model of CLPD-NK had focused on constitutive STAT activation, either based on pronounced cytokine exposure of the precursor or via activating *STAT3* mutations; and (2) although confirming *STAT3/5B* variants in approximately one-third of cases (32%), Pastoret et al provide the first evidence of loss-of-function variants of *TET2* in another third (34%) of CLPD-NK. They illustrate the cooccurrence of mutated *TET2* in the myeloid lineage and postulate a *TET2*-based ancestral trajectory that is expanded and refined in the figure.

Collectively, the landmark paper by Pastoret et al is an important contribution to the fields of LGL and of general leukemogenesis. It establishes *TET2* mutations as a diagnostic marker in CLPD-NK, including its use in a new clonality score or as an informative lesion to define a clinicopathological subset of CLPD-NK that is set apart from cases with an underlying STAT signature. Pastoret et al also have set the stage for further exploration (eg, single-cell resolved approaches to sequential samples) to refine our concepts of lesion-based clonal relationships in perturbed hematopoiesis and its translational implications. Related questions include the leukemogenic factors that cooperate with mutated *TET2* to increase its penetrance and provision of context-specificity (ie, lineage commitment), such as particular comutations or permissive milieus of protracted inflammation.

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**LYMPHOID NEOPLASIA**

*Comment on Thurner et al, page 3251*

# Mantle cell lymphoma continues to surprise, and inform!

**Michael E. Williams** | University of Virginia Cancer Center

**In this issue of *Blood*, Thurner and colleagues from the European MCL Network report a subset of cases with B-cell receptor (BCR) reactivity against the self-antigen LRPAP1 (LDL receptor–related protein–associated protein 1), and that these patients have an improved clinical outcome.[1]**

In the 30 years since the identification of the hallmark molecular marker of mantle cell lymphoma (MCL), the t(11;14)(q13;q32) that leads to dysregulated expression of cyclin D1, the remarkable biologic and clinical complexity of the disease continues to amaze.[2,3] Thurner et al, following up on their initial discovery,[4] now have analyzed sera obtained during the Network's phase 3 trials in previously untreated MCL. The MCL Younger Trial studied the role of high-dose cytarabine plus autologous stem cell transplant (ASCT) consolidation, and the MCL Elderly Trial assessed the role of maintenance rituximab after chemoimmunotherapy. Surprisingly, they found that patients with anti-LRPAP1 seropositivity experienced improved 5-year failure-free and overall survival (OS) independent of other established prognostic markers. The presence of LRPAP1 autoantibodies did not correlate with presenting clinical characteristics.

MCL patients may exhibit slow-paced disease that can be observed for months or years without therapy, while others have highly aggressive lymphoma with poor survival. Correlative research has established a number of MCL prognostic factors, most in the context of chemoimmunotherapy rather than agents that target the BCR or BCL2 pathways (see table). However, no biomarker nor the Mantle Cell International Prognostic Index (MIPI) scoring system currently is used in clinical practice to determine the timing or type of initial therapy, although the role of consolidative ASCT in TP53-mutated or deleted MCL has been questioned due to typically short remission durations in these patients.[5] A high tumor cell proliferation rate is the common theme among those with poor treament outcomes, as demonstrated by a Ki-67 score >30%, blastoid morphology, or a high-risk MCL35 proliferation assay score.[5,6]

Achieving a deep initial treatment response is emerging as the strongest single determinant of outcome, as reflected by the presence or absence of measurable residual disease (MRD) in peripheral

**MCL: prognostic factors at diagnosis**

| Biomarker | Favorable | Unfavorable |
|---|---|---|
| MIPI or MIPI-c score | Low | High |
| Ki-67 score | <30% | ≥30% |
| Chromosome 17p | Intact | Deleted |
| TP53 | Wild-type | Mutated |
| Clinical/morphologic | Leukemic/non-nodal subtype | Blastoid or pleomorphic MCL |
| Postinduction MRD | Negative | Positive |
| MCL35 proliferation assay | Low risk | High risk |
| Anti-LRPAP1 seropositive (proposed) | Present | |

