SUPPLEMENTARY APPENDIX

Genetic lesions in *MYC* and *STAT3* drive oncogenic transcription factor overexpression in plasmablastic lymphoma

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Supplementary Data

Supplementary Methods.

Case selection and sample collection

Twenty-eight new cases diagnosed as plasmablastic lymphoma were retrieved from the files of the Pathology Department of the Hospital Universitario Marqués de Valdecilla. Available Clinical data were retrieved. 10 samples were retrieved from the files of the University of Texas MD Anderson Cancer Center (Houston) Hematopathology Department files and 4 cases were received from the department of Pathology of San Bortolo Hospital, Vicenza, Italy. Material Transfer Agreements were signed by IDIVAL and the corresponding institutions to share the material in the project. The study and sample collection were approved by the local ethics committee (CEIC Cantabria, IRB code 2016.168) and complies with the Declaration of Helsinki. Formalin-fixed and paraffin-embedded tissue was available to construct two tissue microarrays, following conventional protocols. Whole sections were used in the rest of the cases to perform the immunohistochemical, chromogenic in situ hybridization and fluorescent in situ hybridization analysis. All cases were diagnosed according to the WHO classification of Hematolymphoid Neoplasms. Specifically, negativity for pan B cell markers (CD20), HHV-8 and ALK was required in every case to be included. The phenotype of the cases was consistent with a plasma cell differentiation program as described previously. The clinical features of the cases including age, gender, anatomic site of the biopsy, HIV status, previous transplantation or other source for immunesupression, CRAB features, M component and bone marrow biopsy infiltration were recorded and a summary is available in Supplementary Table 1.

Immunohistochemistry and in situ hybridization.

Immunohistochemical reactions were performed following conventional automated procedures (DAKO, Autostainer and Omnis automated platforms).

Primary antibodies against CD20 (DAKO, RTU), PAX-5 (DAKO, RTU), CD138 (DAKO, RTU), CD38 (Leica, 1:200), IRF4/MUM-1 (DAKO, RTU), Blimp-1 (CNIO, 1:5), Kappa (DAKO, RTU), Lambda (DAKO, RTU), BCL-6 (DAKO, RTU), BCL-2 (DAKO, RTU), CD10 (DAKO, RTU), KI67 (DAKO, RTU), CMYC (Abcam, 1:50), HHV-8 (Novus Biologicals, 1:10), EBV-LMP1 (DAKO, RTU), CD30 (DAKO, RTU), ALK (DAKO, RTU), p53 (DAKO, RTU), Phospho-STAT3 (Tyr705) (Clone EP2147Y, Millipore 1:100), PD-L1 (clone 22C3, DAKO), PD1 (clone NAT105, CNIO 1:5), CD3 (DAKO, RTU), CD4 (DAKO, RTU), CD8 (DAKO, RTU), CD163 (DAKO, RTU) and HLA-DP/DR (clone JS76 CNIO, 1:400) were used.

EBV-EBER was considered positive when ≥80% of the large atypical cells were positive. Fluorescent in situ hybridization for the detection of *MYC* rearrangement was done using a dual color break apart rearrangement probe set specific for the *MYC* gene locus on chromosome 8q24 (Abbot Molecular). At least 10% of cells with a break apart signal were required for a case to be regarded as positive for *MYC* rearrangements. At least 15% of cells with extra-copies of the *MYC* gene were required to identify a case as positive for copy number gains of the *MYC* gene.

Quantification of the cellular composition of the tumor and transcription factor abundance.

Quantification of different lymphoid and histiocytic/dendritic subpopulations, identified with CD3, CD8, PD1, CD163, PD-L1 and MHCII/HLA DP/DR and absolute quantification of the number of nuclei showing expression of MYC and Phospho-STAT3 (Tyr705) was done according to the following method:

Microphotographs of 3 representative high-power fields (40x magnification) were acquired for each case using a Leica photomicroscope (DM2000LED) with an attached camera (LEICA ICC50 W). Hotspots with higher positivity were chosen. All the above referenced immunohistochemistry markers were quantified visually averaging the number of positive cells quantified in triplicate in tissue sections. For nuclear markers we counted the positive and negative nuclei. For cytoplasmic and membrane bound markers we counted separately the positive cells with circumferential staining and the negative nuclei. For specific markers such as PD-L1, the expression was quantified in both neoplastic cells and microenvironment cells.

