number 1 P01CA229100 (EC), Generalitat de Catalunya Suport Grups de Recerca 2017-SGR-709 (SB), 2017-SGR-1142 (EC), and the European Regional Development Fund “Una manera de fer Europa”, CERCA Programme/Generalitat de Catalunya. EC is an Academia Researcher of the "Institució Catalana de Recerca i Estudis Avançats" of the Generalitat de Catalunya. Miriam Prieto is supported by "Acció instrumental d'incorporació de científics i tecnòlegs PERIS 2016" (SLT002/16/00347) from Generalitat de Catalunya. Alfredo Rivas-Delgado is supported by “Josep Font” grant from Hospital Clínic de Barcelona.

Acknowledgements

The authors would like to thank the IDIBAPS Genomics Core Facility and the Hematopathology Collection from Hospital Clínic/IDIBAPS; the Molecular Cytogenetic Platform of IMIM, Hospital del Mar (Barcelona) for providing one IGK BAC clone. Miriam Prieto, Silvia Martín, Cándida Gómez, and Amparo Arias for their excellent technical assistance and Montserrat Puiggròs and Romina Royo from Barcelona SuperComputing Center. This work was developed at the Centro Esther Koplowitz (CEK), Barcelona, Spain.

Cyclin D1+ mantle cell lymphoma (MCL) is molecularly characterized by the t(11;14)(q13;q32) or rearrangements of *CCND1* gene with the immunoglobulin (IG) light chains.^{1,2} Most MCL can be diagnosed based on the characteristic pathologic features and cyclin D1 expression without the need for demonstrating the genetic translocation. However, in cases with atypical morphologic or phenotypic features other B-cell neoplasms that sometimes also have cyclin D1 positivity may be in the differential diagnosis.¹ In these situations the detection of the *CCND1* rearrangements may assist in the diagnosis since most other lymphomas do not carry translocations of the gene.³⁻⁷ A subset of plasma cell myelomas express cyclin D1 associated with the t(11;14) but are usually not in the differential diagnosis of MCL and are SOX11-negative.⁵ Nevertheless, there are occasional lymphoid neoplasms with MCL features in which cyclin D1 is strongly expressed without an apparent gene rearrangement using conventional cytogenetics or fluorescence in situ hybridization (FISH) with fusion or break-apart probes. The mechanisms of cyclin D1 overexpression in these cases are unclear and the MCL diagnosis may be questioned.

In this study, we have identified 4 MCL and one mature B-cell lymphoma with marked plasmacytic differentiation with strong cyclin D1 overexpression but in which *CCND1* rearrangements could not be detected by conventional cytogenetics or FISH using fusion or break-apart probes. To determine the mechanism leading to cyclin D1 overexpression in these cases we analyzed the index case by whole-genome sequencing (WGS) followed by FISH studies with custom probes for the IG light chain enhancer regions in all cases and demonstrated the presence of cryptic translocations of the enhancer region of the IG light chains with *CCND1* in the four cyclin D1-positive MCL.

The study was approved by the Institutional Review Board of the Hospital Clinic of Barcelona and informed consent was obtained in accordance with the Declaration of Helsinki. Lymphomas were studied by immunohistochemistry with a panel of antibodies (Online Methods, Supplementary Table S1) and reviewed by four pathologists. Tumor genomic DNA was isolated from formalin-fixed paraffin-embedded tissue biopsies (cases 2, 3, and 5), fresh bone marrow aspirate (case 1) and peripheral blood cells (case 4). Paired-end WGS was performed on tumor and germline DNA from case 1 (index case) using standard Illumina protocols and analyzed as

previously described.⁸ *CCND1* rearrangement was analyzed by FISH using *CCND1* and IG commercial and custom BAC-labeled probes (Online Supplementary Table S2). Copy number alterations were investigated using Oncoscan FFPE or SNP6.0 (ThermoFisher Scientific, Waltham, MA).^{8,9} The mutational status of 115 genes was examined by targeted next-generation sequencing (NGS) strategy (Online Supplementary Table S3).¹⁰ Further details can be found in Online Methods.

The clinical and pathological features of the patients are summarized in Table 1. All patients were in stage IV with peripheral blood and bone marrow involvement. Cases 1-3 presented with generalized lymphadenopathy, whereas case 4 had asymptomatic lymphocytosis and splenomegaly. Case 5 had an unusual clinical history and evolution. The patient was exposed to extensive radiation due to atomic bomb tests in the early 1960s and developed several solid tumors (thyroid papillary carcinoma, basal cell carcinoma, melanoma and pleomorphic sarcomas) that were treated without further relapses. In 2003 he was diagnosed with a lymphoproliferative disorder consistent with atypical CLL which did not require treatment until 2010, when chlorambucil was started. Two years later the patient developed splenomegaly and lymphadenopathy, that was biopsied. The bone marrow biopsy from 2005 showed a nodular and interstitial lymphoid infiltration. The patient had an IgM lambda paraprotein, which was stable for several years but progressively increased in the final phases of the disease. The patient required several lines of therapy without response and died of progressive disease 11 years after the initial diagnosis. The other 4 patients received different treatments. Case 2 died of disease and cases 1, 3, and 4 were alive at the last follow-up.

Cases 1 and 2 had classic MCL cytology, whereas case 3 showed a large cell pleomorphic component with unusual clear cytoplasm intermingled with abundant atypical small cells. Cyclin D1 was strongly positive in both components. Case 4 had small cell morphology and case 5 showed small cells with marked plasmacytic differentiation and occasional Dutcher bodies (Figure 1). CD5 was positive in all cases except case 5 and the bone marrow cells of case 4. SOX11 was positive in cases 1 and 2 and negative in cases 3 to 5. Four cases had kappa light chain restriction and case 2 expressed lambda. Case 5 had strong cytoplasmic IgM/kappa expression (Table 1).

All cases were negative for *CCND1* rearrangements by FISH using commercial fusion and break-apart probes on the diagnostic biopsies (Table 1, Online Supplementary Figure S1A-B). In cases 1 and 5 the FISH analyses were performed in multiple samples. The karyotype in case 1 was 46,XY,der(11)t(3;11)(q13;q25)[9]/46,XY[11]. The unbalanced chromosome 11 translocation with chromosome 3 did not involve the *CCND1* locus (11q13), and was further confirmed by whole chromosome painting (Online Supplementary Figure S2). Case 2 had a complex karyotype, 44-46,XY,-Y[2],del(6)(q21q23),del(7)(p15p22),add(9)(p11.2),del(11)(q21q23.1),del(13)(q11q34)[2],add(22)(p11.2)[6][cp7]/46,XY[9], without the t(11;14) translocation.

We performed WGS of case 1 and identified a rearrangement involving IGK in chromosome 2 and *CCND1* in chromosome 11. A 412 Kb region of the IGK, including the IGK enhancer (IGKenh) and the IGK constant (IGKC) region was inserted 226.3 Kb upstream of *CCND1* gene (Figure 2A-B). We confirmed the rearrangement by PCR, Sanger sequencing and FISH using custom fusion probes combining *CCND1* gene (red) and IGKenh probes (green) that we had used previously (Figure 2C).⁸ FISH using the commercial IGK break-apart probe confirmed the rearrangement detected by WGS (Supplementary Figure 1C). The finding of the cryptic rearrangement of IGK with *CCND1* in case 1, prompted us to analyze this cryptic rearrangement in the remaining four cases by FISH. The IGKenh/*CCND1* rearrangement was also detected in cases 2 and 3, both in the small and large cells (Figure 2D-E). However, cases 4 and 5 were negative. We next tested the combination of *CCND1* with IGLenh and case 4 was positive (Figure 2F) whereas case 5 was negative for both IGKenh and IGLenh with *CCND1* probes.

