Post-transplant molecularly defined Burkitt lymphomas are frequently *MYC*-negative and characterized by the 11q-gain/loss pattern

Burkitt lymphoma (BL) is a biologically and molecularly defined tumor hallmarked by *IG*-mediated t(8q24) resulting in up-regulation of *MYC*.[1,2] Recent studies of 59 molecularly defined BL (mBL) identified a novel aberration manifested by a specific 11q-gain/loss pattern in two cases (3%) lacking the *MYC* translocation.[3] The aberration was subsequently detected in 15 MYC-negative high-grade B-cell lymphomas resembling BL and two cell lines derived from high-grade B-cell lymphomas. Further studies defined the minimal gained and lost regions at 11q23.3 and 11q24.1qter, respectively, and identified candidate genes potentially affected by these imbalances: the constantly overexpressed *PAFAH1B2/11q23.3*, and *FLI1* (down-regulated) and *ETS1* (recurrently mutated) targeted by a homozygous 11q24 microdeletion.

We provide evidence here that this peculiar 11q-gain/loss aberration is particularly frequent in BL in immunodeficient hosts, as it was identified in three out of seven patients with mBL after solid organ transplantation and under immunosuppressive maintenance therapy. The cases were selected from a cohort of 174 post-transplant patients diagnosed with post-transplant lymphoproliferative disorders (PTLD) between 1989 and 2012 at the University Hospitals of KU Leuven (Leuven, Belgium). The study was approved by the Ethical Committee of the University Hospitals Leuven. The cohort mainly comprised cases of diffuse large B-cell lymphoma (DLBCL, 75%).[4,5] Other entities were less frequent and included plasmacytoma and plasmablastic non-Hodgkin lymphoma,[6] T-cell non-Hodgkin lymphoma,[7] BL, small cell B-non-Hodgkin lymphoma and unspecified cases. The seven post-transplant BL (PT-BL) cases reported here were analyzed using conventional cytogenetics, array comparative genome hybridization (CGH), fluorescence *in situ* hybridization (FISH), immunohistochemistry, gene expression profiling and bioinformatics (*Online Supplementary Information*). As controls, we included four cases of typical *MYC*-translocation-positive BL from immunocompetent hosts (IC-BL). All cases fulfilled the morphological and immunological criteria of BL defined by the 2008 World Health Organization classification[8] (Table 1).

Relevant clinical, pathological and cytogenetic features of the studied cases are summarized in Table 2. The PT-BL patients, all men, had undergone liver (n=3), heart (n=2) or kidney (n=2) transplantation. The median age at time of PTLD was 47.5 years (range, 15-70 years). Five cases were Epstein Barr virus (EBV)-negative and two adolescent cases (n. 3 and 4) were EBV-positive. Patients developed BL a median of 40.7 months (range, 11-66 months) following transplantation. The interval was significantly shorter for EBV-positive cases than EBV-negative cases (12 *versus* 52.2 months, respectively). All seven patients were treated with either rituximab and/or CHOP. Most of them achieved complete remission but four patients died within 4-11 months after diagnosis (average 6 months), including two patients (n. 6 and 7) who died due to disease-related complications. Three patients are alive, including both EBV-positive patients, and their survival ranges from 34 to 99 months (median 70 months) (Table 2).

Based on a global gene expression pattern, all seven PT-BL cases (as well as control IC-BL cases) showed the molecular profile of BL and were readily distinguished from PT-/IC-DLBCL[5] using two classifiers of mBL[1,2] (*Online Supplementary Figure S1*). Cytogenetics and/or FISH demonstrated t(8q24/*MYC*) in four PT-mBL, while three cases (n. 5-7, all EBV-negative) appeared to be negative for the *MYC* translocation. Interestingly, karyotypes of the two latter cases revealed various 11q aberrations, which after additional FISH analysis (*data not shown*) were described as der(11)(11pter->11q23.3::11q23.3->11q13::8q22q24.3) and der(11)t(11;18)(q23.3;q12) (Figure 1A). Array CGH analysis performed in all 11 cases detected the characteristic 11q-gain/loss pattern in the three *MYC*-translocation-negative

Table 1. Morphology and immunophenotype of the reported post-transplant and immunocompromised BL cases.