Nuclear atypia was used to differentiate the neoplastic cells from others (i.e macrophages). MHCII/HLA DP/DR was quantified in neoplastic cells and the pattern of expression was recorded (membrane or cytoplasmic staining).

Next Generation Sequencing using amplicon-based library generation.

A TruSeq® Custom Amplicon Low Input Library containing exonic regions of 35 selected genes of interest was used to isolate the DNA for sequencing (Illumina). The list of genes was *CARD11, ARID1A, NOTCH1, TCF3, SMARCA4, STAT6, EP300, CREBBP, MLL2, BTK, NOTCH2, TNFRSF14, ATM, FOXO1, B2M, PLCG2, CD79B, TP53, STAT3, BCL2, MEF2B, CD79A, CXCR4, PTPN1, MYD88, FAT2, PRDM1, TNFAIP3, SGK1, CCND3, PIM1, EZH2, BRAF, MYC, NOTHC2*.
Of note, variants occurring in regions outside the coverage of our targeted design, were not explored using this approach.

Depending on the availability of DNA, between 6ng and 400ng of DNA were used for libraries preparation. Two different libraries of FFPE samples (one for each DNA strand) were prepared and required per protocol in order to eliminate false C-T mutations that commonly appear during formalin fixation. After library preparation and quantification by Qubit (ThermoFisher Scientific) libraries from 30 out of 42 samples met the quality control criteria and were pooled for sequencing on a HiSeq instrument (Illumina, paired end, 2x150) at the National Genomic Analysis Center (CNAG, Barcelona, Spain).

Sequencing data interpretation and reporting.

Reads were mapped to human genome build hg19 with decoy sequences (hs37d5) using the GEM toolkit (version 3). The Genome Analysis Tool Kit (GATK) was used for local realignment and base quality score recalibration. Variant calling was done using HaplotypeCaller from GATK following the recommended best practices. Functional annotations were added using SnpEff with the GRCh37.75 database. Variants were annotated with SnpSift using population frequencies, conservation scores and deleteriousness predictions from dbNSFP. Other sources of annotations, such as gnomAD and Clinvar were also used.

Only variants with a coverage ≥300 reads were selected for downstream analysis. Both DNA strands were available in all 30 cases. Only variants in which both libraries had a coverage greater or equal to 300 reads and had the same genotype were selected for downstream analysis.

Subsequently only missense, frameshift, and nonsense somatic mutations with variant frequency>10% were considered (supplementary Table 2). SNPs were filtered out based on the comparison of the VAF of the variant with the estimation of the amount of neoplastic cells by morphology and IHC, after search in dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and after comparison with a germline variants database collected from an in house analysis of 89 germline DNA from patients with DLBCL. The COSMIC (http://cancer.sanger.ac.uk/cosmic) database was also checked in every case and the COSMIC Id was annotated. Three algorithms were used to predict the functional consequences of the variants found, including SIFT (http://sift.bii.astar.edu.sg/), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) and Condel (http://bg.upf.edu/fannsdb/). Selected variants were visualized using the Integrative Genomics Viewer (IGV).

Finally, 34 somatic mutations (31 missense, 3 nonsense) in 14 genes were considered (Table 1 in the main text).

Statistical analysis.

XLSTAT Biomed software (version 19.4) was used for statistical analysis. Descriptive statistics were performed.

Supplementary Table 1.

The clinical features of the cases including age, gender, anatomic site of the biopsy, HIV status, previous transplantation or other source for immunesupression, CRAB features, M component and bone marrow biopsy infiltration are shown.