Targeted sequencing identified mutations in 24 different genes (Online Supplementary Table S4). Cases 1-3 had mutations already reported in MCL,⁹ including *ATM*, *TP53*, *NOTCH2*, *KMT2D*, *NFKBIE*, *ARID1A*, *SMARCA4*, and *CARD11*. Case 4 had mutations in *KLHL6*, *DTX1* and *SETD2*, whereas case 5 had a clonal (allelic frequency of 44.4%) p.L265P *MYD88* mutation (Online Supplementary Figure S3). The genomic profile was complex in cases 1-3 with copy number alterations commonly found in MCL (+3q, -9p, -9q, -11q, -13q, and -17p), whereas case 4 did not show any copy number alterations, in line with its indolent clinical course and SOX11-negativity

(Online Supplementary Table S5). Case 5 showed 8 copy number alterations including +2p, +17q, -6q and -9p.

In summary, cyclin D1 overexpression in 4 out of 5 cases was associated with cryptic *CCND1* rearrangements that involved the enhancers of IGK and IGL in 3 and 1 cases, respectively. Similar to conventional rearrangements with IGH, the IG light chain translocated fragments (including the enhancers) could be responsible for the dysregulation of cyclin D1 in MCL. These findings are similar to our recent observations in cyclin D1-negative MCL overexpressing cyclin D2 or cyclin D3 which carried cryptic insertions of the IGK and IGL enhancers near *CCND2* or *CCND3*, respectively.⁸ The detection of cryptic rearrangements of *MYC* and *BCL2* with regulatory regions of IG genes has been recently reported in B-cell neoplasms.¹¹⁻¹³

The findings in case 5 were intriguing and its specific taxonomic classification difficult. The IgM, kappa paraprotein and plasmacytic differentiation was consistent with a lymphoplasmacytic lymphoma, and concordantly the tumor carried the p.L256P *MYD88* mutation. However, cyclin D1 was diffusely expressed without evidences of *CCND1* rearrangements. The lack of *CCND1* rearrangement detection with our probes does not completely rule out other alternative rearrangements. In this sense, a recent study of a MCL without apparent *CCND1* rearrangements has detected an insertion of the entire *CCND1* coding region into the IGH locus which was not detected by standard probes and would not have been detected with our IG light chain probes.¹⁴ The characteristics of our case with marked plasmacytic differentiation, strong cyclin D1 expression and *MYD88* mutation are similar to a previously reported case but in which the t(11;14) could be demonstrated by FISH.¹⁵ Whether these cases should be classified as lymphoplasmacytic lymphoma with *CCND1* rearrangements or MCL with *MYD88* mutations is debatable. Independent of the possible taxonomy of these tumors, it is important to recognize their clinical and biological peculiarities.

In conclusion, cryptic translocations of the IG light chain regulatory region with *CCND1* may be an alternative mechanism to deregulate this gene in MCL. FISH testing for the IG light chain enhancer region could be incorporated into the diagnostic work up of MCL negative for the t(11;14) or *CCND1* rearrangements with standard probes, especially in cases with atypical pathological or clinical features.

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Table 1. Clinical and pathological data of the five Cyclin D1+ B-cell lymphomas.

	Case 1 (index)	Case 2	Case 3	Case 4	Case 5
Age/gender	72/M	67/M	70/M	60/M	71/M
Lymphocytosis	No	NA	No	Yes	Yes
LDH increased	No	NA	Yes	No	NA
LN involvement	Yes	Yes	Yes	No	Yes
PB involvement	Yes	No	Yes	Yes	Yes
BM involvement	Yes	Yes	Yes	Yes	Yes
Splenomegaly	NA	No	Yes	Yes	Yes
GI involvement	Yes	Yes	Yes	No	No
Stage	IV A	IV A	IV B	IV A	IV A
First line treatment	R-Benda+ Ibrutinib	Immunoche motherapy	R-CHOP	Abstention /R-Ibrutinib	Multiple Chemotherapy ^a
Response	Complete	Unknown	Refractory	Under treatment	Partial
Relapse (months)	Colon (36 m)	No	No	No	Lymphadenopathy High IgM paraprotein (120 m)
Follow up (months)	AWD (62 m)	DD (108 m)	AWD (7 m)	Alive, (42 m)	DD (130 m)
Biopsy site	Colon	LN	LN	BM	LN
Growth pattern	NA	Nodular/ Diffuse	Diffuse	Interstitial	Diffuse
Morphology	Classic	Classic	Pleomorphic /Classic	Small cell	Small cell with plasmacytic differentiation
CD20	+	+	+	+	+
CD5	+	+	+	- BM/+ PB	-
CD23	-	-	-	-	-
Cyclin D1	+	+	+	+	+
SOX11	+	+	-	-	-
Light chain restriction	Kappa	Lambda	Kappa	Kappa	Kappa
IgD	ND	ND	-	+	- ^b
Ki67 (%)	30	30-40	>50	10-30	Very variable
FISH <i>CCND1</i> BAP	- (BM)	-	-	-	-
FISH <i>CCND1</i> Fusion	- (Colon)	-	-	-	-
FISH IGKenh/ <i>CCND1</i>	+	+	+	-	-
FISH <i>CCND1</i> /IGLenh	ND	ND	ND	+	-

AWD: Alive with disease; BAP: break-apart FISH probe; BM: Bone marrow; DD: Dead of disease; LN: Lymph node; M: Male; NA: not applicable; ND: not done; PB: Peripheral blood; GI: Gastrointestinal involvement; +: positive; -: negative.

^aChlorambucil (2010), splenectomy and R-CVP (2011), R-CHOP (2012), Ofatumumab (2013), Velcade, cyclophosphamide and dexamethasone (2014).

^bIncreasing IgM paraprotein throughout the course of disease (3.7 g/l in 2005, 11.2 g/l in 2011 and 80 g/l in the final phases).

Figure Legends

Figure 1. Morphological and phenotypic features of cases 1, 3, and 5. (A, B, C) Case 1, Haematoxylin and eosin (40x) **(A)**, positive Cyclin D1 (40x) **(B)**, positive SOX11 expression (10x) **(C)**. **(D, E, F)** Case 3, Haematoxylin and eosin (20x) **(D)**, positive Cyclin D1 (20x) **(E)**, negative SOX11 expression in large and medium cells in case 3 (20x) **(F)**. **(G, H, I, J)** Case 5, Haematoxylin and eosin with occasional Dutcher bodies (inset) (20x) **(G)**, positive Cyclin D1 (10x) **(H)**, Kappa light chain restriction (10x) **(I)** and Lambda negative (10x) **(J)**.

