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Molecular diagnosis of vitreoretinal lymphoma

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Abstract:

Vitreoretinal lymphoma (VRL) is a rare ocular malignancy that involves the retina, the retinal pigment epithelium, and the vitreous. It is a subtype of primary central nervous system lymphoma (CNSL). Most cases of VRL and CNSL are classified as diffuse large B-cell lymphoma. Despite its indolent nature, VRL can lead to permanent vision loss and even death due to CNS involvement. The gold standard for diagnosing VRL is the identification of lymphoma cells in a vitreous biopsy. However, diagnosis is challenging due to the rarity and fragility of lymphoma cells. Consequently, various diagnostic methods, such as interleukin level measurement, immunoglobulin clonality assays, flow cytometry, and molecular analysis have been developed to improve diagnostic accuracy. Tools from molecular biology, such as next-generation sequencing and single-cell based analyses, are being investigated as emerging diagnostic modalities. This review aims to discuss the conventional and up-to-date molecular tools for VRL diagnosis and to present important genetic variations and their clinical implications in VRL.

Keywords:

Genetic profile, molecular diagnosis, vitreoretinal lymphoma

Introduction

Vitreoretinal lymphoma (VRL), formerly known as primary intraocular lymphoma, is a rare malignancy predominantly seen in elderly patients. Most cases (>95%) are classified as diffuse large B-cell lymphomas (DLBCLs), categorizing them as high-grade diseases with poor outcomes.[1] These are grouped under "large B-cell lymphomas of immune-privileged sites" along with central nervous system lymphoma (CNSL) and testicular lymphoma.[2] One reason for the poor prognosis is the delay in diagnosis, which results from VRL's clinical similarity to uveitis; both conditions can present with vitreous opacity and subretinal lesions. Even when diagnostic tests are conducted following clinical suspicion, the low yield of malignant cells in intraocular samples makes diagnosis challenging.[3] Consequently, various molecular diagnostic methods have been developed to aid in diagnosis. These include the interleukin (IL)-10/IL-6 ratio, immunoglobulin heavy chain (IGH) and light chain monoclonality tests, flow cytometry, and *MYD88* L265P mutation analysis

The purpose of this review is to describe the advantages and limitations of various molecular diagnostic tools. In addition, we introduce novel molecular diagnostic methods for VRL, including next-generation sequencing analysis, single-cell analysis, and micro-RNA (miRNA) analysis. The molecular profile and clinical manifestations of genetic variation in VRL are also described.

Cytopathological Diagnosis

The gold standard for the diagnosis of VRL is cytological examination; however, diagnostic rates can vary widely, possibly due to subjective factors in cytology examination[4,5] (31%,[6] 50%,[7,8] and 87.5%[9]).

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Possible reasons for this low rate include the effect of corticosteroids from misdiagnosis as uveitis, the fragile nature of lymphoma cells, cell damage by the vitreous cutter, or the effects of whole-brain irradiation performed before vitrectomy in patients with CNSL.[1,7] Currently, B-cell markers such as CD20, CD79a, and PAX5, along with a T-cell marker (CD3), are used in cytologic diagnosis.[10] In addition, Ki-67 staining is employed to detect the increased proliferation rate of malignant cells.[11] To increase the yield of lymphoma cells, undiluted vitreous can be obtained without infusion or under air. New modifications have been developed to improve cytological diagnostic rates. In a study that examined vitreous cell block (CB) specimens and compared them to histological specimens from enucleated eyes, both types of specimens tested positive for CD20.[12] Other markers, such as Bcl-6 and MUM-1, were also positive in some of both types of specimens, showing that CB specimens can be an additional tool to improve cytological diagnosis.[12] However, the sensitivity of CB analysis can vary from 23% to 93.3%.[3,12]

