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REVIEW

# Diffuse large B-cell lymphoma: can genomics improve treatment options for a curable cancer?

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**Abstract** Gene-expression profiling and next-generation sequencing have defined diffuse large B-cell lymphoma (DLBCL), the most common lymphoma diagnosis, as a heterogeneous group of subentities. Despite ongoing explosions of data illuminating disparate pathogenic mechanisms, however, the five-drug chemoimmunotherapy combination R-CHOP remains the frontline standard treatment. This has not changed in 15 years, since the anti-CD20 monoclonal antibody rituximab was added to the CHOP backbone, which first entered use in the 1970s. At least a third of patients are not cured by R-CHOP, and relapsed or refractory DLBCL is fatal in ~90%. Targeted small-molecule inhibitors against distinct molecular pathways activated in different subgroups of DLBCL have so far translated poorly into the clinic, justifying the ongoing reliance on R-CHOP and other long-established chemotherapy-driven combinations. New drugs and improved identification of biomarkers in real time, however, show potential to change the situation eventually, despite some recent setbacks. Here, we review established and putative molecular drivers of DLBCL identified through large-scale genomics, highlighting among other things the care that must be taken when differentiating drivers from passengers, which is influenced by the promiscuity of activation-induced cytidine deaminase. Furthermore, we discuss why, despite having so much genomic data available, it has been difficult to move toward personalized medicine for this umbrella disorder and some steps that may be taken to hasten the process.

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Published by Cold Spring Harbor Laboratory Press

doi: 10.1101/mcs.a001719

## INTRODUCTION

Although diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma diagnosis, it is in reality a heterogeneous, overlapping group of subentities defined with varying degrees of precision (Xie et al. 2015). The name is a morphologic description that may cover DLBCL not otherwise specified (DLBCL-NOS), primary mediastinal large B-cell lymphoma (PMBL), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, Epstein–Barr virus–positive DLBCL of the elderly (EBV+ DLBCL, NOS), T-cell-/histiocyte-rich large B-cell lymphoma (THRLBCL), and others (National Comprehensive Cancer Network 2016). Meanwhile, molecular subtypes of DLBCL-NOS that have been extensively characterized in laboratory studies, particularly those derived from different cells of origin (discussed in detail below), are not yet recognized as separate

pathologic diagnoses, despite clear distinctions in their underlying pathogenesis. Moreover, DLBCL may be de novo or may result from transformation of indolent B-lymphomas (Campo et al. 2011; Testoni et al. 2015), a scenario resulting in inevitable relapse of the underlying indolent disease even if the aggressive transformed clone is eliminated by therapy. The CHOP chemotherapy combination (cyclophosphamide, doxorubicin, vincristine, and prednisone), which remains the backbone of frontline therapy, was introduced in the mid-1970s. The early 2000s saw addition of the anti-CD20 monoclonal antibody rituximab, which increased 5-year failure-free survival from 40%–45% to 55%–60% (Coiffier et al. 2002, 2010; Sehn et al. 2005; Habermann et al. 2006; Pfreundschuh et al. 2006; Roschewski et al. 2014; Bachy and Salles 2015). R-CHOP remains the standard of care for newly diagnosed DLBCL, though several clinical, pathologic, and molecular methods reliably identify patients with increased likelihood of failing it.

Such high-risk patients clearly need better options, but in the 15 years since rituximab's United States Food and Drug Administration (FDA) approval as part of frontline therapy for DLBCL (the last drug to win such approval) efforts to improve on R-CHOP have been largely unsuccessful. It has long been thought that intensified chemotherapy regimens might replace the CHOP backbone for many patients once evaluations in randomized clinical trials could be completed. Particular attention has focused on dose-adjusted (da) R-EPOCH, which contains the same drugs as R-CHOP, plus etoposide, and doses the etoposide, doxorubicin, and vincristine infusionally over 4 days each cycle, typically during an in-patient admission (Wilson et al. 2002). A retrospective analysis suggested improved outcomes among patients with the especially high-risk finding of double-hit lymphoma (having dual chromosomal rearrangements involving *MYC* and either *BCL2* or *BCL6*) if they were treated with da-R-EPOCH rather than R-CHOP (Oki et al. 2014). A high-profile single-arm trial, meanwhile, showed overall survival near 100% for patients with PMBL treated with the regimen (Dunleavy et al. 2013), and another single-arm trial showed 81% overall survival in DLBCL-NOS after more than 5 years follow-up (Wilson et al. 2012). However, data from the ongoing CALGB/Alliance 50303 study presented at the recent 2016 American Society of Hematology (ASH) meeting in San Diego, California did little but reinforce the difficulty of improving on DLBCL's established frontline. This phase III randomized trial compares R-CHOP to da-R-EPOCH in untreated DLBCL. Event-free and overall survival were the same between the treatment arms, whereas toxicities, especially hematologic events, were significantly higher with da-R-EPOCH (Wilson et al. 2016). Additional negative data for frontline DLBCL treatment at ASH 2016 included the GOYA trial, a randomized comparison of R-CHOP versus G-CHOP, the latter regimen containing the second-generation anti-CD20 antibody obinutuzumab, engineered to increase antibody-dependent cellular cytotoxicity of targeted cells. G-CHOP showed no prolonged progression-free survival or any other advantage over R-CHOP in this trial after more than 2 years of median follow-up (Vitolo et al. 2016).

DLBCL patients who are failed by initial therapy—at least one-third of patients overall—constitute another group in urgent need of better therapeutic options. Current salvage therapies lead to long-term disease-free survival in only ~10% of these relapsed/refractory (rr-DLBCL) patients (Friedberg 2011). Better, more rational therapies are therefore needed both for high-risk patients in the up-front setting and for those with rr-DLBCL. In addition, even those currently cured up-front or, especially, after salvage therapy and stem-cell transplant for rr-DLBCL face long-term toxicities, not the least of which are secondary malignancies that include the almost universally fatal treatment-related acute myeloid leukemia (Sud and Friedberg 2008; Bari et al. 2011; Ng et al. 2011; Raut and Chakrabarti 2014).