Figure 2. Cryptic insertions of IG light chain genes near *CCND1* gene. (A-C) case 1. **(A)** Circos plot with copy number alterations (blue for gains and red for losses) in the outer circle and structural variants detected by whole-genome sequencing. The interchromosomal (black lines) and intrachromosomal (blue for gain, red for loss, grey for inversion) rearrangements are represented in the inner circle. The rearrangement between chr2 (IGKenh) and chr11 (*CCND1*) is indicated with a dashed line. **(B)** Schematic representation of IGK (chr2) and *CCND1* (chr11) loci in normal cells (left) and derivative chromosomes after the rearrangement (right). The rearrangement consisted of an inverted insertion of IGK 226 Kb upstream of *CCND1* gene. The chromatin states in two MCL cell lines (Z138 and JVM2) were displayed for the entire fragment of IGK inserted region, the orange part represents the enhancer region which was placed proximal to *CCND1* coding region. **(C)** Verification of the cryptic IGKenh/*CCND1* insertion by FISH using the custom fusion probe IGKenh (green) and *CCND1* (red). Juxtaposition of one red and one small green signals was observed in most cells (yellow arrows). **(D-F)** FISH verification of cryptic *CCND1* rearrangements in cases 2 to 4. Cells positive for the cryptic rearrangement IGKenh/*CCND1* in case 2 **(D)** and case 3 **(E)**, including medium and large cells. **(F)** Cells positive for the cryptic rearrangement *CCND1*/IGLenh in case 4. In all cases the juxtaposition of one red and one green signal was highlighted with yellow arrows.