Immunological Diagnosis

Analyses of IL-10 and IL-6 are important for distinguishing VRL from uveitis. IL-10 is a B cell growth and differentiation factor, which is elevated in the blood of non-Hodgkin's lymphoma patients.[13] It is suggested that by secreting IL-10, lymphoma cells decrease the leakage of the blood-retinal barrier and prevent the immune system from recognizing them.[14] On the other hand, IL-6 is a pro-inflammatory cytokine that is secreted under inflammatory conditions.[10] IL-10 and IL-6 levels can be obtained from enzyme-linked immunosorbent assays or cytokine multiplex assays of vitreous samples. Studies show that an IL-10/IL-6 ratio >1.0 is highly suggestive of lymphoma, with a sensitivity ranging from 88% to 91.7%[7,15-17] In addition, an increased IL-10 level of more than 150 pg/mL supports the diagnosis of VRL.[18,19] IL-10 and IL-6 can also be obtained from aqueous humor, which is easier and safer to collect than the vitreous samples. The diagnostic threshold values for aqueous humor are IL-10/IL-6 >1.55 and IL-10 >76.7 pg/mL.[20] Furthermore, serial changes in the aqueous humor IL-10 level can be used to monitor disease progress.[21] Elevated IL-10 levels in the cerebrospinal fluids (CSFs) (with a cutoff value of 8.2 pg/ml) of VRL patients also shows high sensitivity (95.7%); however, baseline CSF IL-10 levels were not able to predict clinical outcomes.[22] One limitation of this analysis is that the ratio may not be interpreted in the same manner for patients with extensive and severe sub-RPE or retinal infiltration and those with T-cell VRL.[16] The sensitivity of this analysis ranges from 73% to 83%.[23,24] Recently, IL Score for IntraOcular Lymphoma Diagnosis (ISOLD) was proposed to estimate the probability of VRL from IL-10 and IL-6 levels with high sensitivity (93%) and specificity (95%) for both aqueous humor and vitreous samples.[13]

Flow Cytometry

Flow cytometry has shown superior sensitivities (60%–82.4%) to cytopathology in many studies.[24-27] It can be used to identify a clonal B-cell population, assess cell size and detect clonal expression of immunoglobulin kappa (IGK) or lambda (IGL) light chain surface antigens.[24] This technique can identify antigen patterns characteristic of certain lymphoma subtypes; however, definite subtyping is only available for a few entities that play a minor role in VRL.[28] Another limitation of flow cytometry is that it requires a significant number of viable lymphoma cells for analysis (10^5–10^6 cells).[24] Moreover, the absence of large lymphocytes on cytology is associated with negative flow cytometry results.[25] Therefore, the presence of only a few lymphoma cells, along with other inflammatory cells in the vitreous sample and the fragility of the lymphoma cells remain critical hurdle for this technique.[1]

Clonality Analysis

The determination of monoclonality by evaluating IGH and IGK rearrangements for B-cell lymphoma, and T-cell receptor (TCR) gene rearrangement for T-cell lymphoma, is a valuable diagnostic tool.[18] *CDR3* in the *IGH* gene and *TCR gamma* in the *TCR* gene are the most common sites of gene rearrangement.[29-33] Detection of clonal rearrangements in the *IGK* gene can improve clonality detection rates in B-cell lymphomas that are heavily somatically mutated.[34] PCR analysis yields multiple amplicons for polyclonal cells and a single amplicon for monoclonal and neoplastic cells.[1] Clonality analysis has multiple advantages over cytopathology; it is less subjective, has a rapid turnaround time, and requires a relatively lower number of cells compared to cytopathology or flow cytometry.[10] The sensitivity of this test ranges from 46% to 96%.[3,4,7,8,35,36] One limitation of this analysis is common false positives due to the low cellularity of lymphoma cells. Scanty cells can lead to a misinterpretation as pseudo-monoclonality instead of polyclonality for non-lymphomatous patients.[10]