case ID	Age	Sex	Anatomic Site	HIV	EBV in tumor cells	Transplant	Other immune deficiency	CRAB	M Component	Bone Marrow Biopsy
2	41	M	Maxillary sinus	pos	pos	no	none	no	---	negative
4	57	M	Maxillary sinus	pos	pos	no	none	no	---	---
5	50	M	Oral cavity	pos	pos	no	none	no	---	---
7	38	M	Rectum	pos	pos	no	none	no	---	negative
8	36	M	Lymph node	pos	pos	no	none	---	---	---
11	33	F	Perineal region	pos	pos	no	none	no	negative	negative
14	56	M	Oral cavity	pos	pos	no	none	bone lesions	negative	negative
17	30	M	Rectum	pos	pos	no	none	no	negative	negative
20	29	M	Lymph node	pos	pos	no	none	---	---	---
21	36	M	Soft tissue	pos	pos	no	none	no	positive	negative
23	44	M	Perineal region	pos	pos	no	none	no	negative	negative
28	53	M	Nasopahringeal area	pos	pos	no	none	no	---	negative
30	37	F	Ovary	pos	pos	no	none	no	negative	negative
31	50	M	Lymph node	pos	pos	no	none	no	negative	negative
33	37	M	Oral cavity	pos	pos	no	none	no	negative	negative
24	66	M	Lymph node	neg	pos	no	none	no	---	---
25	62	F	GI tract	neg	pos	Renal Transplant	none	no	---	---
1	66	M	Lymph node	neg	neg	alloSCT (for relapsed CLL)	none	no	negative	negative
3	64	M	Lymph node	neg	neg	no	none	no	---	---

9	75	M	Lymph node	neg	neg	no	none	no	negative	negative
10	58	M	GI tract	neg	pos	no	none	no	---	negative
12	92	F	Nasal region	neg	neg	no	none	no	---	---
16	62	M	Maxillary sinus	neg	pos	no	none	no	---	negative
19	79	F	Lymph node	neg	pos	no	none	---	---	---
22	76	M	Skin	neg	neg	no	none	no	---	negative
13	75	M	Nasal region	---	neg	---	---	---	---	---
15	82	M	Oral cavity	---	neg	---	---	no	---	---
18	56	F	Small intestine	---	neg	no	none	no	negative	---
26	43	M	Paranasal region	---	pos	---	---	no	---	---
27	76	M	Paranasal region	---	pos	---	---	no	---	---

Supplementary Table 2.

Complete list of variants identified after quality control and annotation. Only missense, frameshift, and nonsense somatic mutations with variant frequency>10% are depicted. This list includes SNPs that were filtered out in a subsequent step.

POS: Genomic position, REF: reference base, ALT: altered base, QUAL: quality score, DP: number of reads for the allele, AF: Variant Allele Frequency.

Id	Gene	CHR	POS	REF	ALT	QUAL	Annotation	DP	AF	cDNA_pos	CDS_pos	Protein_pos	AA	Codons	Existing_variation
8	ARID1A	1	27100181	CGCA	C	2181,4	disruptive_inframe_deletion	597	0,23	4349-4351	3978-3980	1326-1327	PQ/P	ccGCAg/ccg	COSM298325
8	EP300	22	41546030	C	G	10951	missense_variant	917	0,49	3864	2645	882	P/R	cCa/cGa	COSM4385247
8	PRDM1	6	1,07E+08	G	A	9400,4	missense_variant	2090	0,30	2546	2312	771	G/D	gGc/gAc	rs80257572
8	SMARCA4	19	11135047	G	A	436,44	missense_variant	543	0,16	3295	3014	1005	R/Q	cGa/cAa	-
3	ARID1A	1	27023285	G	A	4731,4	missense_variant	380	0,57	762	391	131	G/R	Ggg/Agg	-
3	ARID1A	1	27106544	G	C	4235,4	missense_variant	1915	0,21	6526	6155	2052	C/S	tGc/tCc	-
3	TNFRSF14	1	2488153	A	G	4635,4	missense_variant	786	0,36	349	50	17	K/R	aAa/aGa	rs4870
3	MYD88	3	38182641	T	C	100	missense_variant	250	0,24		794	265	L/P	cTg/cCg	COSM85940
9	EZH2	7	1,49E+08	C	G	19555	missense_variant	4508	0,28	675	553	185	D/H	Gac/Cac	COSM3762469
9	NOTCH2	1	1,2E+08	G	A	1776,4	stop_gained	1784	0,16	7418	7198	2400	R/*	Cga/Tga	COSM36210
9	TNFRSF14	1	2488153	A	G	21798	missense_variant	2336	0,49	349	50	17	K/R	aAa/aGa	rs4870
9	TP53	17	7579472	G	C	48088	missense_variant	1754	0,99	405	215	72	P/R	cCc/cGc	COSM250061
4	EP300	22	41573745	G	A	2213,4	missense_variant	758	0,24	7249	6030	2010	M/I	atG/atA	-
4	STAT3	17	40475330	C	A	2579,4	missense_variant	1239	0,21	2009	1696	566	D/Y	Gac/Tac	COSM220689
10	CD79A	19	42383208	G	A	1076,4	stop_gained	778	0,17	413	228	76	W/*	tgG/tgA	COSM5493940
10	PRDM1	6	1,07E+08	G	A	6990,4	missense_variant	2130	0,22	1295	1061	354	S/N	aGc/aAc	rs143040512
11	MYC	8	1,29E+08	C	G	21143	missense_variant	1598	0,59	578	68	23	T/S	aCc/aGc	-
11	MYC	8	1,29E+08	T	A	7615,4	missense_variant	796	0,48	775	265	89	Y/N	Tac/Aac	-
11	MYC	8	1,29E+08	T	C	5362,4	missense_variant	890	0,37	899	389	130	F/S	tTc/tCc	COSM4171775
11	MYC	8	1,29E+08	C	G	4032,4	missense_variant	1315	0,25	945	435	145	I/M	atC/atG	-