Great strides have been made in classifying different subgroups of DLBCL along with identification of their corresponding pathogenic drivers, largely through the discovery of

genomic techniques such as next-generation sequencing (NGS) and gene expression profiling (GEP). Although driver identification through genomics can help usher in the era of personalized medicine, potentially improving frontline responses and identifying those likely to fail chemotherapy, few small-molecule targeted inhibitors have gained regulatory approval and exclusively in the rr setting. Here, we review recent advances in understanding of DLBCL through genomics and look to the future of how these data might define targets to enhance therapeutic options for patients.

## THE DIVISION OF DLBCL INTO SEPARATE ENTITIES

Standard pathologic analyses have long recognized subentities within DLBCL (e.g., THRLBCL). At the turn of the century, GEP began shedding new light on the underlying biology of subtype distinctions and made further distinctions possible, most notably cell-of-origin (COO) classifications. More recently, NGS has identified many key molecular drivers, defined by recurrently mutated oncogenes and tumor suppressors, some of which are common across subtypes, but many others that further highlight key differences in biology (Orsborne and Byers 2011; Tirado et al. 2012; Intlekofer and Younes 2014; Jardin 2014). The first high-profile GEP study, by Alizadeh et al. (2000), using a microarray of genes preferentially expressed in lymphoid cells, immunology, and cancer called the "Lymphochip" (Alizadeh et al. 1999) established the COO classification of DLBCL. Subsequent studies not only corroborated this classification, but further refined it to consist of three main subgroups—GCB (germinal center B-cell-like; originating from centroblasts in the dark zone), ABC (activated B-cell-like; derived from activated B cells that are in transition to becoming plasmablasts), and PMBL (primary mediastinal B-cell-like lymphoma; from thymic B cells), with prognostic and clear biological differences (Rosenwald et al. 2002; Shipp et al. 2002; Rosenwald and Staudt 2003; Wright et al. 2003; Lossos et al. 2004). Alternate GEP classifications have since been proposed, such as the "consensus cluster" (Monti et al. 2005) and clusters based on stromal gene signatures (Lenz et al. 2008b). Although all these different classifications are reproducible, they do not overlap, highlighting not only the heterogeneous nature of DLBCL and potential contamination from nontumor cells from the microenvironment, but the constraints of interpreting data obtained on different platforms and analyzed with different algorithms.

Responses to treatment may differ among patients because patient factors such as age and comorbidities affect treatments, but the heterogeneous disease entities all included in the same diagnostic grouping is clearly a major reason. Therefore, clearer differentiation of DLBCL into separate entities has been targeted by researchers and clinicians, allowing tailored therapies to be used against specific subtypes by using therapies targeted to their particular drivers (discussed in further detail below). The ABC subtype, for example, is characterized by constitutive activation of the nuclear factor kappa B (NF-κB) pathway (Davis et al. 2001; Compagno et al. 2009; Pasqualucci and Zhang 2016). Inhibitors that interfere with malignant activation of this pathway, such as the immune modulatory agent lenalidomide and the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, have shown promising preclinical and clinical results and even synergistic ABC cell death (Yang et al. 2012; Chiappella et al. 2013; Tilly et al. 2013; Roschewski et al. 2014; Younes et al. 2014; Zheng et al. 2014; Nowakowski et al. 2015; Wilson et al. 2015), but phase 3 evaluations are still pending (NCT01122472, NCT02285062, NCT02443077, NCT01855750, and NCT01804686).

Opportunities to improve therapeutic options for DLBCL using what we have learned about its pathogenesis in genomic studies therefore depend on substantial additional work to understand how, or even whether, targeting individual molecular alterations will lead to clinically meaningful benefits.

## SOMATIC, TARGETABLE ABERRATIONS AFFECTING SUBGROUPS OF DLBCL

The coding genome of DLBCL is more complex (3.3–4.21 mutations per Mb) (Lohr et al. 2012; Morin et al. 2013; Lawrence et al. 2014) than other hematological malignancies (e.g., CLL has approximately one mutation per Mb) (Puente et al. 2011; Quesada et al. 2012), but less so than some solid tumors (e.g., 12.9 mutations per Mb in melanoma) (Hodis et al. 2012; Lawrence et al. 2014). Nevertheless, genomic studies overall have emphasized the complexity of DLBCL with, on average, 30 to more than 100 genetics aberrations (such as point mutations, deletions, amplifications) per case (Pasqualucci 2013, and references therein). These studies have also helped further differentiate the genetic makeup of different DLBCL subtypes as well as the genomes of those that respond to R-CHOP versus rr-DLBCL. Figure 1 represents a snapshot of the frequency of nonsynonymous gene mutations in ~10% of DLBCL cases pooled across several discovery-genomics studies (Pasqualucci et al. 2011b; Lohr et al. 2012; Morin et al. 2013; Dubois et al. 2016), and the roles of many of these have been extensively characterized and reviewed elsewhere (Table 1; Tirado et al. 2012; Pasqualucci 2013; Watson et al. 2013; Jardin 2014; Bohers et al. 2015; Jiang and Melnick 2015; Pasqualucci and Dalla-Favera 2015; Testoni et al. 2015; Pasqualucci and Zhang 2016). We will only briefly touch upon some examples among these and instead focus primarily on potential DLBCL disease drivers whose roles remain to be clearly defined.