MYD88 Mutation

MYD88 is an adaptor protein that links Toll-like receptors to critical downstream intracellular signaling pathways.[37] A gain-of-function mutation in *MYD88* leads to oncogenic cascades in DLBCLs.[38] In DLBCLs, 39% of tumor samples contained mutations in *MYD88*, and 29% of them were *MYD88* L265P.[39] In a different study, the frequencies of this mutation in immune-privileged

sites such as the CNS and testes were 60% and 77.1%, respectively.[40] This mutation was detected in the vitreous of more than 88% of VRL patients.[41,42] Studies have shown that this mutation can also be detected in the aqueous humor of VRL patients. Unlike vitreous, aqueous humor can easily be obtained by anterior chamber paracentesis. The sensitivity of the test can be as high as 67%–83%.[43,44] The *MYD88* mutation can be detected in 10 out of 21 (48%) eyes of VRL patients without anterior segment involvement.[45] In addition, detection of the *MYD88* mutation in aqueous humor can be useful for serial monitoring of the treatment response. *MYD88* mutation ceased to be detected in patients with clinical improvement who underwent multiple intravitreal methotrexate injections; however, it was redetected once the disease recurred.[38,46] *MYD88* mutations were also detected in CSF from VRL patients with a sensitivity of 63.2%.[22]

Next-generation Sequencing

Next-generation sequencing (NGS) is a precision medicine strategy that can be used to identify actionable genomic alterations in VRL. Vitreous samples from VRL patients can be sent to the laboratory for targeted panel sequencing or whole-exome sequencing. Institutions typically employ custom gene panels consisting of hundreds of candidate genes. Detected genetic variants are then classified into tiers based on their level of clinical significance in cancer diagnosis, prognosis, and/or therapeutics, following the standards and guidelines established by the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists.[23] In one study, out of 26 VRL patients, 22 showed significant mutations from vitreous NGS.[23] The most frequent mutations were *MYD88* (91%), *CDKN2A* (36%), *PIM1* (32%), *IGLL5* (27%), *ETV6* (23%), *BTG1* (18%), *KMT2D* (18%), and *SETD1B* (15%).[23] Another study that included 23 eyes showed that VRL-related mutated genes included *MYD88* (78%), *ETV6* (48%), *PIM1* (48%), *BTG2* (30%), *IRF4* (30%), *CD79B* (26%), and *LRP1B* (26%).[47] Some common trends can be observed in these results when compared with NGS data from CNSL. Previously reported mutation frequencies in CNSL include *MYD88* (40%–79%), *CD79B* (30%–44%), *CARD11* (11%–30%), *PIM1* (20%–44%), *TBL1XR1* (7%–23%), *BTG2* (22%–30%), *PRDM1* (7%–20%), and *TNFAIP3* (11%–20%).[48,49] Similarly, efforts have been made to use a multiplex gene panel for cell-free DNA with only four genes: *MYD88*, *CD79B*, *BTG2*, and *PIM1*.[50] Such a small panel is advantageous in terms of time and cost. The frequencies of *MYD88*, *CD79B*, *BTG2*, and *PIM1* mutations in 86 VRL cases were 64%, 47%, 38%, and 29%, respectively. At least one of these mutations was found in 97% of all cases.[50]

Single-cell Analysis

Single-cell analysis is a method that uses single-cell DNA or RNA sequencing to profile the transcriptome of individual cells, allowing for the unbiased characterization of mixed populations of cells and the identification of novel cellular populations. The analysis of tumor heterogeneity and the microenvironment using single-cell analysis has been applied to various solid and hematologic malignancies. Single-cell DNA sequencing of VRL, using a real-time imaging-based digital cell sorting system that utilizes dielectrophoresis to capture and isolate cells of interest, showed that analyses of clonality, copy number aberration, *BCL2/JH* t (14;18) translocation, and *MYD88* mutations can all be performed from single B-cells.[51] Although this study included only 7 VRL patients and 4 chronic inflammation patients, single-cell analysis was able to differentiate VRL from chronic inflammation by dominant *IGH* clonality and *MYD88* mutations. While copy number profiling revealed a high degree of similarity among B cells from the same patient, clustering analysis of the copy number profiles from different patients revealed no common genome-wide signatures.[51] Currently, such technology is available in specialized laboratories. As far as we know, single-cell RNA sequencing analysis of VRL has not yet been reported; however, previous single-cell studies on CNSL provide background knowledge that can be used to compare data from future single-cell RNA sequencing of VRL. Single-cell analysis of CSF from CNSL revealed active cell proliferation and energy metabolism properties, as well as heterogeneity in cell cycle state and cancer-testis antigen expression.[52] In a single-cell analysis of CNSL tissue, six main cell populations were identified, including B cells, T cells, macrophages, dendritic cells, oligodendrocytes, and meningeal cells.[53] Within the B cells, three subpopulations with different marker genes were clustered.