Case	Localization	Morphology	Immunohistochemistry									EBV latency profile
			CD20	CD10	MYC (%)	TdT	BCL2	BCL6	MUM1	Ki67 (%)	EBER	
***MYC*-translocation-positive PT-mBL**												
1	LN	medium and large-sized cells, limited starry sky	pos	pos	0		pos[a]	pos	neg	100	neg	
2	LN	large-sized cells, starry sky	pos	pos	35	neg	neg	pos	neg	100	neg	
3	GALT	medium-sized cells, starry sky	pos	pos	100		neg	pos	neg	95	pos	intermediate
4	LN	medium-sized cells, starry sky	pos	pos	100	neg	neg	pos	neg	95	pos	intermediate
***MYC*-translocation-negative PT-mBL**												
5	WR	large-sized cells, starry sky	pos	pos	0	neg	neg	pos	neg	90	neg	
6	LN	medium-sized cells, starry sky	pos	pos	25 (w)	neg	neg	pos	neg	99	neg	
7	T	large-sized cells, starry sky	pos	pos	75 (w)		neg	pos	neg	99	neg	
***MYC*-translocation-positive IC-mBL**												
8	GALT	large-sized cells, starry sky	pos	pos	50	neg	neg	pos	pos	100	neg	
9	LN	medium-sized cells, starry sky	pos	pos	90	neg	neg	pos	pos	100	neg	
10	LN	medium-sized cells, limited starry sky	pos	pos	0	neg	neg	pos	neg	90	neg	
11	LN	medium-sized cells, starry sky	pos	pos	25	neg	neg	pos	neg	95	neg	

[a]*Normal FISH BCL2 pattern; PT: post-transplant; IC: immunocompetent; mBL: molecular Burkitt lymphoma; LN: lymph node; GALT: gut associated lymphoid tissue; WR: Waldeyer ring; T: testis; pos: positive; neg: negative; w: weak.*

cases (Figure 1B). This pattern was associated with a dup(11)(q13q23.3) in case 5, focal gain-and-amplification of an approximately 4 Mb region at 11q23.3 in case 6 (confirmed by FISH, Figure 1C, *Online Supplementary Figure S2*) and complex 11q imbalances in case 7 (Table 2). Interestingly, the dup(11)(q13q23.3) identified in case 5 was associated with an inversion, as in several previously reported cases.[3,9] Losses, resulting from different non-reciprocal translocations in cases 5 and 6, constantly targeted the 11q23.3q24.1qter region. Homozygous deletions were not detected. The array CGH data enabled definition of the minimal gained region (MGR) (~4 Mb) and minimal lost

Table 2. Relevant clinical, pathological and genetic data of the reported post-transplant and immunocompetent BL cases.