Several of these aberrations are putatively targetable, and specific inhibitors are already under evaluation. For example, somatic mutations of histone modifying proteins are a hallmark of DLBCL with increased epigenetic heterogeneity linked to poor outcome (Morin et al. 2011; Pasqualucci et al. 2011a; Jiang and Melnick 2015). The GCB subtype, in particular, is enriched in mutations affecting histone marks (Jiang and Melnick 2015). EZH2, for example, is a histone methyltransferase important for bivalency at key promoters that regulate the GC B-cell phenotype (Raaphorst et al. 2000; Velichutina et al. 2010; Chase and Cross 2011; Béguelin et al. 2013; Caganova et al. 2013). Although present in 21.7% of GCB DLBCLs, *EZH2* mutations are absent in the ABC subtype (Morin et al. 2010; Béguelin et al. 2013). The mutations, which increase trimethylation at H3K27 compared with wild-type, occur in the protein's SET domain, maintaining centroblast proliferation while blocking terminal differentiation (Sneeringer et al. 2010; Yap et al. 2011; McCabe et al. 2012a; Béguelin et al. 2013). Several EZH2 inhibitors arrest proliferation and induce apoptosis of *EZH2*-mutant cells by blocking H3K27me3, resulting in the reactivation of silenced gene targets (Knutson et al.

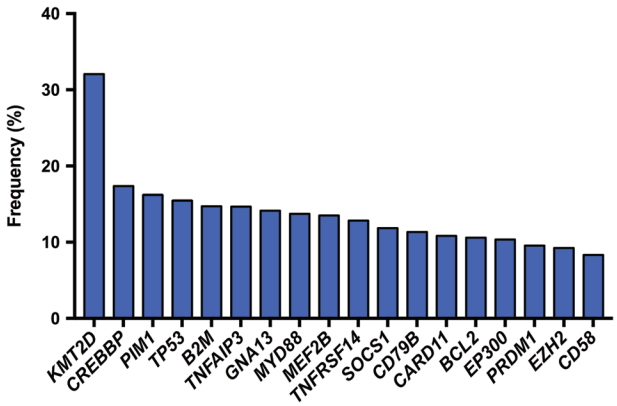


**Figure 1.** Frequency of nonsynonymous mutations in ~10% of diffuse large B-cell lymphoma (DLBCL) cases. Data pooled from Dubois et al. (2016), Lohr et al. (2012), Morin et al. (2013), and Pasqualucci et al. (2011b) (see also Table 1).

**Table 1.** Subtype distribution of the most mutated genes in diffuse large B-cell lymphoma (DLBCL) (see also Fig. 1)

| Gene | Total (%)[a] | ABC (%)[b] | GCB (%) | Functional characterization of gene mutations in DLBCL |
|---|---|---|---|---|
| *KMT2D* | 32.1 | 40.5 | 46.0 | Ortega-Molina et al. 2015; Zhang et al. 2015 |
| *CREBBP* | 17.3 | 6.0 | 31.0 | Pasqualucci et al. 2011a |
| *PIM1* | 16.4 | 33.0 | 8.5 | Kumar et al. 2005; Peters et al. 2016 |
| *TP53* | 15.7 | 18.0 | 15.5 | – |
| *B2M* | 14.7 | 8.5 | 18.0 | Challa-Malladi et al. 2011 |
| *TNFAIP3* | 14.7 | 15.0 | 11.0 | Compagno et al. 2009; Honma et al. 2009 |
| *GNA13* | 14.1 | 8.5 | 12.0 | Muppidi et al. 2014 |
| *MYD88* | 13.7 | 28.0 | 10.0 | Ngo et al. 2011 |
| *MEF2B* | 13.5 | 12.0 | 23.0 | Pon et al. 2015; Ying et al. 2013 |
| *TNFRSF14* | 12.8 | 2.0 | 17.0 | Boice et al. 2016 |
| *SOCS1* | 11.8 | 6.0 | 15.5 | – |
| *CD79B* | 11.3 | 25.0 | 2.5 | Davis et al. 2010 |
| *CARD11* | 10.8 | 13.5 | 7.0 | Lenz et al. 2008a |
| *BCL2* | 10.6 | 1.0 | 24.0 | Schuetz et al. 2012 |
| *EP300* | 10.4 | 15.0 | 14.5 | Pasqualucci et al. 2011a |
| *PRDM1* | 9.6 | 16.0 | 6.0 | Calado et al. 2010; Mandelbaum et al. 2010 |
| *EZH2* | 9.2 | 0.0 | 18.0 | Béguelin et al. 2013; Velichutina et al. 2010 |
| *CD58* | 8.3 | 6.0 | 10.0 | Challa-Malladi et al. 2011 |

ABC, activated B-cell-like; GCB, germinal center B-cell-like.
[a]Mutation frequencies were pooled from Pasqualucci et al. 2011b; Lohr et al. 2012; Morin et al. 2013; Dubois et al. 2016. All subentities were included.
[b]Mutation frequencies in ABC only or GCB only from Dubois et al. 2016.

2012, 2014; McCabe et al. 2012b; Qi et al. 2012; Béguelin et al. 2013). The histone acetyltransferases *CREBBP* and *EP300* are mutated in ~25% of DLBCLs, with preference but not exclusivity for the GCB subtype (Goodman and Smolik 2000; Morin et al. 2011; Pasqualucci et al. 2011a). Perturbed acetylation of histones and other targets, such as BCL6 and p53, through inactivating mutations of *CREBBP* and *EP300* may drive lymphomagenesis, making histone deacetylase (HDAC) inhibition seem like a promising therapeutic strategy (Bereshchenko et al. 2002; Pasqualucci et al. 2011a; Intlekofer and Younes 2014; Havas et al. 2016). However, in one of many cautionary tales of translating seemingly strong preclinical potential to benefits for patients, HDAC inhibitors show weak single-age clinical activity in DLBCL (Marks and Xu 2009; Prince et al. 2009; Copeland et al. 2010).