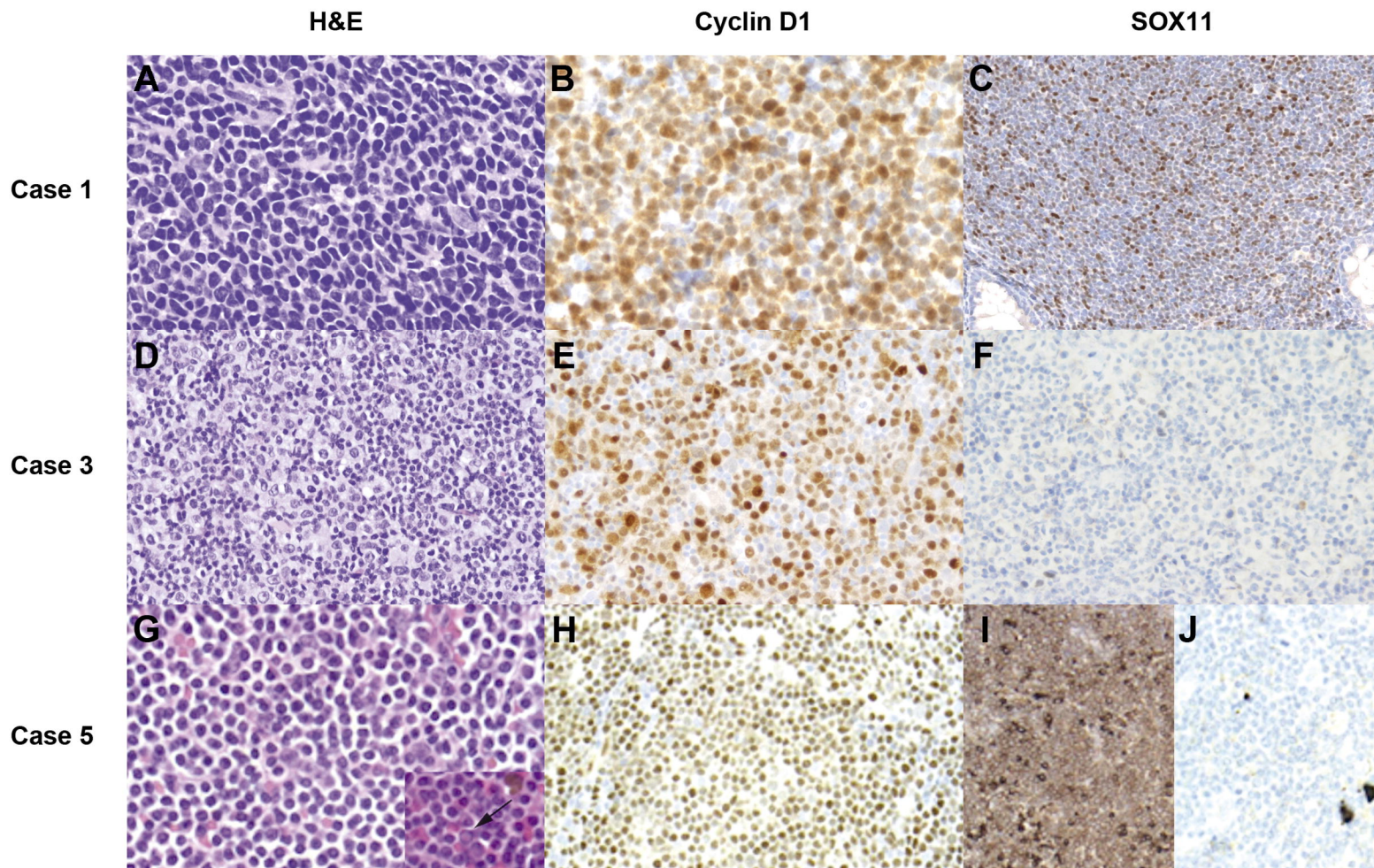


Figure 1

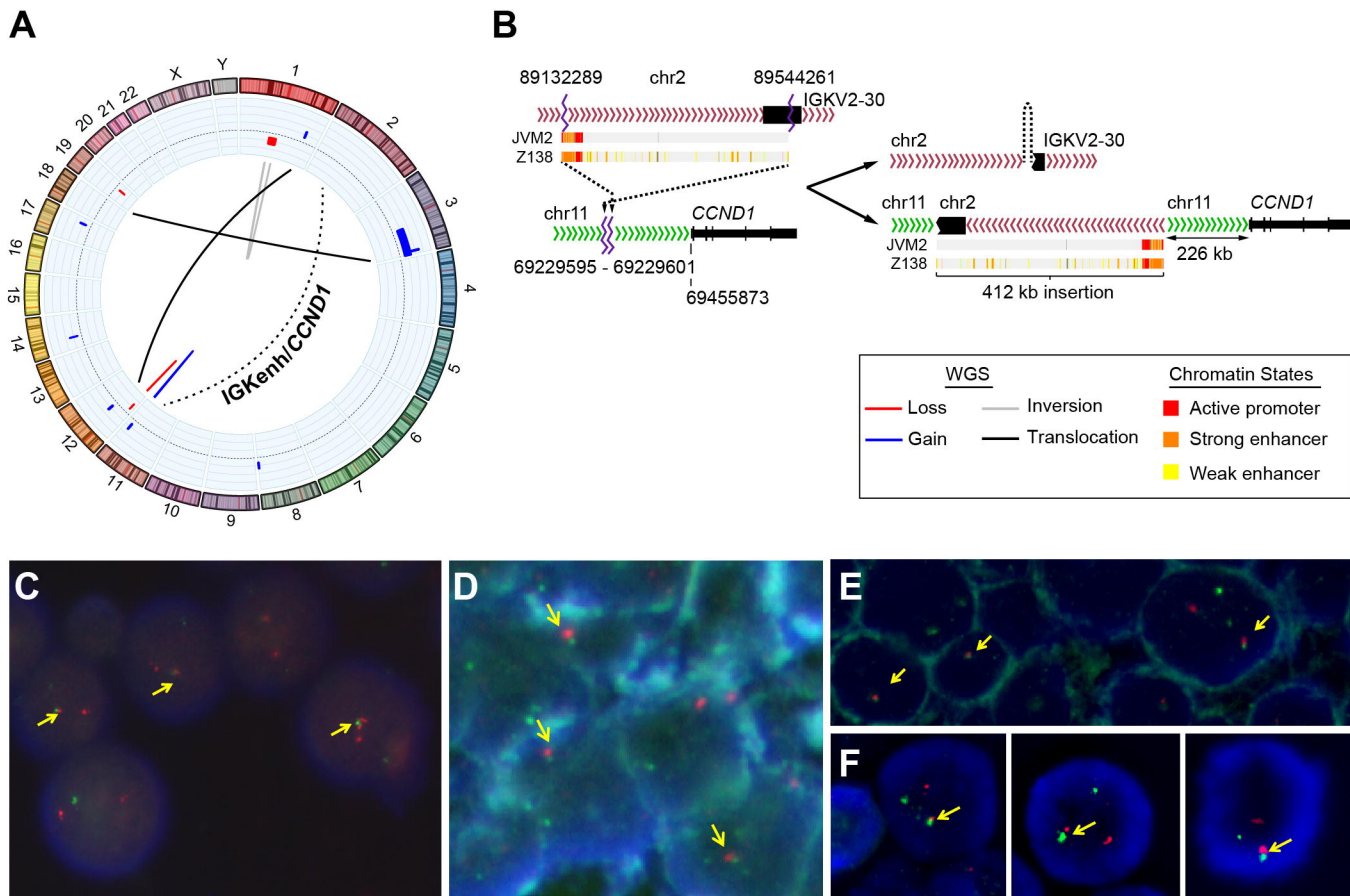


Figure 2

Supplementary Material

Cryptic insertions of the immunoglobulin light chain enhancer region near *CCND1* in t(11;14)-negative mantle cell lymphoma

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SUPPLEMENTARY METHODS

Case selection and immunohistochemistry

We studied 4 mantle cell lymphoma and one mature B-cell neoplasm with marked plasmacytic differentiation, all with strong cyclin D1 expression but the t(11;14) translocation or *CCND1* rearrangements were not found using conventional cytogenetics or FISH with fusion or break-apart probes. All the original haematoxylin and eosin stained sections or newly stained sections were reviewed. Immunohistochemical stains were performed for each case on 2 µm thick sections using a peroxidase-labeled detection system, standard antigen retrieval protocols, and an automated immunostainer (AutostainerLink 48, Dako, Glostrup, Denmark or BenchmarkXT, Roche Diagnostics, Basel, Switzerland) as previously described¹ or phenotype information was retrieved from the original reports (Online Supplementary Table S1).

FISH analysis

CCND1 rearrangement was analyzed by FISH on formalin-fixed paraffin-embedded tissue sections or peripheral blood fixed cells. The FISH panel including commercial and BAC-labeled probes is detailed in Online Supplementary Table S2. DNA labeling and hybridization was performed according to standard procedures.² Digital images were obtained using the ISIS FISH Imaging System (MetaSystems, Altlussheim, Germany). Control FISH experiments were performed in 2 non-neoplastic lymphoid tissues. Whole chromosome painting of chromosomes 3 and 11, and FISH with a chr12 centromeric probe and LSI BCL6-BAP probe were performed in case 1 for refinement of the derivative chromosomes. Conventional cytogenetics was performed on G-banded chromosomes for cases 1 and 2 and results were described according to International System for Human Cytogenomic Nomenclature.³

Copy number and next-generation sequencing (NGS)

Copy number alterations were investigated using Oncoscan FFPE or SNP6.0 Array (ThermoFisher Scientific, Waltham, MA) and analyzed as described previously using Nexus

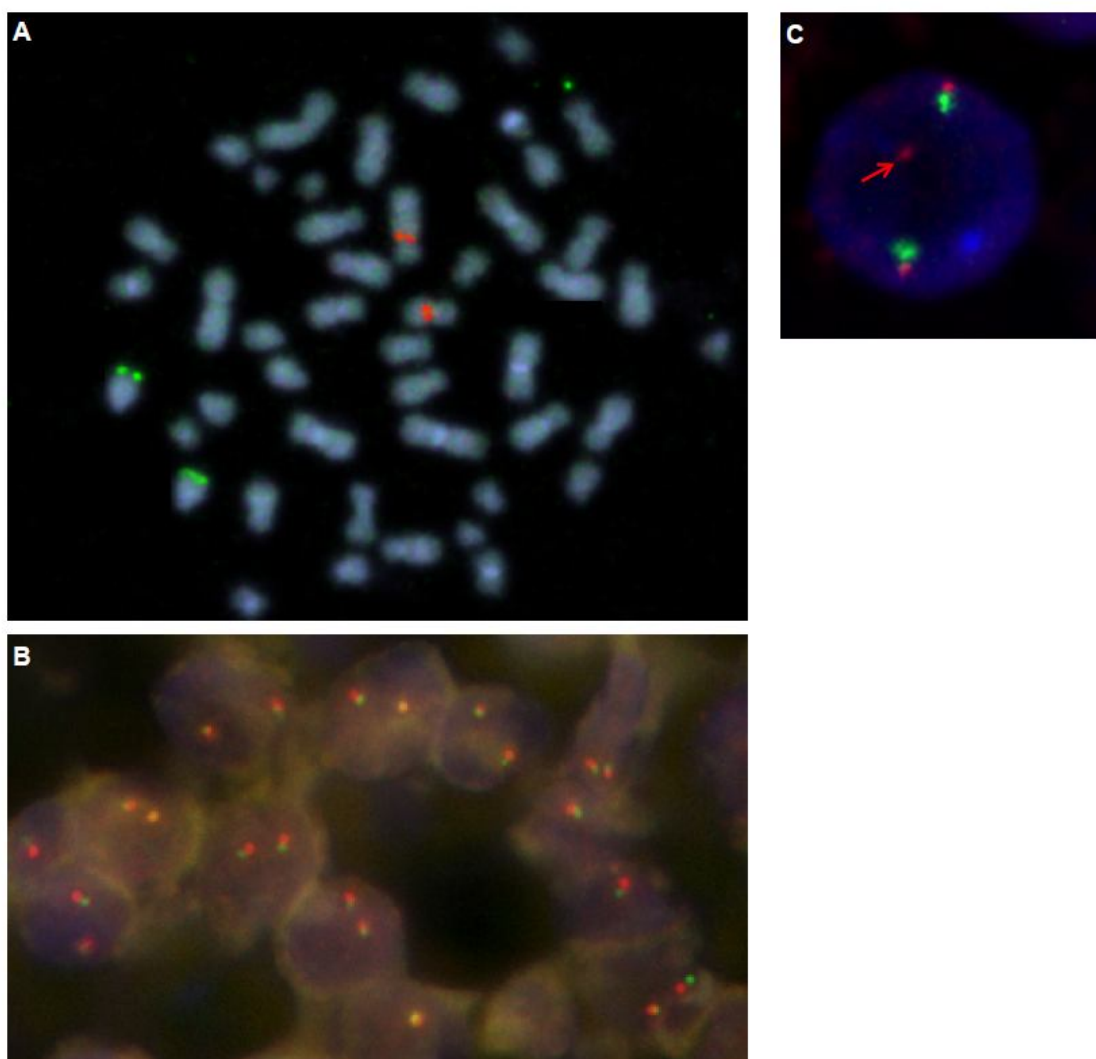
Biodiscovery v9 (Biodiscovery, Hawthorne, CA, USA).^{4,5} Paired-end whole-genome sequencing was performed on tumor and germline DNA from case 1 using standard Illumina protocols and sequenced in an Illumina HiSeq 2000 instrument.⁴ Smufin,⁶ Lumpy,⁷ and custom algorithms were used to detect genome-wide structural variants (SV) and potential cryptic *CCND1* rearrangements. Single nucleotide variant and indel calling was performed by Smufin and Sidrón,⁸ and copy number alterations analysis was performed by Battenberg (<https://github.com/cancerit/cgpBattenberg>) (manuscript with additional details in preparation).