blood and bone marrow upon completion of induction therapy. A recent study showed significantly improved progression-free survival and OS for MCL patients who were MRD negative by real-time quantitative polymerase chain reaction assays with a minimal sensitivity of at least $10^{-4}$ following completion of 4 cycles of R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and *cis*-platinum) and prior to ASCT consolidation.[7] The ongoing ECOG-ACRIN EA4151 clinical trial (clinicaltrials.gov identifier NCT03267433) is prospectively testing risk-adapted postinduction ASCT consolidation based upon MRD status at completion of induction therapy; MRD-positive patients all proceed to ASCT consolidation followed by maintenance rituximab, while MRD-negative patients are randomized to ASCT plus maintenance vs maintenance rituximab alone. The results of this trial will inform the benefit of ASCT in patients who have already achieved deep clinical response by negative positron emission tomography imaging and MRD. Other MRD-based studies are exploring risk-adapted therapy to convert MRD-positive patients to negative utilizing anti-CD20 monoclonal antibody therapy and/or targeted agents.

What insights with regard to mantle cell lymphomagenesis are informed by LRPAP1 autoreactivity? It is well established that chronic active BCR signaling is integral to the pathogenesis of most B-cell lymphoproliferative malignancies. This activation may arise via mutations within the signaling pathway or by ligand binding of the tumor cell BCR. An external antigen may directly or indirectly engage the BCR, as in gastric mucosa-associated lymphoid tissue lymphoma with *Helicobacter pylori* infection, or it may bind to a "self" antigen as may arise during cellular apoptosis.[4,8] LRPAP1 is the first such autoantigen clearly defined for MCL. Functional relevance was demonstrated by LRPAP1-induced MCL proliferation in cell lines and primary patient samples with LRPAP1-specific BCRs, and by induction of in vitro cell death in cells exposed to toxin-conjugated LRPAP1.[4] The latter observation supports the idea that this receptor specificity may allow therapeutic targeting of LRPAP1-reactive MCL, as suggested by Thurman et al.

Further development of anti-LRPAP1 antibody detection as a biomarker for MCL will need to account for the recognition that serum LRPAP1 antibodies also may arise in patients with esophageal squamous cell cancer, colorectal carcinoma, and other solid tumors and in the setting of cardiovascular disease, including acute ischemic stroke or myocardial infarction.[9] Additional analysis of this biomarker in MCL will be of particular interest utilizing samples from recent front-line MCL trials incorporating targeted agents in order to confirm whether or not anti-LRPAP1 remains prognostic in such therapeutic contexts. As noted, the potential of BCR with LRPAP1 specificity to serve as a therapeutic target or offer novel insights into MCL pathogenesis requires further exploration.

MCL thus continues to surprise. Initially identified as a difficult-to-diagnose and poor-prognosis non-Hodgkin lymphoma with only transient treatment response, recent advances have led to dramatic improvement in outcomes and survival with an array of therapeutic options for front-line and relapsed disease. Despite the universal presence of the t(11;14) translocation and cyclin D1 overexpression (or, rarely, cyclin D2 or D3) as the unifying molecular event, the clinical spectrum includes in situ MCL, the clinically indolent non-nodal leukemic subtype, as well as classical MCL and highly aggressive disease with blastoid transformation. The genomic and epigenomic abnormalities that underlie the MCL subtypes reveal a remarkably complex array of changes that in turn reflect the heterogeneity of clinical presentation and progression,[10] holding promise for continued progress in predicting an individual patient's course and informing treatment optimization.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