The ABC subtype, as mentioned, is characterized by multiple aberrations causing constitutive activation of the NF-κB pathway. This, accordingly, provides potential opportunities for targeted therapies depending on the specific upstream mechanism leading to activation, such as BCR or toll-like receptor (TLR) signaling. Although tonic BCR signaling is required for the maintenance of B cells (Lam et al. 1997; Srinivasan et al. 2009), ABC DLBCL cells exploit chronically active BCR signaling that is sustained, in part, by mutations in CD79A/B (Davis et al. 2010). Downstream activation of BTK suggests potential activity of ibrutinib in the treatment of such cases (Davis et al. 2010; Bohers et al. 2015). The most frequent single-nucleotide variants in ABC DLBCL, however, seen in approximately one-third of cases, are gain-of-function changes in *MYD88*, stimulating TLR signaling that activates both NF-κB and JAK/STAT (Ngo et al. 2011; Choi et al. 2013; Fernández-Rodríguez et al. 2014; Bohers et al. 2015). The most frequent mutation, *MYD88*-L265P, activates signaling through the

spontaneous assembly and activation of a complex with the IRAK1 and IRAK4 kinases, suggesting that IRAK-inhibitors or inhibitors against the toll-like receptors may be beneficial (Dufner and Schamel 2011; Loiarro et al. 2013; Ansell et al. 2014; Yang et al. 2014; Nowakowski et al. 2015). Furthermore, 24% of ABC DLBCLs promote NF-κB signaling by selecting for truncating mutations and/or deletions of *A20* (*TNFAIP3*), an NF-κB repressor that is involved in curbing activity caused by BCR and/or TLR stimulation (Compagno et al. 2009; Kato et al. 2009; Wang et al. 2014). Such mutations that suppress negative NF-κB pathway regulation pose particular therapeutic challenges, however, as clinical compounds to directly inhibit NF-κB mediators do not exist (Davis et al. 2001, 2010; Lam et al. 2008; Compagno et al. 2009; Ngo et al. 2011; Young et al. 2015; Pasqualucci and Zhang 2016). In addition to the above-mentioned use of lenalidomide and ibrutinib, the activities of enzastaurin and sotrastaurin (AEB071) (protein kinase C-β [PKC-β] inhibitors) (Robertson et al. 2007; Naylor et al. 2011), fostamatinib (SYK inhibitor) (Friedberg et al. 2010; Cheng et al. 2011; Chen et al. 2013b), and IMO-8400 (TLR-8 and -9 inhibitors) (Brenner et al. 2014) are all currently under investigation.

Abnormalities in several targetable pathways have been linked to PMBL, a subtype of DLBCL with many similarities to classical Hodgkin's lymphoma (Dunleavy and Steidl 2015). Aberrant JAK/STAT signaling, for example, may result from mutations in *SOCS1*, *PTPN1*, and *STAT6* as well as *JAK2* amplification (Guiter et al. 2004; Melzner et al. 2005; Weniger et al. 2006; Mottok et al. 2007; Lu et al. 2008; Ritz et al. 2009, 2013; Steidl and Gascoyne 2011; Schif et al. 2013; Gunawardana et al. 2014), suggesting potential exploitation by inhibitors such as pacritinib and ruxolitinib, both of which may also have activity in ABC-DLBCL (Younes et al. 2012). Mutations in *IL4R*, *B2M*, and members of the interferon regulator factor gene family affect interferon α, β, and γ signaling (Andersson et al. 2010; Challa-Malladi et al. 2011; Raia et al. 2011; Mareschal et al. 2016). Additionally, acquired immune privilege leading to a loss of major histocompatibility (MHC) class I and II expression along with increased *PDL1*, and *PDL2* expression may be exploited using various immune checkpoint inhibitors, including nivolumab, pembrolizumab, and pidilizumab (Rigaud et al. 2001; Rosenwald et al. 2003; Savage et al. 2003; Wessendorf et al. 2007; Armand et al. 2013; Chen et al. 2013a; Twa et al. 2014; Ansell et al. 2015; Kline and Bishop 2015).

The strategies discussed above represent only the tip of the iceberg of targeted therapies currently under evaluation as single agents, in combination with other such inhibitors, or in combination with chemotherapy (Bachy and Salles 2015; Mehta-Shah and Younes 2015). Importantly, there are also several recurrently altered genes that have yet to be well characterized, and their roles in DLBCL pathogenesis, if any, remain unclear. Disease-driving mutations that arise early in pathogenesis, so-called founder mutations, appear in most or all subsequent clones and are therefore, in theory, the best therapeutic targets (Green et al. 2013). Many of DLBCL's well-characterized driver mutations, however, including *EZH2*, *MYD88*, *CARD11*, and *CD79B* often are found only in subclonal populations (Morin et al. 2013). This complicates assessment of additional uncharacterized recurrently mutated genes also, because the progression of tumors is much more complex than mere linear acquisition of different mutations (Watson et al. 2013). Further complications arise from the actions of the enzyme activation-induced cytidine deaminase (AID, encoded by *AICDA*), which can make highly mutated alleles appear to be drivers when they are in fact passengers mutated by aberrant somatic hypermutation (SHM, see next section) (Liu and Schatz 2009; Gu et al. 2012; Jiang et al. 2012; Khodabakhshi et al. 2012; Gu et al. 2016).

## DRIVERS VERSUS PASSENGERS: THE AID EFFECT

Somatic hypermutation and class switch recombination are essential processes in the germinal center (GC) that allow for the generation of highly specific antibodies and B cells with