miRNA Analysis

miRNAs are small non-coding regulatory RNAs (18–25 nucleotides long) that bind to mRNAs to suppress gene translation or degrade mRNA.[54] At the same time, they can serve as biomarkers because they are located in tumor-related genomic regions or fragile sites.[55] Researchers have studied the diagnostic potential of miRNAs that are upregulated in the CSF of CNSL patients, including miR-92, miR-19b, and miR-21.[56] MiR-92 and miR-19b are members of polycistronic microRNA-17-92 cluster, which promotes lymphomagenesis. MiR-21 is overexpressed in most tumor types and acts as a key oncogene in B-lymphomagenesis.[57] One study showed that miR-92, miR-19b, and miR-21 were all upregulated in the vitreous samples of VRL patients compared to vitritis patients.[58] Another study reported that serum

miR-326 and miR-6513-3p expression levels in VRL patients were upregulated compared to those in uveitis patients with vitreous opacity or macular hole/epiretinal membrane patients, respectively.[59] In a different study, vitreous miR-155 was elevated in the uveitis patients compared to the VRL patients.[56] Interestingly, a negative correlation between miR-155 and IL-10 was found.[56] Overall, despite significant differences in the miRNA levels of VRL patients, the lack of consensus on specific miRNAs indicates that improvements, such as unifying the protocols for miRNA analysis, are needed for the clinical application of this technology.

Comparison of Sensitivities of Conventional Diagnostic Tests

Many studies have compared the sensitivities of conventional diagnostic tests [Table 1]. In a meta-analysis of 33 studies published between 2011 and 2021, the test with the lowest coefficient of variation and the highest sensitivity was the *MYD88* mutation analysis (sensitivity 74%).[24] A review of 29 retrospective studies showed slightly different results. While IL-10/IL-6 ratio >1 had the highest sensitivity (89.39%), the sensitivity for *MYD88* mutation was 70%, which was lower than the sensitivities of flow cytometry (88%) or IgH monoclonality (85.10%).[60] In another meta-analysis of 87 articles, the most sensitive diagnostic method was the IL-10/IL-6 ratio > 1 from both vitreous (sensitivity 93%) and aqueous humor (sensitivity 98%).[61] Similarly, other studies also showed that the IL-10/IL-6 ratio had higher sensitivity (82%) compared to flow cytometry (62%–63%) and IGH gene rearrangement (73%–77%).[3,4] However, sensitivity analysis of *MYD88* mutation was not included in these studies. The diagnostic test with the widest range of sensitivities was flow cytometry (50%–88%).[5,60] In a consensus recommendation from the members of the International Uveitis Study Group for the diagnosis of VRL, IL-10/IL-6 >1 and *MYD88* mutation analysis were most recommended, emphasizing the importance of these two molecular diagnostic tests among others.[16] Although the number of studies is still limited, many NGS analyses of vitreous have shown high sensitivity in general (85%–100%), demonstrating potential as a "next-generation" diagnostic test for VRL.[23,62,63] In summary, we recommend the following approach in diagnosing VRL for patients with negative tumor cytology. We suggest including IL-10, IL-6, and aqueous humor *MYD88* mutation tests in the diagnostic assay. Although IgH monoclonality and flow cytometry have been widely used, our review shows that IL-10/IL-6 > 1 and *MYD* 88 mutation generally exhibit higher sensitivity and specificity. Therefore, we suggest that patients with cytology-negative vitreous samples but a positive

Table 1: Reported sensitivities and specificities of molecular diagnostic tests for vitreoretinal lymphoma