The mutational status of 115 genes previously described in aggressive B-cell lymphoma was examined by targeted NGS strategy (Online Supplementary Table S3). Libraries were prepared with 150 ng of genomic DNA using SureSelect XT Target Enrichment System Capture strategy (Agilent Technologies Inc.) and sequenced in a MiSeq instrument (Illumina, 2x150bp). The bioinformatics analysis was performed using an updated version of our previously validated pipeline.⁹ The mean coverage was 564x (range 363x-1020x) with >90% of target region covered >200x. Synonymous, intronic variants, and polymorphisms reported in dbSNP149 database with a European population frequency higher than 1% (1000 Genomes Project, ExAC, or gnomAD database) or present in our custom chronic lymphocytic leukemia (CLL) database¹⁰ were removed.

SUPPLEMENTARY FIGURES

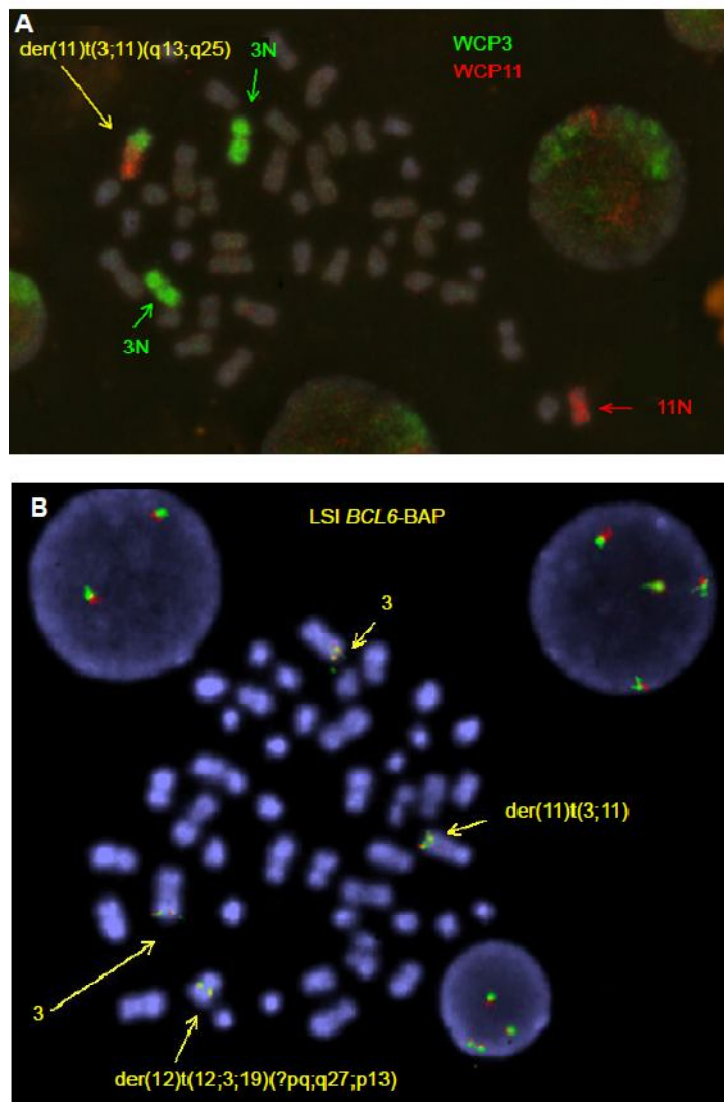
Supplementary Figure S1. Absence of conventional *CCND1* rearrangement in case 1.

(A) Tumor metaphase hybridized with the dual-color dual fusion *CCND1*/IGH probe showing two non-rearranged IGH signals (green) in both normal chr14 and two non-rearranged *CCND1* signals, one in the normal chr11 and one in the derivative chr11 (the larger one). **(B)** FISH normal pattern of *CCND1* break-apart probe in a bone marrow formalin-fixed paraffin-embedded sample, all cells show two green and two red signals juxtaposed (non-split). **(C)** FISH with commercial IGH break-apart probe showing two normal non-rearranged genes and one extra red signal (red arrow) corresponding to a portion of the probe containing the inserted fragment.



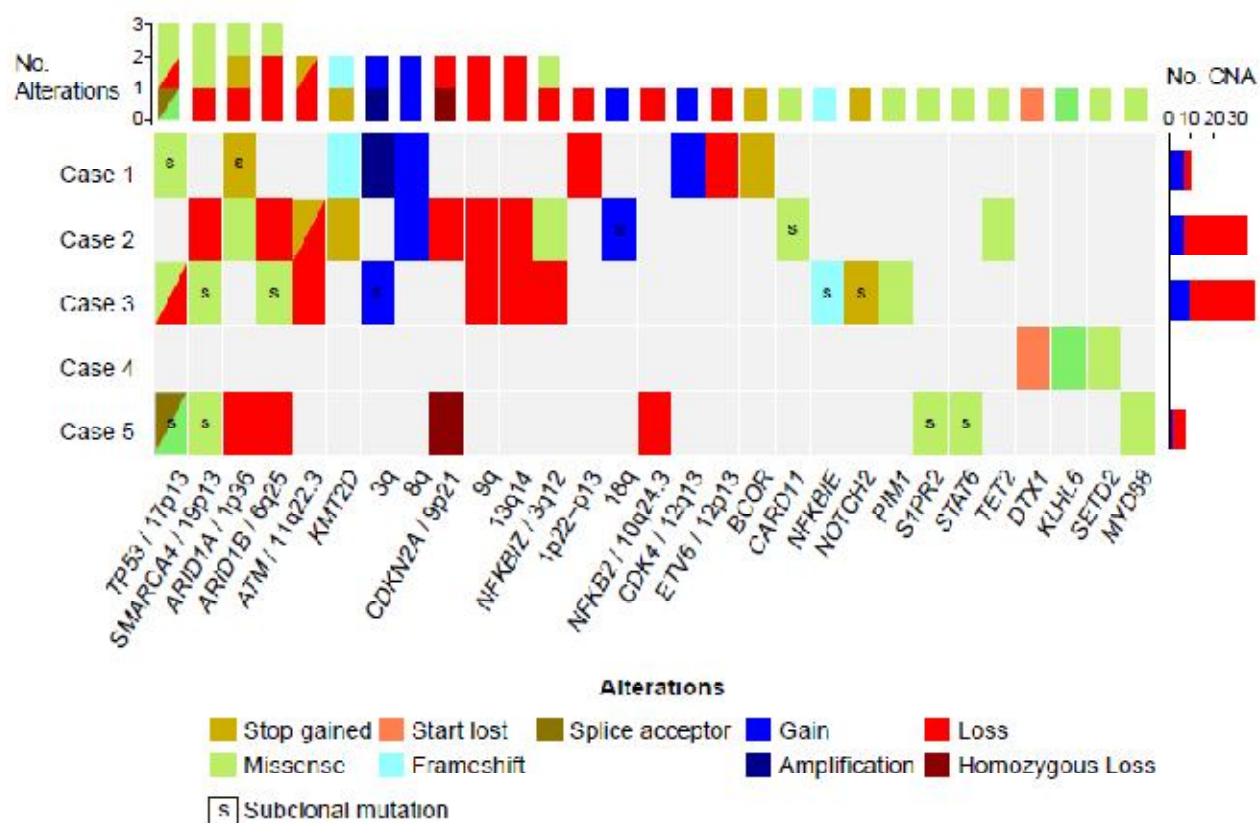
Supplementary Figure S2. Refinement of the two derivative chromosomes in case 1.