distinct effector functions (Di Noia and Neuberger 2007). However, because they induce breaks in the genome of GC B cells, where DNA damage checkpoints are already down-regulated, errors are believed to contribute to lymphomagenesis. AID targets immunoglobulin (Ig) locus genes for SHM, where it deaminates cytosines, resulting in a C:G to U:G mismatch that is subsequently repaired through either the base excision or DNA mismatch repair pathways, with each favoring different substitutions (Di Noia and Neuberger 2007). The targeting of cytosines by AID leads to a high ratio of transition to transversion, and the majority of C mutations fall within WRCY motifs (in which W is an A or T; R is an A or G; and Y is a C or T), whereas the A mutation is more likely when A is in the coding strand, and T mutations are found less frequently (Milstein et al. 1998; Rogozin and Diaz 2004). AID-induced SHM is dependent on transcription and targeted to the 5′ region of the gene, with the majority of mutations lying within the first 1–2 kb downstream from the transcription start site (Both et al. 1990; Meng et al. 2014). Initially the *BCL6* and *CD95* genes were identified as non-Ig targets of SHM, but with numerous genome- and exome-sequencing studies in the past decade it is clear that more than 40 genes exhibit these hallmarks of AID mutator activity (enrichment in mutations targeted to WRCY motifs, high transition-to-transversion and C:G to A:T ratios) (Pasqualucci et al. 1998, 2011b; Müschen et al. 2000; Khodabakhshi et al. 2012; Lohr et al. 2012; Zhang et al. 2013; Peters et al. 2016). The most well-defined SHM off-target genes based on AID hallmarks include *BCL2*, *BCL6*, *MYC*, *RHOH/TTF*, *PIM1* (see below), *PAX5*, *IRF4*, *ST6GAL1*, *BCL7A*, *CIITA*, *LRMP*, and *SOCS1*. Recent analyses have identified that some of these frequent AID off-target genes, such as *PIM1*, *MYC*, *CD79B*, and *PAX5*, are associated with sites of convergent transcription and the presence of super enhancer elements, which supports the finding that transcription is required for targeting by AID (Maul and Gearhart 2010; Meng et al. 2014; Qian et al. 2014). Despite considerable data published in recent years on the targets of aberrant SHM in DLBCL, the significance of most such mutations remains unclear. Specifically, questions linger about whether these mutations are selected for pro-oncogenic functions or simply a secondary result of GC biology. Overexpression of the oncogene *MYC* by the Ig λ promoter results in pre-GC lymphomas that lack mutations in the Ig variable region, whereas in IμHABCL6 mice, *BCL6* mRNA expression is deregulated, driving GC-derived lymphomas. A lack of AID, however, blocks lymphoma development only in the *BCL6*-dependent GC IμHABCL6 model and has no effect on *MYC*-driven, pre-GC lymphomas (Pasqualucci et al. 2008). It is possible AID has a role other than the specific mutations it generates, but this remains speculative for now.

## PIM1

The PIM1 proto-oncogene serine/threonine kinase was originally identified as a site of frequent proviral insertion by the Moloney leukemia virus that synergizes potently with MYC in lymphomagenesis (Cuypers et al. 1984). Subsequently, two highly homologous additional family members, PIM2 and PIM3, were identified through their abilities to replace PIM1 in oncogenesis models (Breuer et al. 1989; Feldman et al. 1998). All three family members are constitutively active kinases expressed downstream from growth factor and cytokine signaling pathways and control pro-growth and pro-survival signaling outputs. Elevated PIM expression is seen in multiple malignancies, particularly those derived from hematopoietic cells. Surprisingly, the only phenotype of *PIM1/2/3* triple-knockout mice is diminished body size and an impaired response of hematopoietic cells to cytokine (Mikkers et al. 2004). *PIM1* is among the list of most frequently targeted genes by aberrant SHM found in numerous studies in DLBCL, but the mutational pattern is curious for a constitutively active kinase, given the much higher probability that random point mutations would lead to a nonfunctional protein (Pasqualucci et al. 2011b; Zhang et al. 2013; Meng et al. 2014; Mareschal et al. 2016). We recently asked the question whether these mutations impacted the function