Case	Age/ Sex	Immune status	Graft	Immuno-suppression	TX-PTLD interval (months)	Stage	EBV	Treatment	Response	Outcome (months)	Cytogenetic and FISH findings	Array CGH imbalances (> 4Mb)[a] Gains	Losses
***MYC*-translocation-positive PT-mBL**													
1	65/M	ID	heart	CNI+AM	61	IIIA	–	R	CR	D/du (11)	47-48,XY,dup(1)(q21q32)[8],t(8;14)(q24;q32),+12[3],del(13)(q14q22)[cp20]. nuc ish (MYCx2)(5'MYC sep 3'MYCx1)[150/200]	1p11.2q32.1	13q14.13q31.1
2	70/M	ID	liver	CNI	31	IVA	–	CHOP/R	CR	D/dr (4)	46,XY,del(6)(q23),t(8;22)(q24;q11), inc[15].nuc ish (MYCx2)(5'MYC sep 3'MYCx1)[33/200]	NF	NF
3	16/M	ID	kidney	CNI+AM +CS	13	IVA	+	CHOP/R	CR	A (34)	NM.nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[160/200]	1q21.2q25.3; 3q27.2q29; 12p13.33p11.22; 12q14.1q24.21; 13q31.1q31.3; 15q24.3q26.2	16p13.3p13.3
4	15/M	ID	liver	CNI+AM+CS	11	IIIA	+	Intensive CT	CR	A (79)	NM.nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[190/200]	no	no
***MYC*-translocation-negative PT-mBL**													
5	54/M	ID	heart	CNI+AM	66	IIA	–	CHOP/R	CR	A (99)	44-47,XY,add(7)(p22)[3], der(11)(11pter->11q23.3::11q23.3->11q13::8q22q24.3), +1-2mar[cp5].nuc ish(MYCx2)[200]	8q22.3q24.23; 11q13.1q23.3; 12p13.32q13.13	8p23.3p23.2; 8q12.1q13.1; 11q23.3q25; 20q11.23q13.13; 21q21.1q21.2
6	68/M	ID	liver	CNI	46	IA	–	CHOP/R	PD	D/dr (4)	42-44,XY,-4,add(10)(p11), der(11)t(11;18)(q23.3;q12)[cp4].nuc ish(MYCx2)[200]	11q23.3q23.3; 16q21.1q24.3; 18q12.1q23	4p16.3q35.2; 10p15.3p11.4; 11q23.3q25; 20q11.23q13.33
7	44/M	ID	kidney	CNI+AM	57	IVB	–	CHOP/R	CR	D/dr (5)	ND.nuc ish(MYCx2)[200]	2q23.3q37.3; 7q32.3q36.3; 11p15.4p15.1; 11q13.4q14.1; 11q22.3q24.1; 12p13.33q24.33; 13q32.1q34; 17q22q23.2	11q14.1q22.3; 11q24.1q25; 13q31.1q32.1;
***MYC*-translocation-positive IC-mBL**													
8	77/M	IC	–	–	–	IA	–	CHOP	CR	D/du (105)	ND.nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[55/100]	3p26.3q12.2; 3q26.33q27; 18q12.1q23	3q13.11q26.32; 20q11.23q13.12
9	36/M	IC	–	–	–	IIIB	–	Intensive CT	CR	A (98)	ND.nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[80/100]	no	no
10	18/M	IC	–	–	–	IVB	–	CHOP/R	CR	A (106)	ND. nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[62/100]	7p22.3q36.3; 12p13.33q24.33; 21q11.2q22.3	1p36.33p36.23; 2q21.2q24.1; 4q21.1q21.23
11	75/M	IC	–	–	–	IVB	–	CHOP/R	CR	A (45)	ND.nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[65/100]	7p22.3q36.3; 8q22.3q24.3; 9q21.11q3	5q35.2q35.3; 6q12q16.3

[a]: mosaic/subclonal regions are underlined; PT: post-transplant; IC: immunocompetent; mBL: molecular Burkitt lymphoma; M: male; ID: immuno-deficient; IC: immunocompetent; CNI: calcineurin inhibitor; AM: antimetabolite; CS: low dose corticosteroids; TX: transplantation; PTLD: post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CT: chemotherapy; R, rituximab; CR: complete remission; PD: progressive disease; A: alive; D/du: dead, disease unrelated; D/dr: dead, disease related; NM: no mitosis; ND: not done; NF: not informative.