(A) A representative tumor metaphase hybridized with whole chromosome painting (WCP) of chr3 (green) and chr11 (red) showing 2 normal chr3 (3N) and one normal chr11 (11N), and the derivative larger chromosome 11 with extra material of 3q, der(11)t(3;11)(q13;q25) (yellow arrow). **(B)** A representative tumor metaphase and two tumor interphase nuclei (right) hybridized with a locus specific identifier (LSI) *BCL6* break-apart (BAP) probe. No *BCL6* split signals were observed but there were 4 copies of *BCL6* per cell: two in both normal chr3, one copy in the derivative chromosome 11 [der(11)t(3;11)], and the fourth *BCL6* copy was in a derivative chr12 together with material from 19p13, as supported by a combination of whole-genome sequencing analysis, FISH and cytogenetics.



Supplementary Figure S3. Copy number and mutational profiles of the five cyclin D1+ lymphomas.

Each case is represented in a row and regions or genes in columns. Losses and homozygous losses were represented in red and bordeaux, respectively, whereas gains and amplifications were represented in blue and dark blue, respectively. Each mutation type was represented in different color and the subclonal mutations (<20% VAF) were indicated with an "s". Genes affected by different alterations (mutation + deletion) were represented by both colors. The upper bar graph indicates the total number of alterations in each region/gene and the bar graph in the right indicates the number of copy number alterations detected in each case (gains in blue and losses in red).



SUPPLEMENTARY TABLES

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

Antibody	Clone	Source	Secondary antibody	Dilution
CD20	L26	Roche	Mouse	RTU
CD79a	SP18	Roche	Rabbit	RTU
CD23	SP23	Roche	Rabbit	RTU
CD5	SP19	Roche	Rabbit	RTU
BCL2	124	Roche	Mouse	RTU
BCL6	GI191E/A8	Roche	Mouse	RTU
Cyclin D1	SP4-12	Roche	Rabbit	RTU
Ki67	30-9	Roche	Rabbit	RTU
p53	DO-7	Roche	Mouse	RTU
SOX11	MRQ	Roche	Mouse	RTU
SOX11	143	Atlas Antibodies, Sigma Aldrich	Mouse	RTU

RTU: Ready to use

Supplementary Table S2. Commercial and bacterial artificial chromosomes (BAC)-labeled probes used for FISH analyses of *CCND1* rearrangements.

BAC/Probe	Chromosome Location (hg19)	Source	Genes	Fluorescent dye
LSI <i>CCND1</i>/IGH XT DC-DF	11q13.3/14q32.3	Vysis	<i>CCND1</i> /IGH	Orange(<i>CCND1</i>)/ Green (IGH)
BAP XL <i>CCND1</i>	11q13.3	MetaSystems	<i>CCND1</i>	Orange 5'/ Green 3'
BAP XL IGH	2p11	MetaSystems	IGH	Orange 3'/ Green 5'
RP11-1134E24	chr2:89135166-89284041	Custom	IGKenh	Green
RP11-15J7	chr2:89140332-89302455	Custom	IGKenh	Green
RP11-729G4	chr22:23064879-23240697	Custom	IGLenh	Green
RP11-300I6	chr11:69453281-69614785	Custom	<i>CCND1</i>	Red

BAP: break-apart; DC-DF: Dual Color, Dual Fusion; enh: enhancer

Supplementary Table S3. List of 115 genes sequenced using target NGS panel in the 5 cyclin D1+ lymphomas.

<i>ACTB</i>	<i>CD79A</i>	<i>GNAI2</i>	<i>MAP2K1</i>	<i>PIK3CD</i>	<i>STAT3</i>
<i>ARID1A</i>	<i>CD79B</i>	<i>HIST1H1B</i>	<i>MAPK1</i>	<i>PIM1</i>	<i>STAT6</i>
<i>ARID1B</i>	<i>CD83</i>	<i>HIST1H1C</i>	<i>MCL1</i>	<i>POU2F2</i>	<i>TBL1XR1</i>
<i>ARID5B</i>	<i>CDKN2A</i>	<i>HIST1H1D</i>	<i>MEF2B</i>	<i>PRDM1</i>	<i>TCF3</i>
<i>ATM</i>	<i>CDKN2B</i>	<i>HIST1H1E</i>	<i>MFHAS1</i>	<i>PRKCB</i>	<i>TET2</i>
<i>B2M</i>	<i>CIITA</i>	<i>HLA-A</i>	<i>MIR147*92</i>	<i>PTEN</i>	<i>TMEM30A</i>
<i>BCL10</i>	<i>CREBBP</i>	<i>HLA-B</i>	<i>MYC</i>	<i>PTPRD</i>	<i>TMSB4X</i>
<i>BCL2</i>	<i>CXCR4</i>	<i>HLA-C</i>	<i>MYD88</i>	<i>REL</i>	<i>TNFAIP3</i>
<i>BCL6</i>	<i>DDX3X</i>	<i>HVCN1</i>	<i>NFKBIA</i>	<i>RHOA</i>	<i>TNFRSF14</i>
<i>BCOR</i>	<i>DIS3</i>	<i>ID3</i>	<i>NFKBIE</i>	<i>RRAGC</i>	<i>TNIP1</i>
<i>BRAF</i>	<i>DTX1</i>	<i>IRF2BP2</i>	<i>NFKBIZ</i>	<i>S1PR1</i>	<i>TOX</i>
<i>BTG1</i>	<i>EBF1</i>	<i>IRF4</i>	<i>NOTCH1</i>	<i>S1PR2</i>	<i>TP53</i>
<i>BTG2</i>	<i>EP300</i>	<i>IRF8</i>	<i>NOTCH2</i>	<i>SETD1B</i>	<i>XBP1</i>
<i>BTK</i>	<i>ETS1</i>	<i>ITPKB</i>	<i>NRAS</i>	<i>SETD2</i>	<i>XPO1</i>
<i>CARD11</i>	<i>ETV6</i>	<i>KLHL14</i>	<i>OSBPL10</i>	<i>SF3B1</i>	<i>ZEB2</i>
<i>CCND3</i>	<i>EZH2</i>	<i>KLHL6</i>	<i>P2RY8</i>	<i>SGK1</i>	
<i>CD274</i>	<i>FAS</i>	<i>KMT2D</i>	<i>PARP2</i>	<i>SMARCA4</i>	
<i>CD36</i>	<i>FBXW7</i>	<i>KRAS</i>	<i>PAX5</i>	<i>SOCS1</i>	
<i>CD58</i>	<i>FOXO1</i>	<i>MALT1</i>	<i>PCBP1</i>	<i>SPEN</i>	
<i>CD70</i>	<i>GNA13</i>	<i>MAML1</i>	<i>PIK3CA</i>	<i>SPIB</i>	

Supplementary Table S4. Mutations identified by targeted NGS in the 5 Cyclin D1+ B-cell lymphomas.