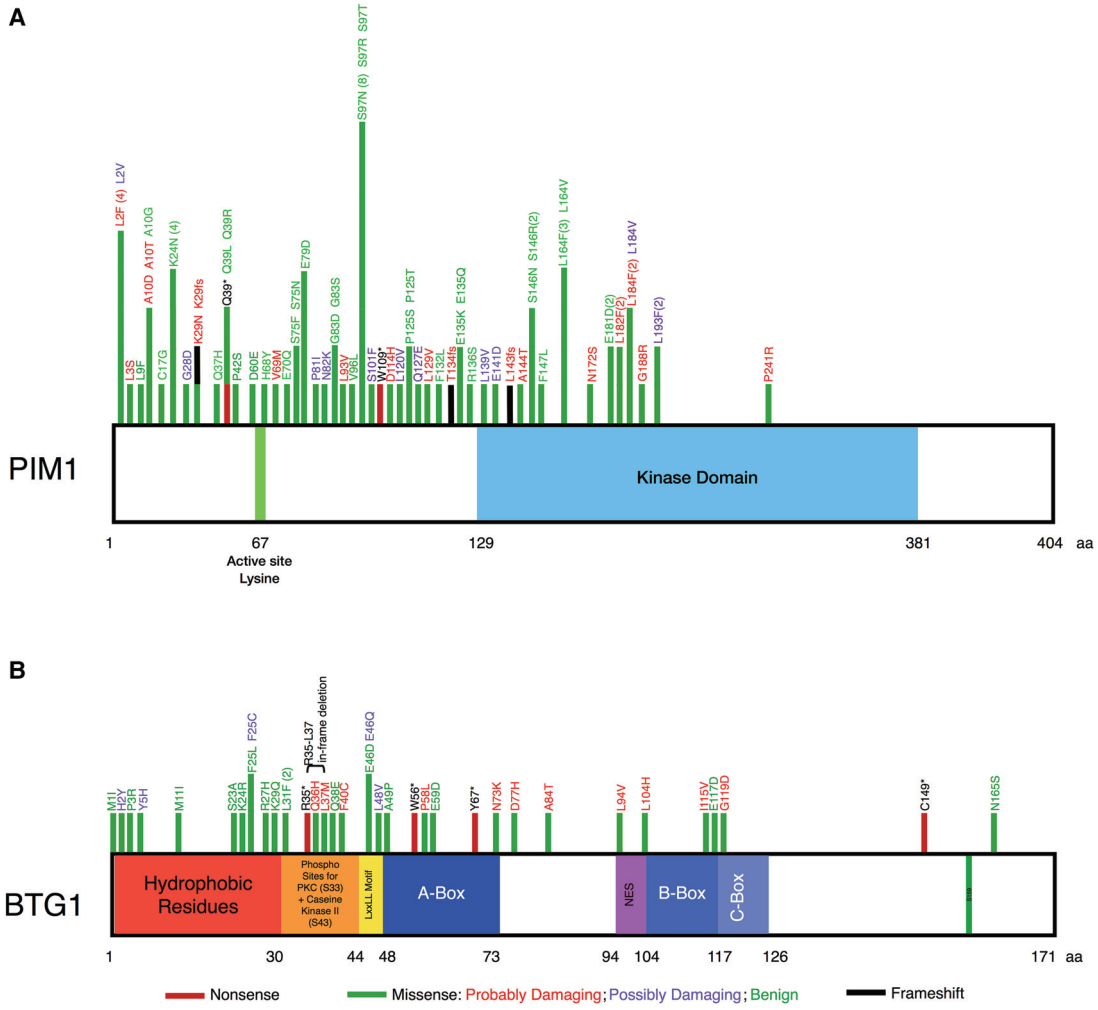


**Figure 2.** Mapping the known mutations for PIM1 and BTG1. (*A*) *PIM1* mutational pattern adapted from Peters et al. 2016. (*B*) *BTG1* mutations mapped using the Catalogue of Somatic Mutations in Cancer (COSMIC; http ://cancer.sanger.ac.uk/cosmic) database and Lohr et al. 2012.

of the kinase. We performed a meta-analysis of whole-genome and -exome sequencing and identified 92 substitutions resulting in missense mutations, of which 53 were recurrent (Fig. 2A; Peters et al. 2016). We tested these mutations for their ability to enrich in cytokine-deprived FL 5.12 cells, a murine pro-B cell line for which PIM expression is the major survival target of cytokine stimulation. The vast majority of mutations behaved identically to wild-type *PIM1* (and none conferred resistance to the pan-PIM kinase inhibitor PIM447) (Peters et al. 2016). These results suggest that the high frequency of SHM at the *PIM1* locus is not a disease-driving process, at least not through the mutations themselves. If anything, it could even be a bottleneck because for the most part only those mutations that preserve kinase function are found in surviving clones.

## BTG1

BTG1 is a member of the BTG/Tob family that regulates cell cycle progression and apoptosis, gene transcription in the nucleus, cytoplasmic mRNA deadenylation and turnover, and

protein–protein interactions (Winkler 2010). Several studies have reported mutations in *BTG1*, with several patients even exhibiting more than one mutation (Morin et al. 2011; Lohr et al. 2012; Zhang et al. 2013). Mutations are predicted to generally favor loss of function of the protein (Morin et al. 2011) and occur in both coding and noncoding regions, suggesting altered codon use or defects in *BTG1* mRNA stability (Lohr et al. 2012). A predictive "classification tree model," however, identified *BTG1* as one of 101 high-interest genes that are likely to be targets of AID (Duke et al. 2013). Indeed, modeling *BTG1*'s mutational pattern using the Catalogue of Somatic Mutations in Cancer (COSMIC; http://cancer.sanger.ac.uk/cosmic) database strongly suggests that this recurrently mutated gene is not a driver of DLBCL, but is instead a consequence of AID-mediated mutations because of the clustering of mutations at the amino terminus (Fig. 2B; Pasqualucci et al. 2001; Qian et al. 2014).

The above are just two examples, but they highlight the care that must be taken when determining the driver status of the large number of frequently mutated DLBCL genes unearthed through large-scale genomics, with considerable efforts required to confirm whether the contribution of AID renders them merely passengers.

## BCL10

An important bottleneck for NF-κB activation required for ABC-DLBCL is the CBM complex, consisting of the proteins CARMA1 (CARD11), BCL10, and MALT1 (Thome 2004; Staudt 2010; Yang et al. 2014). *BCL10* and *MALT1* amplifications, mutations, and translocations are well-established in MALT lymphoma (Willis et al. 1999; Zhang et al. 1999; Isaacson and Du 2004; Sagaert et al. 2006; Hailfinger et al. 2014). Although *CARMA1* mutations are well-described in ABC-DLBCL oncogenesis (Lenz et al. 2008a) and *MALT1*'s protease activity also plays a role (Ferch et al. 2009; Hailfinger et al. 2009; Baens et al. 2014), genomic data suggest *BCL10* mutations may also drive DLBCL pathogenesis. Morin et al. (2011, 2016) reported evidence for DLBCL's selection of inactivating mutations in *BCL10*. Why would DLBCL cells select for mutations that inactivate a protein that is an integral member of a complex required for oncogenic NF-κB signaling? Perhaps the answer to this conundrum lies in the supposed dual functions of BCL10 in activating NF-κB signaling while also inducing apoptosis in some cells, each function carried out by separate unique portions of the protein (Willis et al. 1999; Zhang et al. 1999). Indeed, although the IκB kinase-β is required for CBM complex formation through phosphorylation of the amino terminus of BCL10, it subsequently phosphorylates downstream residues of BCL10 to attenuate this signaling (Wegener et al. 2006; Zeng et al. 2007). Our laboratory is currently investigating whether putative separation-of-function mutations in BCL10 are true drivers of the disease.

## FAS

As recently reviewed by Testoni et al. (2015), mutations in *FAS* may be important contributors to DLBCL pathogenesis. FAS induces apoptosis as part of the death-inducing signaling complex (DISC). DLBCL cells, accordingly, modulate FAS's pro-apoptotic activity via loss-of-function mutations, deletions, and copy loss, protecting the cancer cells from immune surveillance and apoptosis following chemotherapy (Gronbaek et al. 1998; Kojima et al. 2006; Morin et al. 2011, 2016; Mian et al. 2012; Monti et al. 2012; Testoni et al. 2015). The driver status of FAS, however, remains to be established with respect to DLBCL.

## SGK1

Like BCL10 and FAS, the PI3K-regulated serine/threonine protein kinase SGK1 (serum and glucocorticoid-regulated kinase 1) shows a propensity for inactivating mutations particularly in GCB DLBCL (Morin et al. 2011) and is in a region of Chromosome 6q that is recurrently deleted in DLBCL, FL, and other B-cell lymphomas (Lenz et al. 2008c; Oricchio et al.