22	NOTCH2	1	1,21E+08	G	C	7845,4	missense_variant	880	0,47	277	57	19	C/W	tgC/tgG	rs11810554
23	EP300	22	41548008	A	G	9499,4	missense_variant	1380	0,39	4208	2989	997	I/V	Att/Gtt	rs20551
12	CARD11	7	2962848	G	A	6196,4	missense_variant	602	0,54	2464	2060	687	A/V	gCg/gTg	rs41493047
12	EP300	22	41548008	A	G	8543,4	missense_variant	658	0,65	4208	2989	997	I/V	Att/Gtt	rs20551
12	TNFRSF14	1	2488153	A	G	44442	missense_variant	1795	1,00	349	50	17	K/R	aAa/aGa	rs4870
13	ATM	11	1,08E+08	G	A	31006	missense_variant	5357	0,35	5942	5557	1853	D/N	Gat/Aat	COSM41596
13	EZH2	7	1,49E+08	C	G	170330	missense_variant	5215	1,00	675	553	185	D/H	Gac/Cac	COSM3762469
13	NOTCH2	1	1,21E+08	G	C	8499,4	missense_variant	2632	0,26	277	57	19	C/W	tgC/tgG	rs11810554
13	TNFRSF14	1	2488153	A	G	70550	missense_variant	6973	0,52	349	50	17	K/R	aAa/aGa	rs4870
13	TP53	17	7577120	C	T	98089	missense_variant	7897	0,59	1008	818	273	R/H	cGt/cAt	COSM10660
13	TP53	17	7579472	G	C	91137	missense_variant	3400	1,00	405	215	72	P/R	cCc/cGc	COSM250061
24	NOTCH2	1	1,21E+08	G	C	9698,4	missense_variant	932	0,53	277	57	19	C/W	tgC/tgG	COSM132738
24	TNFRSF14	1	2488153	A	G	55725	missense_variant	2190	0,98	349	50	17	K/R	aAa/aGa	rs4870
14	STAT3	17	40474459	T	A	13963	missense_variant	1179	0,59	2255	1942	648	M/L	Atg/Ttg	-
14	STAT3	17	40474482	T	A	13870	missense_variant	1179	0,59	2232	1919	640	Y/F	tAc/tTc	COSM1155743
26	ATM	11	1,08E+08	G	A	48248	missense_variant	5546	0,47	5942	5557	1853	D/N	Gat/Aat	COSM41596
26	NOTCH2	1	1,21E+08	G	C	3762,4	missense_variant	1080	0,26	277	57	19	C/W	tgC/tgG	rs11810554
26	PRDM1	6	1,07E+08	C	G	34258	missense_variant	2422	0,58	843	609	203	D/E	gaC/gaG	rs811925
26	TNFRSF14	1	2488153	A	G	48412	missense_variant	4358	0,55	349	50	17	K/R	aAa/aGa	rs4870
27	EP300	22	41548008	A	G	20536	missense_variant	1638	0,58	4208	2989	997	I/V	Att/Gtt	rs20551
27	NOTCH2	1	1,21E+08	G	C	3165,4	missense_variant	577	0,35	277	57	19	C/W	tgC/tgG	COSM132738
27	PRDM1	6	1,07E+08	C	G	31926	missense_variant	3046	0,53	843	609	203	D/E	gaC/gaG	rs811925
27	TP53	17	7579472	G	C	40713	missense_variant	1503	1,00	405	215	72	P/R	cCc/cGc	COSM250061
15	BRAF	7	1,4E+08	C	G	27862	missense_variant	2185	0,62	1467	1406	469	G/A	gGa/gCa	COSM459
15	EP300	22	41548008	A	G	5628,4	missense_variant	655	0,45	4208	2989	997	I/V	Att/Gtt	rs20551
15	NOTCH2	1	1,21E+08	G	C	3181,4	missense_variant	288	0,54	277	57	19	C/W	tgC/tgG	rs11810554
5	ATM	11	1,08E+08	A	C	61148	missense_variant	6156	0,51	4747	4362	1454	K/N	aaA/aaC	COSM22501
5	ATM	11	1,08E+08	G	A	54734	missense_variant	5588	0,51	5942	5557	1853	D/N	Gat/Aat	COSM41596