Case	Gene	Chr	Position (hg19)	Transcript	Exon	Ref	Var	cDNA	Protein	VAF (%)	Mutation type
case 1	KMT2D	chr12	49444834	NM_003482.3	10/54	CAG	C	c.2630_2631delCT	p.Pro877fs	26,8	frameshift
case 1	TP53	chr17	7578406	NM_000546.5	5/11	C	T	c.524G>A	p.Arg175His	7	missense
case 1	ARID1A	chr1	27106165	NM_006015.4	20/20	G	T	c.5776G>T	p.Gly1926*	2,5	stop_gained
case 1	BCOR	chrX	39932926	NM_001123385.1	4/15	G	C	c.1673C>G	p.Ser558*	68,8	stop_gained
case 2	CARD11	chr7	2984141	NM_032415.4	5/25	A	C	c.389T>G	p.Phe130Cys	2,6	missense
case 2	ARID1A	chr1	27023222	NM_006015.4	1/20	A	G	c.328A>G	p.Arg110Gly	78	missense
case 2	KMT2D	chr12	49426190	NM_003482.3	39/54	G	A	c.12298C>T	p.Gln4100*	32,3	stop_gained
case 2	NFKBIZ	chr3	101568755	NM_031419.3	1/12	C	A	c.283C>A	p.Gln95Lys	52,7	missense
case 2	TET2	chr4	106197552	NM_001127208.2	11/11	C	T	c.5885C>T	p.Pro1962Leu	42,6	missense
case 2	ATM	chr11	108137910	NM_000051.3	17/63	A	T	c.2479A>T	p.Lys827*	50,3	stop_gained
case 3	TP53	chr17	7577129	NM_000546.5	8/11	A	G	c.809T>C	p.Phe270Ser	54	missense
case 3	SMARCA4	chr19	11144110	NM_003072.3	26/35	G	A	c.3691G>A	p.Ala1231Thr	18,1	missense
case 3	PIM1	chr6	37138805	NM_001243186.1	3/6	C	A	c.511C>A	p.Leu171Met	46,5	missense&splice
case 3	NOTCH2	chr1	120458087	NM_024408.3	34/34	C	A	c.7258G>T	p.Glu2420*	2	stop_gained
case 3	ARID1B	chr6	157488191	NM_020732.3	10/20	G	A	c.2897G>A	p.Gly966Asp	1,3	missense
case 3	NFKBIE	chr6	44232738	NM_004556.2	1/6	TGTAA	T	c.759_762delTTAC	p.Tyr254fs	3,2	frameshift
case 4	KLHL6	chr3	183273248	NM_130446.2	1/7	A	G	c.194T>C	p.Leu65Pro	39,3	missense
case 4	KLHL6	chr3	183273251	NM_130446.2	1/7	G	T	c.191C>A	p.Thr64Asn	39,6	missense
case 4	SETD2	chr3	47144852	NM_014159.6	7/21	T	A	c.4901A>T	p.Asn1634Ile	49,1	missense
case 4	DTX1	chr12	113495999	NM_004416.2	1/9	T	C	c.2T>C	p.Met1?	51,8	start_lost
case 5	TP53	chr17	7577539	NM_000546.5	7/11	G	A	c.742C>T	p.Arg248Trp	2,2	missense
case 5	TP53	chr17	7577610	NM_000546.5	6/10	T	A	c.673-2A>T		4	splice_acceptor & intron
case 5	S1PR2	chr19	10334881	NM_004230.3	2/2	G	A	c.701C>T	p.Thr234Met	1,2	missense
case 5	SMARCA4	chr19	11106922	NM_003072.3	10/35	G	A	c.1627G>A	p.Asp543Asn	2,7	missense
case 5	MYD88	chr3	38182641	NM_002468.4	5/5	T	C	c.794T>C	p.Leu265Pro	44,4	missense
case 5	STAT6	chr12	57499303	NM_001178078.1	8/22	G	A	c.760C>T	p.Arg254Trp	2,5	missense

Chr: chromosome; Ref: reference; VAF: variant allele frequency; Var: variant.

Supplementary Table S5. Copy number (CN) and CN neutral loss of heterozygosity (CNN-LOH) alterations in the 5 Cyclin D1+ B-cell lymphomas.

Case	Chromosome Region (hg19)	Event	Length	Cytoband	Probe Median	No. Probes	No. Genes
Case 1	chr1:95980272-119185887	CN Loss	23234551	p21.3 - p12	-0.386806935	15044	297
Case 1	chr1:204475348-206870479	CN Gain	2195132	q32.1	0.234532431	1335	62
Case 1	chr3:115931660-197962430	CN Gain	82087478	q13.31 - q29	0.298049167	51924	1009
Case 1	chr8:143764253-144237636	CN Gain	547757	q24.3	0.279687643	187	18
Case 1	chr11:116815711-119029148	CN Gain	2213438	q23.3	0.246547163	1531	91
Case 1	chr12:11733676-12185234	CN Loss	451559	p13.2	-0.365388989	501	1
Case 1	chr12:55470862-58163695	CN Gain	2692834	q13.2 - q14.1	0.248957023	1425	144
Case 1	chr14:35528384-35827142	CN Gain	298759	q13.2	0.356962919	146	7
Case 1	chr17:61169570-62926364	CN Gain	1833525	q23.3 - q24.1	0.255203933	895	67
Case 1	chr19:36815688-37322591	CN Loss	506904	q13.12	-0.383535266	302	29
Case 2	chr1:0-40,927,011	CNN-LOH	40927012	p36.33 - p34.2	0.025316545	3438	761
Case 2	chr3:109,186,681-109,992,943	CN Loss	806263	q13.13	-0.515734315	53	2
Case 2	chr6:25,919,210-26,680,732	CN Loss	761523	p22.2	-0.367333472	52	49
Case 2	chr6:26,680,732-27,106,766	CN Gain	426035	p22.2 - p22.1	0.270689368	25	6
Case 2	chr6:32,544,871-33,096,448	CN Loss	551578	p21.32	-0.560308367	50	21
Case 2	chr6:71,948,724-72,314,039	CN Loss	365316	q13	-0.45486185	25	5
Case 2	chr6:73,931,285-75,550,312	CN Loss	1619028	q13	-0.434173703	108	15
Case 2	chr6:78,820,394-79,551,342	CN Loss	730949	q14.1	-0.571523607	46	0
Case 2	chr6:85,055,355-85,337,153	CN Loss	281799	q14.3	-0.367947176	24	1
Case 2	chr6:85,616,723-87,030,056	CN Loss	1413334	q14.3	-0.41721952	87	7
Case 2	chr6:91,948,012-92,078,737	CN Loss	130726	q15	-0.847036242	9	0
Case 2	chr6:99,225,719-100,559,527	CN Loss	1333809	q16.1 - q16.2	-0.481905222	89	14
Case 2	chr6:103,850,486-104,216,465	CN Loss	365980	q16.3	-0.553430676	25	0
Case 2	chr6:104,550,864-109,732,895	CN Loss	5182032	q16.3 - q21	-0.530617893	464	36
Case 2	chr6:146,617,365-146,975,320	CN Loss	357956	q24.3	-0.519354463	43	4
Case 2	chr6:148,718,223-150,205,951	CN Loss	1487729	q24.3 - q25.1	-0.507299989	104	19
Case 2	chr6:150,770,418-155,836,923	CN Loss	5066506	q25.1 - q25.3	-0.442086697	395	27
Case 2	chr6:155,836,923-156,146,412	CN Gain	309490	q25.3	0.168327823	21	1
Case 2	chr6:156,146,412-157,902,198	CN Loss	1755787	q25.3	-0.538536727	111	6
Case 2	chr6:159,690,974-160,904,134	CN Loss	1213161	q25.3	-0.589955866	115	19