2011; Monti et al. 2012; Morin et al. 2013). SGK1 has several cellular functions, including ion channel activity regulation in renal cells (Lang and Shumilina 2013), FOXO3 phosphorylation to mediate cell survival signals (Brunet et al. 2001), IκB-α and p300 phosphorylation up-regulating NF-κB signaling (Tai et al. 2009), and FBW7 phosphorylation to induce degradation and ubiquitylation of the NOTCH1-intracellular domain, thereby inhibiting the NOTCH1 signaling pathway (Mo et al. 2011). Recently, a t(6;14)(q22;q32) translocation juxtaposing the IGHG3 switch region to an intron of *SGK1* was predicted to inactivate SGK1 (Ryan et al. 2015). Furthermore, mutation in DLBCL results in a loss of promoter occupancy of several genes, including *SGK1* (Ortega-Molina et al. 2015), and SGK1 confers resistance to PI3K inhibition in breast cancer (Castel et al. 2016). As with BCL10, DLBCL cells seem to paradoxically lose SGK1, despite its role in pro-proliferation pathway activation, with an algorithm suggesting mutations are indeed drivers of DLBCL (Lohr et al. 2012). Our laboratory is currently working to understand how DLBCL's growth might be facilitated through SGK1 loss of function.

### TBL1XR1

The E3 ubiquitin ligase activity of transducin β-like 1 X-linked receptor 1 (TBL1XR1) polyubiquitinates the nuclear receptor corepressor 2/silencing mediator for retinoid or thyroid-hormone receptors (NCoR/SMRT) complex, resulting in transcriptional repression through NF-κB and WNT-mediated signaling pathways (Yoon et al. 2003; Zhang et al. 2006; Perissi et al. 2008; Rossi et al. 2012). This putative tumor-suppressor gene has recurrent mutations activating NF-κB in acute lymphoblastic leukemia (ALL), splenic marginal zone lymphoma (SMZL), and primary central nervous system lymphoma (PCNSL), with the latter also exhibiting a 3q26.32 deletion that encompasses the *TBL1XR1* locus (Parker et al. 2008; Braggio et al. 2011; Zhang et al. 2011; Gonzalez-Aguilar et al. 2012). Further evidence was presented at ASH 2016 to support the tumor-suppressive role of *TBL1XR1* in which in silico modeling and functional characterization of *TBL1XR1* mutations indicate their inactivating nature through heightened proliferation and putative perturbed interactions with CD79B/MYD88 in DLBCL as well as PCNSL (Chapuy et al. 2016). It is perhaps unsurprising that *TBL1XR1* mutations have been observed in two out of six ABC DLBCL samples (Mareschal et al. 2016), because studies have shown a high degree of correlation between ABC and PCNSL mutational patterns (Bruno et al. 2014). Furthermore, focal deletions and single-nucleotide variants (SNVs) of *TBL1XR1* have been previously reported in DLBCL (Pasqualucci et al. 2011b; Lohr et al. 2012; Scott et al. 2012; Morin et al. 2013). Gene fusions are also evident in some GCB DLBCL (6/115 GCB; 0/138 non-GCB) and FL cases (1/81) (Scott et al. 2012). A report that links deletions in *TBL1XR1* to glucocorticoid resistance may suggest a role for *TBL1XR1* inactivating mutations in facilitating R-CHOP resistance (Jones et al. 2014; Mareschal et al. 2016). Further support for this comes from one study that saw *TBL1XR1* mutations only at relapse but not at diagnosis (Morin et al. 2016). This warrants further investigation as combining R-CHOP therapy with agents modifying the E3 ubiquitin ligase activity of TBL1XR1 might prevent the onset of resistance in some cases of DLBCL. The amplification of *TBL1XR1* is seen in breast cancer, in which its inactivation is associated with decreased tumor cell invasion (Kadota et al. 2009), suggesting that the oncogenic properties of *TBL1XR1* differ between solid tumors and hematological malignancies.

New genomic data presented at ASH 2016 emphasize the power of having large numbers of cases to better contextualize putative drivers. Zhang et al. (2016) carried out what could possibly be the largest whole-exome sequencing study of any individual cancer type, by analyzing the genomes of 1001 de novo DLBCL patients. Forty-two novel drivers were identified, including the aforementioned *BTK*. This elaborate study further separated genes into functionally related subnetworks and found that the majority of genes within

each subnetwork were mutated in mutually exclusive patterns. Furthermore, several new genes emerged as positive or negative prognostic biomarkers. *EZH2* and *CD70* mutations, for example, associated with favorable prognosis in GCB-DLBCL, whereas mutations in *KLHL14* associated with poor prognosis in ABC cases. Interestingly, *TP53* mutations were found only to be prognostic when associated with both *MLL2* mutation and high *BCL2* expression (Zhang et al. 2016). A number of potentially clinically useful findings emerge from this study, aiding therapeutic selections in precision medicine contexts and generating hypotheses for testing in both clinical trials and laboratory studies.

## THE IMPORTANCE OF FUNCTIONAL STUDIES TO UNDERSTAND THE ROLES OF RECURRENTLY ALTERED GENES

Laboratory functional studies provide the best initial route to elucidate the roles of recurrently altered genes in lymphomagenesis, exemplified by the recent examples of the histone methyltransferase *KMT2D* and the TNFRSF14 receptor gene *HVEM* (herpes virus entry mediator) (Ortega-Molina et al. 2015; Zhang et al. 2015; Boice et al. 2016). KMT2D exerts a widespread effect by controlling the expression of a set of genes that includes the above-mentioned *SGK1* and *FAS*, with *KMT2D* deficiency resulting in altered promoter occupancy. Mutations in *KMT2D*, however, were not associated with outcome to R-CHOP therapy (Ortega-Molina et al. 2015). The results obtained for HVEM's role in FL are particularly enticing. The interactions between HVEM and BTLA (B- and T-lymphocyte attenuator) normally oppose lymphoma development (Costello et al. 2003; Cai and Freeman 2009; Steinberg et al. 2011; Pasero et al. 2012; Bjordahl et al. 2013). In a large number of FL cases, however, this interaction is lost, as HVEM or BTLA are mutated or lost in a mutually exclusive manner. By genetically engineering CD19-targeted chimeric antigen receptor (CAR) T cells to locally and continuously produce the ectodomain portion of the HVEM protein, termed "micropharmacies," the HVEM-BTLA inhibitory axis is restored leading to a significant therapeutic response (Boice et al. 2016). Although this therapy is limited to BTLA-expressing FL cells that have defective HVEM, the use of genetically engineered CAR T cells as micro-pharmacies to secrete tumor-suppressive proteins that are mutated in patients, even restoring protein–protein interactions that have been lost by these mutations, is especially alluring, as CAR T cells, in principle, can attack any tumor antigen (Brentjens et al. 2003; Batlevi et al. 2016). Similar functional analyses can, in principle, uncover the roles for other putative drivers of DLBCL.