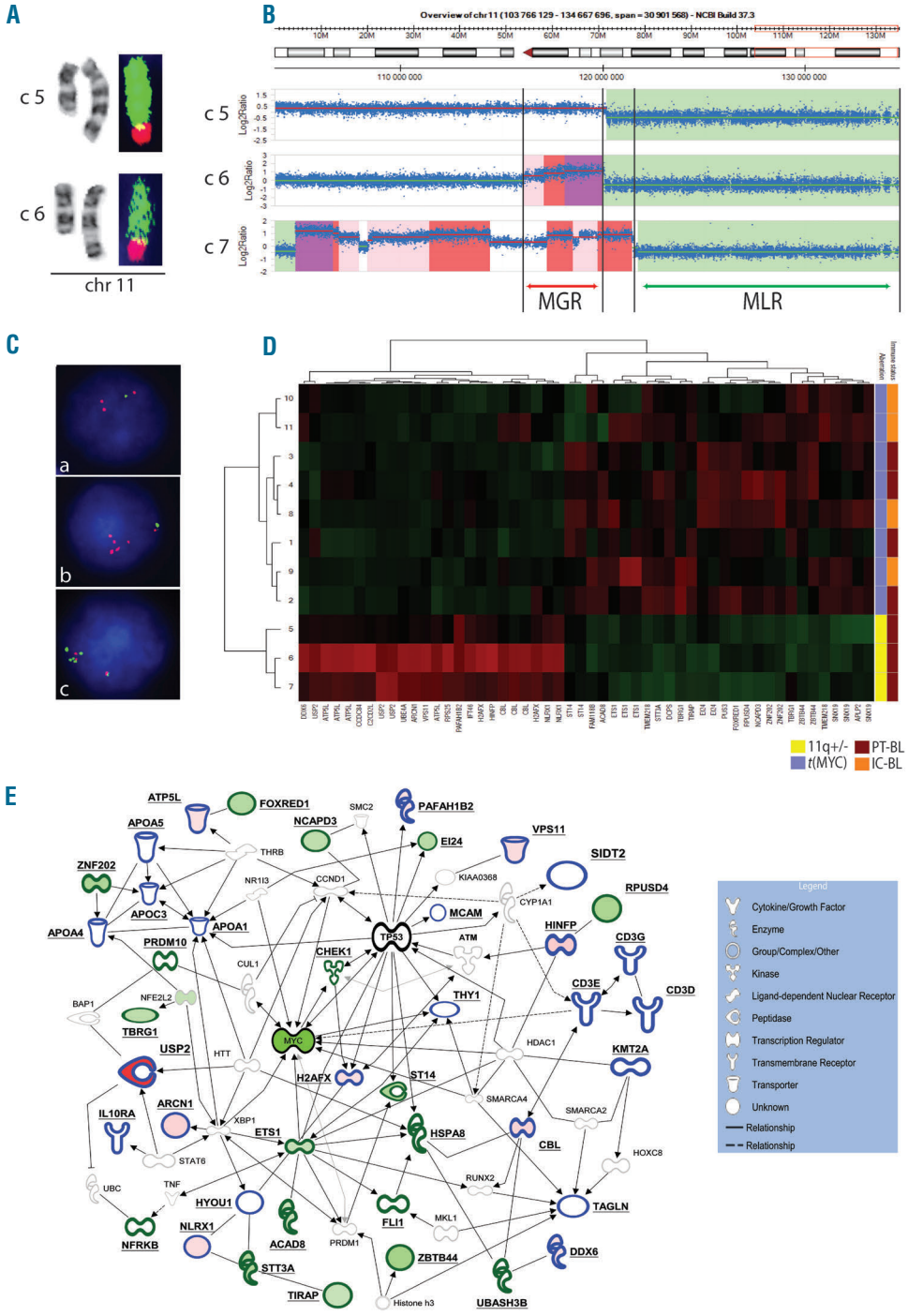

Figure 1. Genomic and transcriptomic data on PT-mBL. (A) Partial karyotype of case 5 (c5) and case 6 (c6) showing chromosome 11 abnormalities and FISH images of both derivative chromosomes painted with WCP11 (green) and WCP8 (red) (case 5), and WCP18 (red) (case 6). The aberrations were eventually described as der(11)(11pter->11q23.3::11q23.3->11q13::8q22q24.3) and der(11)t(11;18)(q23.3;q12), respectively. Note (inverted) duplication of 11q13q23.3 in case 5 and a normal appearance of this region in case 6. (B) Chromosomal view of chromosome 11q23q24 and imbalances identified by array CGH analysis in cases 5-7. Gained regions are highlighted in red-scale (increased intensity reflects an increased amplification level), while lost regions are marked in green. Note a variable level of 11q23.3 gain, a common loss of 11q24qter and the defined MGR (~4 Mb) and MLR (~13.5 Mb). (C) Examples of interphase FISH analysis performed in case 5 (a) and case 6 (b, c). The applied probes include the 11q-MGR/MLR FISH assay (a) (b), and two probes from the duplicated (RP11-284O21-SpectrumOrange) and amplified (RP11-784K23-SpectrumGreen; *Online Supplementary Figure S2*) area in case 6 (c). Note the duplicated and amplified red/11q23.3 signal in (a) and (c), respectively, and loss of the green/11q24 signal in both cases. In (c), note two red and five green signals in the cluster, illustrating various levels of gain within the MGR. (D) Hierarchical clustering of mBL cases using the dysregulated genes located in the MGR and MLR. (E) Interaction network found by Ingenuity Pathway Analysis involving genes targeted by the 11q-gain/loss aberration (bold edges). Solid and interrupted lines represent direct and indirect interactions, respectively. Notably, most of the interactions in this network are direct protein-protein interactions. The molecules with blue and green edges are encoded by MGR- and MLR-associated genes, respectively. The data obtained by comparison of cases 5-7 (PT-mBL with the 11q-gain/loss pattern) (11q+/-) by cases 1-4 (PT-*MYC*-translocation-positive mBL) [(t(*MYC*)] were overlaid in this network. Molecules which are down- and up-regulated in cases with 11q+/- when compared to cases with t(*MYC*) are filled in green and red, respectively.