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THROMBOSIS AND HEMOSTASIS

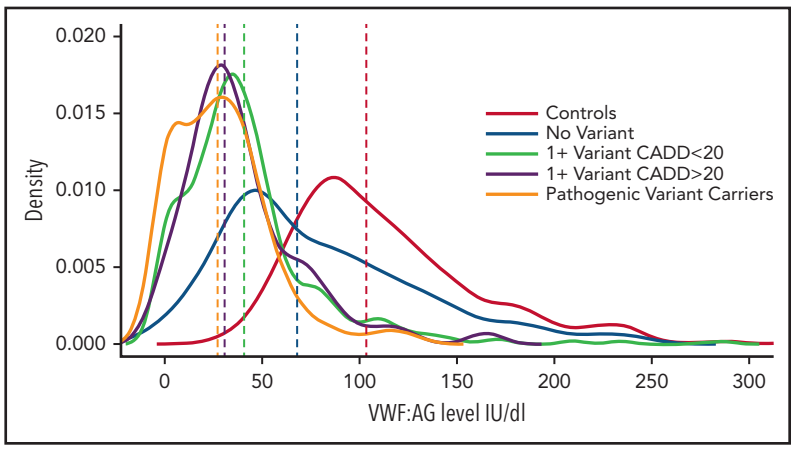
*Comment on Sadler et al, page 3277*

# Unraveling von Willebrand factor deficiency

**Catherine P. M. Hayward** | McMaster University

**von Willebrand factor (VWF) deficiency has important hemostatic consequences but unraveling its genetic determinants has been a significant challenge. In this issue of *Blood*, Sadler and colleagues report that rare nonsynonymous (protein-coding) variants in *VWF* show important and significant association with the severity of VWF deficiency.[1] The authors evaluated this by sequencing the coding regions of the VWF gene for unrelated persons with low VWF and von Willebrand disease (VWD), and normal subjects, followed by testing whether the presence of rare protein-coding variants is predictive of lower VWF antigen levels.**

Sadler et al provide important new knowledge of the determinants of VWF antigen levels, which has emerged to be a complex trait, influenced by *VWF* and additional genes and acquired factors.[2-4] There are several noteworthy findings. First, Sadler and colleagues identified a relationship between the burden (or number) of rare, nonsynonymous *VWF* variants and the severity of VWF deficiency that was significant across all types of VWD. They noted that patients with type 3 VWD (who have the most severe VWF deficiency) had the greatest burden of such variants, although all groups, including those with type 1 or 2 VWD and low VWF, had more rare nonsynonymous variants than normal subjects. It is interesting that in none of the cases did the patients have more than 2 pathogenic or probable pathogenic variants. In Figure 3, Sadler et al provide a helpful illustration of the distribution of VWF antigen levels among normal subjects vs groups with VWF deficiency that do or do not carry rare, nonsynonymous *VWF* variants. It illustrates that the lowest VWF levels are in carriers of rare variants with known or predicted pathogenicity (based on high pathogenicity scores), and the less severe effects of carrying rare variants with low pathogenicity scores (see figure).




VWF factor levels among groups with different types of rare nonsynonymous *VWF* variants. The distributions of VWF antigen levels (vertical lines show medians) in normal subjects are compared with those of groups of subjects with VWD or low VWF who carry pathogenic variants, predicted pathogenic variants (1 + CADD >20), variants with low pathogenicity (1 + CADD <20), or no variants. CADD, combined annotation-dependent depletion. See Figure 3 in the article by Sadler et al that begins on page 3277.

Many rare protein-coding sequence variants are of recent origin,[5] and this may explain the considerable heterogeneity in rare *VWF* sequence variants that Sadler and colleagues found in their study. It is possible that additional determinants of VWF levels will be identified by looking beyond *VWF* for associations between VWF levels and rare protein-coding variants. Indeed, exploring for such relationships by a genome-wide approach has yielded important information for other human traits and diseases in 2 noteworthy studies.[6,7] Given the findings of Sadler et al and the considerable evidence that other genes influence VWF levels,[2,8] it would be particularly interesting to use whole-exome or -genome sequencing to investigate whether rare protein-coding variants (or other mutations) in those other genes would help predict the severity of VWF deficiency among persons with VWD or low VWF.

There are some intriguing questions about causation vs association that future studies could address, given the interesting findings of Sadler et al. For example, family studies of VWD and low VWF, that include index cases with multiple, rare, protein-coding *VWF* variants, would help determine whether the pathogenic or probable pathogenic variants are commonly coinherited with rare nonpathogenic variants that could be markers of a "disease allele." This determination may explain why rare protein-coding variants with low pathogenicity scores show significant association with low VWF levels, whereas variants with known or predicted pathogenicity are associated with even lower VWF levels. In addition, family studies would help address whether VWF levels are significantly lower when both copies of *VWF* contain protein-coding variants with known or probable pathogenicity. The copy numbers of some other *VWF* variants have already been established as