5	EZH2	7	1,49E+08	C	G	58716	missense_variant	5226	0,48	675	553	185	D/H	Gac/Cac	COSM3762469
5	NOTCH2	1	1,21E+08	G	C	2979,4	missense_variant	689	0,30	277	57	19	C/W	tgC/tgG	COSM132738
5	STAT3	17	40474482	T	A	29044	missense_variant	5011	0,35	2232	1919	640	Y/F	tAc/tTc	COSM1155743
16	ATM	11	1,08E+08	T	C	45184	missense_variant	4755	0,48	2504	2119	707	S/P	Tct/Cct	COSM41595
16	NOTCH2	1	1,21E+08	G	C	18815	missense_variant	1928	0,51	277	57	19	C/W	tgC/tgG	rs11810554
16	TP53	17	7579472	G	C	66471	missense_variant	2194	1,00	405	215	72	P/R	cCc/cGc	COSM250061
28	PRDM1	6	1,07E+08	C	G	13852	missense_variant	3293	0,26	843	609	203	D/E	gaC/gaG	rs811925
28	TNFRSF14	1	2488153	A	G	24340	missense_variant	2063	0,60	349	50	17	K/R	aAa/aGa	rs4870
17	ATM	11	1,08E+08	T	A	43593	missense_variant	4493	0,51	763	378	126	D/E	gaT/gaA	COSM22498
17	NOTCH2	1	1,21E+08	G	C	1699,4	missense_variant	844	0,21	277	57	19	C/W	tgC/tgG	rs11810554
17	PRDM1	6	1,07E+08	C	G	25161	missense_variant	2936	0,46	843	609	203	D/E	gaC/gaG	rs811925
17	STAT3	17	40475058	C	G	21942	missense_variant	1498	0,69	2165	1852	618	G/R	Ggc/Cgc	COSM1166777
17	TNFAIP3	6	1,38E+08	T	G	158181	missense_variant	5806	0,99	446	380	127	F/C	tTc/tGc	COSM1685340
17	TNFRSF14	1	2488153	A	G	24580	missense_variant	2386	0,51	349	50	17	K/R	aAa/aGa	rs4870
30	NOTCH2	1	1,21E+08	G	C	6521,4	missense_variant	699	0,48	277	57	19	C/W	tgC/tgG	rs11810554
18	ATM	11	1,08E+08	A	G	115074	missense_variant	4261	1,00	6333	5948	1983	N/S	aAt/aGt	rs659243
18	NOTCH2	1	1,21E+08	G	C	2996,4	missense_variant	1148	0,23	277	57	19	C/W	tgC/tgG	rs11810554
18	SGK1	6	1,34E+08	G	A	30903	missense_variant	5213	0,36	1950	1352	451	S/F	tCc/tTc	-
18	SGK1	6	1,34E+08	G	A	40653	missense_variant	6831	0,36	1737	1139	380	A/V	gCt/gTt	-
18	SGK1	6	1,34E+08	C	T	36890	5_prime_UTR_premature_start_codon_gain_variant	6373	0,35	#N/D	#N/D	#N/D	#N/D	#N/D	#N/D
18	TNFRSF14	1	2488153	A	G	45495	missense_variant	5114	0,47	349	50	17	K/R	aAa/aGa	rs4870
18	TP53	17	7579472	G	C	34947	missense_variant	1764	0,86	405	215	72	P/R	cCc/cGc	COSM250061
7	CD79B	17	62008716	C	T	2934,4	missense_variant	963	0,24	175	100	34	D/N	Gac/Aac	-
7	KMT2D	12	49426460	A	G	25817	missense_variant	1772	0,66	12028	12028	4010	S/P	Tct/Cct	rs80132640
7	KMT2D	12	49448463	C	T	14800	missense_variant	1052	0,57	248	248	83	R/Q	cGg/cAg	rs55865069
7	MYC	8	1,29E+08	A	T	2614,4	missense_variant	794	0,26	1085	575	192	Y/F	tAc/tTc	-
31	ATM	11	1,08E+08	A	G	10575	missense_variant	378	1,00	6333	5948	1983	N/S	aAt/aGt	rs659243