region (MLR) (~13.5 Mb) which were mapped at 11q23.3 [chr11:116072765-120087526bp (hg19)] and 11q24.1q25 [chr11:121499571-135006516bp (hg19)], respectively. Notably, *MYC*-translocation-positive PT-mBL cases had either a balanced karyotype, or two to nine additional imbalances, including subclonal gains/losses, similar to the IC-mBL cases (Table 2). The latter ones, however, showed a frequent gain of chromosome 7 (60%), not seen in PT-mBL cases.

In order to identify genes affected by the 11q imbalances, we compared gene expression profiles of cases 5-7 (11q-gain/loss-positive) and cases 1-4 (*MYC*-translocation-positive), and focused on genes harbored by the MGR (69 genes) and MLR (106 genes). Altogether, 33 genes with a differential expression were identified: 15 in the MGR (all up-regulated) and 18 in the MLR (all down-regulated) (*Online Supplementary Table S1*). The most significantly up-regulated was *USP2* (ubiquitin specific peptidase 2), which showed up to 30.6-fold higher expression in *MYC*-translocation-negative cases than in *MYC*-translocation-positive cases (*Online Supplementary Figure S3*). Differential expression of the remaining MGR genes was much lower (1.35-2.75-fold). Levels of differentially down-regulated genes ranged from -1.32 to -2.35-fold. Notably, both regions harbor several genes which might be implicated in the pathogenesis of *MYC*-translocation-negative mBL. Particularly interesting are two oncogenes, *USP2* and *CBL*, and the previously discussed *PAFAH1B2* located in the MGR.[3] USP2, which was the most significantly up-regulated enzyme in 11q-gain/loss-positive mBL, acts as a modulator of tumor necrosis factor-α-induced nuclear factor-κB signaling and prolongs the half-life of targets such as fatty acid synthase, MDM2 and MDM4/MDMX (negative regulators of p53) and cyclin D1 (G1/S transition). The enzyme, like other deubiquitinases, is implicated in cancer, particularly in prostate carcinomas (reviewed by Fraile *et al.*[10]). Dysregulated genes in the MLR comprise two candidate tumor suppressor genes, *TBRG1* and *EI24*, and five genes either related to cancer or involved in cancer-related processes, including *ETS1, TIRAP, ST14, NCAPD3* and *ZNF202*. Noteworthy, *FLI1*, the candidate target gene,[3] was not differentially down-regulated in our cases (*Online Supplementary Figure S3*). Hierarchical clustering of the studied cases using the set of 11q23/q24 dysregulated genes showed that *MYC*-translocation-negative PT-mBL cases cluster together and separately from *MYC*-translocation-positive PT-/IC-mBL (Figure 1D).