Case 2	chr6:161,361,947-162,274,037	CN Loss	912091	q26	-0.529157043	161	5
Case 2	chr7:25,931,287-26,615,495	CN Loss	684209	p15.2	-0.515489757	59	8
Case 2	chr8:22,392,346-23,113,124	CN Loss	720779	p21.3	-0.513352811	65	19
Case 2	chr8:82,451,644-146,364,022	CN Gain	63912379	q21.13 - q24.3	0.371620208	5413	456
Case 2	chr9:0-102,585,105	CN Loss	102585106	p24.3 - q22.33	-0.468746305	5615	622
Case 2	chr11:90,377,439-115,217,228	CN Loss	24839790	q14.3 - q23.3	-0.409956872	1902	182
Case 2	chr13:24,357,324-115,169,878	CN Loss	90812555	q12.12 - q34	-0.351244003	7567	598
Case 2	chr15:60,239,810-102,531,392	CN Gain	42291583	q22.2 - q26.3	0.209746569	3339	503
Case 2	chr16:0-34,071,208	CN Gain	34071209	p13.3 - p11.2	0.393616796	2438	700
Case 2	chr18:1-78,077,248	CN Gain	78077248	p11.32 - q23	0.079924278	5595	439
Case 2	chr19:10,594,043-14,000,572	CN Loss	3406530	p13.2 - p13.12	-0.325779736	291	125
Case 2	chr22:16,054,713-21,810,492	CN Gain	5755780	q11.1 - q11.21	0.264480948	418	127
Case 2	chr22:22,536,518-24,343,908	CN Loss	1807391	q11.22 - q11.23	-0.49614805	183	42
Case 2	chr22:26,470,387-38,094,460	CN Loss	11624074	q12.1 - q13.1	-0.212323718	876	176
Case 2	chr22:38,587,947-51,304,566	CN Loss	12716620	q13.1 - q13.33	-0.240061574	990	236
Case 3	chr1:1-121,350,750	CNN-LOH	121350750	p36.33 - p11.2	0.093750387	9730	1503
Case 3	chr1:0-19,251,659	CN Gain	19251660	p36.33 - p36.13	0.179936387	1644	381
Case 3	chr3:12,713,954-13,503,246	CN Gain	789293	p25.2 - p25.1	0.346782655	51	7
Case 3	chr3:31,222,672-46,762,047	CN Loss	15539376	p23 - p21.31	-0.426403686	1118	159
Case 3	chr3:46,762,047-49,710,139	CN Gain	2948093	p21.31	0.101522375	250	86
Case 3	chr3:49,710,139-52,314,215	CN Loss	2604077	p21.31 - p21.1	-0.428447634	312	78
Case 3	chr3:52,314,215-52,522,668	CN Gain	208454	p21.1	0.111854121	26	9
Case 3	chr3:52,522,668-67,508,358	CN Loss	14985691	p21.1 - p14.1	-0.447860241	1184	110
Case 3	chr3:67,925,592-70,599,800	CN Loss	2674209	p14.1 - p13	-0.450992733	529	14
Case 3	chr3:72,699,874-90,225,371	CN Loss	17525498	p13 - p11.1	-0.527514279	1329	46
Case 3	chr3:93,517,443-99,661,432	CN Loss	6143990	q11.1 - q12.1	-0.508259714	409	35
Case 3	chr3:101,279,182-104,072,680	CN Loss	2793499	q12.3 - q13.11	-0.505373448	184	14
Case 3	chr3:138,481,903-198,022,430	CN Gain	59540528	q22.3 - q29	0.147937119	4465	478
Case 3	chr7:79,739,785-97,648,154	CN Loss	17908370	q21.11 - q21.3	-0.348251402	1349	100
Case 3	chr7:105,772,996-152,705,396	CN Loss	46932401	q22.3 - q36.2	-0.318359673	3903	401
Case 3	chr9:1,869,321-4,379,060	CN Loss	2509740	p24.3 - p24.2	-0.320553005	167	10
Case 3	chr9:30,149,077-39,184,065	CN Loss	9034989	p21.1 - p13.1	-0.273775578	622	127
Case 3	chr9:70,984,372-72,798,245	CN Gain	1813874	q21.11 - q21.12	0.10734003	121	17

Case 3	chr9:72,798,245-86,897,220	CN Loss	14098976	q21.12 - q21.32	-0.230984032	989	63
Case 3	chr9:104,044,341-128,755,004	CN Loss	24710664	q31.1 - q33.3	-0.234672427	1813	207
Case 3	chr9:138,969,890-140,784,943	CN Loss	1815054	q34.3	-0.306916073	166	98
Case 3	chr11:43,672,857-45,096,829	CN Loss	1423973	p11.2	-0.235927537	129	13
Case 3	chr11:64,412,839-64,666,527	CN Loss	253689	q13.1	-0.329794824	36	13
Case 3	chr11:88,980,982-135,006,516	CN Loss	46025535	q14.3 - q25	-0.197165251	3627	444
Case 3	chr12:14,990,267-19,172,749	CN Loss	4182483	p12.3	-0.353822619	349	22
Case 3	chr12:120,614,579-133,851,895	CN Loss	13237317	q24.23 - q24.33	-0.197701231	909	179
Case 3	chr13:19,073,326-25,654,527	CN Loss	6581202	q11 - q12.13	-0.207541093	456	61
Case 3	chr13:30,294,626-59,038,774	CN Loss	28744149	q12.3 - q21.1	-0.220169753	2378	251
Case 3	chr13:59,038,774-112,003,260	CN Gain	52964487	q21.1 - q34	0.103948779	4411	242
Case 3	chr13:112,003,260-115,169,878	CN Loss	3166619	q34	-0.391424149	247	48
Case 3	chr15:22,752,399-41,435,285	CN Loss	18682887	q11.2 - q15.1	-0.471566498	1297	309
Case 3	chr15:90,742,770-98,903,641	CN Loss	8160872	q26.1 - q26.3	-0.446195483	607	55
Case 3	chr17:0-22,217,883	CN Loss	22217884	p13.3 - p11.1	-0.524609357	1746	459
Case 3	chr17:25,326,941-81,195,210	CN Gain	55868270	q11.1 - q25.3	0.225378588	4678	1130
Case 3	chr20:29,519,156-60,146,222	CN Gain	30627067	q11.21 - q13.33	0.109474625	2300	410
Case 3	chr20:62,493,150-63,025,520	CN Gain	532371	q13.33	0.270182818	37	35
Case 3	chr22:21,461,166-24,343,908	CN Loss	2882743	q11.21 - q11.23	-0.251772046	286	69
Case 3	chr22:25,961,443-29,727,979	CN Loss	3766537	q12.1 - q12.2	-0.288313538	287	41
Case 3	chr22:43,774,169-44,820,727	CN Loss	1046559	q13.2 - q13.31	-0.362747192	71	11
Case 4	No alterations						
Case 5	chr11:0-47,613,870	CNN-LOH	47613871	p15.5 - p11.2	-6.78E-05	3446	561
Case 5	chr1:22,971,471-31,932,838	CN Loss	8961368	p36.12 - p35.2	-0.710997403	749	168
Case 5	chr2:1-87,052,658	CN Gain	87052658	p25.3 - p11.2	0.066282526	6647	658
Case 5	chr6:103,405,413-142,794,913	CN Loss	39389501	q16.3 - q24.1	-0.69513911	3001	250
Case 5	chr9:10,997,956-21,802,107	CN Loss	10804152	p23 - p21.3	-0.702891767	848	60
Case 5	chr9:21,802,107-21,970,167	Homo. Loss	168061	p21.3	-2.311187267	66	3
Case 5	chr9:21,970,167-39,184,065	CN Loss	17213899	p21.3 - p13.1	-0.666557789	1303	152
Case 5	chr10:103,552,035-105,362,804	CN Loss	1810770	q24.32 - q24.33	-0.659816146	185	44
Case 5	chr17:41,605,296-81,195,210	CN Gain	39589915	q21.31 - q25.3	0.422790229	3112	692

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