31	NOTCH2	1	1,21E+08	G	C	5897,4	missense_variant	348	0,76	277	57	19	C/W	tgC/tgG	rs11810554
31	TNFRSF14	1	2488153	A	G	11911	missense_variant	1217	0,51	349	50	17	K/R	aAa/aGa	rs4870
2	ATM	11	1,08E+08	C	G	16840	missense_variant	1591	0,55	2021	1636	546	L/V	Ctg/Gtg	rs2227924
2	ATM	11	1,08E+08	C	T	24400	missense_variant	3367	0,41	2999	2614	872	P/S	Cct/Tct	rs3218673
2	NOTCH1	9	1,39E+08	G	A	13195	missense_variant	938	0,38	1278	1202	401	P/L	cCc/cTc	COSM4745915
2	STAT3	17	40474461	T	A	5089,4	missense_variant	1930	0,23	2253	1940	647	N/I	aAc/aTc	COSM1155744
2	TNFAIP3	6	1,38E+08	T	G	9057,4	missense_variant	1327	0,39	446	380	127	F/C	tTc/tGc	COSM1685340
33	EP300	22	41546030	C	G	4277,4	missense_variant	538	0,35	3864	2645	882	P/R	cCa/cGa	COSM4385247
1	ATM	11	1,08E+08	G	A	62638	missense_variant	6032	0,50	5942	5557	1853	D/N	Gat/Aat	COSM41596
1	BRAF	7	1,4E+08	A	T	61284	missense_variant	5236	0,58	1860	1799	600	V/E	gTg/gAg	COSM476
1	EP300	22	41572907	G	A	93605	missense_variant	#####	0,45	6411	5192	1731	R/H	cGc/cAc	-
1	MYC	8	1,29E+08	C	T	32277	missense_variant	4424	0,41	747	237	79	S	agC/agT	-
1	NOTCH2	1	1,21E+08	G	C	5784,4	missense_variant	1536	0,31	277	57	19	C/W	tgC/tgG	rs11810554
1	SGK1	6	1,34E+08	G	T	3083,4	missense_variant	395	0,43	1018	420	140	N/K	aaC/aaA	COSM1581714
1	SGK1	6	1,34E+08	T	A	2868,4	stop_gained	395	0,42	1004	406	136	K/*	Aag/Tag	-
1	SGK1	6	1,34E+08	C	T	2884,4	missense_variant	395	0,42	978	380	127	R/K	aGg/aAg	COSM220583
1	TNFAIP3	6	1,38E+08	T	G	61438	missense_variant	5765	0,48	446	380	127	F/C	tTc/tGc	COSM1685340
1	TNFRSF14	1	2488153	A	G	110496	missense_variant	4029	0,97	349	50	17	K/R	aAa/aGa	rs4870