PT-mBL cases with the 11q-gain/loss pattern revealed a lower expression of *MYC* mRNA than *MYC*-translocation-positive cases (*Online Supplementary Figure S3*). Using immunohistochemistry with MYC antibody (clone Y69; Epitomics, Burlingame, CA, USA), all studied mBL cases showed highly variable expression of MYC protein, which has not necessarily correlated with rearrangement of *MYC* (Table 1) (*Online Supplementary Figure S4*). These results, however, remain in line with the recently published data of Chisholm *et al.*[11]

To examine whether the 11q-gain/loss aberration also characterizes BL and/or DLBCL cases from immunocompetent patients, among those in our institution, we analyzed by FISH two known cases of *MYC*-translocation-negative BL and five cases of *MYC*-translocation-negative DLBCL harboring 11q aberrations [mostly dup(11q)]. Using the designed 11q23/q24 assay covering the MGR and MLR (*Online Supplementary Figure S2*), the 11q-gain/loss pattern was detected in one of two *MYC*-translocation-negative BL cases (*data not shown*). The second BL case showed a normal FISH pattern, while all five DLBCL revealed gain of 11q23.3, without, however, an associated loss of 11q24. These findings confirm the rare occurrence of the 11q-gain/loss pattern in IC-BL/-DLBCL.

To unravel biological consequences of the 11q-gain/loss aberration in mBL, we explored the MGR/MLR-dysregulated genes using Ingenuity Pathway Analysis software (see *Online Supplementary Methods*). Ingenuity Pathway Analysis showed that the genes are implicated in important biological processes, including cancer, and the majority of them (22/33) are involved in the TP53 and MYC networks, frequently by direct protein-protein interactions (Figure 1E). These findings and the observation that cases with 11q imbalances cluster with *MYC*-translocation-positive mBL (using two mBL classifiers[1,2]) suggest that the 11q-gain/loss aberration is a 'molecular variant' of t(8q24/*MYC*) affecting the same or overlapping pathological pathways. A similar phenomenon has recently been described in BCR-ABL-negative Ph-like ALL showing a spectrum of kinase-activating alterations.[12] The astonishing consistency of the 11q-gain/loss pattern suggests that the driving potential of this aberration results from a concerted overexpression of the defined 11q23.3 genes, including *USP2, CBL* and *PAFAH1B2*, and simultaneous down-regulation of 11q24q25 genes, among others *TBRG1, EI24* and *ETS1*. Interestingly, a similar gain-and-loss pattern has been identified in hepatosplenic T-cell lymphoma characterized by a constant 7p14.1p22.1-loss/7q22.11q31.1-gain pattern,[13] which, it is worth noting, is frequently observed in immunosuppressed patients.

PTLD is typically an EBV-driven process and our recent study of 33 PT-DLBCL (72% EBV-positive and 28% EBV-negative) led to the conclusion that EBV-negative PT-DLBCL were coincidental lymphomas in immunosuppressed patients.[5] Among the reported PT-mBL, only 30% of cases were EBV-positive and they clustered together with EBV-negative PT-mBL and IC-mBL (*Online Supplementary Figure S1*). These findings are in line with observations of Piccaluga *et al.*,[14] who found that all three BL subtypes, sporadic, endemic and human immunodeficiency virus-positive, share a common gene expression signature, distinct from other B-cell malignancies, and suggested that not EBV, but the MYC-dependent signature had a major effect on the clustering.

In summary, we confirmed recurrence of the 11q-gain/loss pattern in high-grade B-cell lymphoma and showed that this aberration is significantly more frequent ($P<0.007$, Fisher exact test) in BL occurring in the setting of transplantation and immunosuppression (43% of all PT-mBL and 60% of EBV-negative PT-mBL) than in immunocompetent patients (3%)[1], suggesting that immunosuppression may favor its formation. Further studies of PT-BL are needed to confirm this association. As identification of patients with the 11q-gain/loss aberration is clinically important but cytogenetically challenging, we recommend the designed 11q-MGR/MLR FISH assay as a useful diagnostic tool to evaluate both post-transplant and immunocompetent BL patients.

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