## THE FEASIBILITY OF TUMOR GENOMICS IN REAL TIME

Fast and accurate identification of DLBCL subtypes and biomarkers can aid in risk stratification and could eventually drive choices of alternate therapies for patients predicted to fail standard regimens like R-CHOP. The gene-expression studies that identified and validated ABC versus GCB versus PMBL COO subtypes required fresh-frozen tumor samples from which high-quality RNA could be extracted, techniques that are not practical in routine clinical practice. Efforts to simplify COO identification have been the subjects of intensive efforts ever since. For example, although several thousand cDNA clones were used in the Lymphochip microarray that initially established the COO classification of DLBCL (Alizadeh et al. 1999, 2000), subsequently, 27-gene (Wright et al. 2003), 17-gene (Rosenwald et al. 2002), six-gene (Lossos et al. 2004), and even two-gene (Rimsza et al. 2008) models have been used for predicting overall survival (OS) after chemotherapy. It is necessary that COO be reliably identifiable from formalin-fixed paraffin-embedded (FFPE) tumor samples, and encouraging

results have been obtained with the Lymphoma/Leukemia Molecular Profiling Project's digital gene expression (NanoString)-based Lymph2Cx assay (Scott et al. 2014). Here, a 20-gene assay accurately categorized COO subtypes from FFPE tissue samples with a low misassignment score that is on par with currently used immunohistochemistry (IHC)-based algorithms (Hans et al. 2004; Choi et al. 2009; Meyer et al. 2011) and a turnaround time of <36 h. The use of synthetic oligonucleotides that are run alongside patient samples for normalization was designed to increase assay stringency by accounting for potential lot-to-lot probe variation and suggests that routine clinical implementation of such techniques as predictors of OS is within grasp (Scott et al. 2014). Furthermore, OS prediction following CHOP and R-CHOP from paraffin samples has been achieved using real-time PCR on a handful of genes (Malumbres et al. 2008; Alizadeh et al. 2011) providing further options for fast and reliable patient management.

Although identifying patients who are likely to respond to chemotherapy via GEP is helpful, pinpointing targetable pathways and aberrations to treat those who are unresponsive (or resistant) to therapy is a higher priority as the field stands currently. Furthermore, the high degree of stromal contamination found in clinical lymphoma specimens, for example, would require techniques such as deep sequencing to identify relevant alterations in tumors, some of which may be subclonal (Lohr et al. 2012). The use of NGS routinely in the clinic is appealing because of the sheer amount of information one can garner for each patient to direct the most targeted and relevant therapies, with companies, such as Foundation Medicine, making real-time targeted exome sequencing a reality (Wagle et al. 2012; Frampton et al. 2013; Intlekofer and Younes 2014). Despite this, however, the modes of patient treatment have not substantially changed. Researchers and clinicians have capabilities now to generate a plethora of data about any given patient's tumor, but we do not yet understand enough about various alterations, their mechanisms of action, and whether they are indeed relevant enough to change current treatment practices. Once the impact of these genetic changes is better understood, NGS may become useful to tailor therapies that will exploit them.

## CONCLUSION

The international prognostic index (IPI), established in 1993 (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993; Shipp 1994; Sehn et al. 2007; Zhou et al. 2014), predicts patients likely to fail standard therapy. It gives no insight, however, into tumor biology, nor does it suggest more effective treatments. Furthermore, although current guidelines recognize the importance of the COO classification and the presence of *MYC* rearrangements (Ghielmini et al. 2013; Zelenetz 2014), R-CHOP or R-EPOCH remain the recommended course of therapy (Testoni et al. 2015). Concerted efforts are underway to identify relevant disease drivers that are therapeutically targetable using the wealth of genomic data that has been amassed through technological advancements and evolving bioinformatic power. Additionally, uncovering potential causes of resistance to chemotherapy is of the utmost importance. Immunohistochemistry is one method that is currently used, with *ALDH1A1*, for example, identified as causing resistance to CHOP via the JAK/STAT pathway (Jiang et al. 2016). Genomic data can also greatly aid in this process, and, as discussed above, mutations in *TBL1XR1* have been identified as a potential cause of R-CHOP resistance—a hypothesis that requires further confirmation. To simplify efforts, we must unify these fragmented global data sets, obtained by different sequencing platforms, using different algorithms to call mutations, stored in different data formats, while preserving ethical practices when using any such data (Grossman et al. 2016; Siu et al. 2016). Various global efforts are ongoing to achieve this, such as President Obama's "Moonshot" program to cure cancer (McCarthy 2016), The Cancer Genome Atlas (TCGA) (The Cancer Genome Atlas Research Network

et al. 2013), the Actionable Cancer Genome Initiative (ACGI), which aims to identify "actionable" genes in several cancers (Lawler et al. 2015), the NCI Genomic Data Commons (GDC) established through the collective efforts of the National Cancer Institute, the University of Chicago, the Ontario Institute for Cancer Research, and Leidos Biomedical Research (Grossman et al. 2016), and others (for review, see Siu et al. 2016). Wading through all the genomic data in AML and FL have helped illuminate the complexities of these diseases. The same goal will be attainable in DLBCL through data "harmonization," providing hope that personalized medicine can soon be implemented to treat each individual.

**Competing Interest Statement**

The authors have declared no competing interest.

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