Molecular tests	Study	Patients included (*n*)	Sensitivity (%)	Specificity (%)
IL-10/IL-6>1	Zhao *et al.*[61]	NA (7 studies)	93 (vitreous)/98 (aqueous humor)	NA
	Santos *et al.*[5]	117	91	NA
	Huang *et al.* (2023)[60]	311	89	NA
	Kwak *et al.*[23]	24	83	83
	Takase *et al.*[3]	102	82	100
	Tanaka *et al.*[4]	56	82	100
	Sehgal *et al.*[24]	239	73	NA
IgH monoclonality	Zhao *et al.*[61]	NA (22 studies)	92	NA
	Huang *et al.* (2023)[60]	416	85	NA
	Sehgal *et al.*[24]	246	80	NA
	Takase *et al.*[3]	91	77	93
	Santos *et al.*[5]	101	76	NA
	Tanaka *et al.*[4]	56	73	85
	Kwak *et al.*[23]	25	68	50
Flow cytometry	Huang *et al.* (2023)[60]	75	88	NA
	Zhao *et al.*[61]	NA (8 studies)	88	NA
	Sehgal *et al.*[24]	75	64	NA
	Tanaka *et al.*[4]	56	63	97
	Takase *et al.*[3]	73	62	96
	Santos *et al.*[5]	103	50	NA
MYD88 mutation	Sehgal *et al.*[24]	196	74	NA
	Huang *et al.* (2023)[60]	90	70	NA
	Kwak *et al.*[23]	15	67	83
NGS gene panel	Chen *et al.*[62]	17	100	67
	Bonzheim *et al.*[63]	31	100	100
	Kwak *et al.*[23]	26	85	83

IL=Interleukin, NGS=Next-generation sequencing, NA=Not available

IL-10/IL-6 >1 or *MYD88* mutation result should be managed as having VRL.

Molecular Profile of Vitreoretinal Lymphoma

DLBCL exhibits striking heterogeneity in gene expression profiles and clinical outcomes depending on the organ involved [Table 2]. This heterogeneity makes subclassification of DLBCL challenging. However, genomic profiling has allowed DLBCLs to be subclassified into germinal center B-cell (GCB) type and activated B-cell type (ABC).[72] The t (14;18)(q32;q21)/IGH-BCL2 translocation is more commonly detected in the GCB subtype, while NF-κB activation is found in the ABC subtype.[73] Although classified as a type of CNSL, VRL presents more challenges in classification. The t (14;18) translocation, more commonly detected in GCB subtypes, is frequently found in VRLs.[74] However, a recent gene expression profiling study of VRL showed a pattern closer to that of the ABC subtype.[64] *MYD88* L265P mutation, frequently detected in VRL and CNSL, is typically found in the ABC subtype.[75] The high prevalence (0%–94%) of the *MYD88* L265P mutation in VRL, CNSL, and testicular DLBCL suggests that this mutation is associated with the pathogenesis of DLBCL in immune-privileged organs.[40] Most *MYD88* mutations in VRL affect the toll-like receptor domain of MYD88, which is thought to lead to NF-κB and JAK-STAT3 signaling.[37]

Recent studies have proposed new genetic subtypes of DLBCL based on shared genomic abnormalities. These include six genetic subtypes referred to as MCD (co-occurrence of *MYD88* and *CD79B* mutations), BN2 (*BCL6* fusion and *NOTCH2* mutation), N1 (*NOTCH1* mutation) EZB (*EZH2* mutation and *BCL2* translocation), A53 (*TP53* mutation and deletion), and ST2 (*SGK1* and *TET2* mutations) subtypes [Figure 1].[76,77] The MCD and N1 subtypes are predominantly ABC subtypes and show poorer outcomes than other subtypes.[75] The frequencies of *MYD88* (78%–100%) and *CD79B* (14%–55%) mutations in VRL suggest that VRL closely resembles the MCD subtype.[23,47,63] The prevalence of the *MYD88* mutation appears to be higher in VRL compared to CNSL, whereas the *CD79B* mutation seems to have a stronger association with CNSL.[66] Reports indicate that VRL patients with the *CD79B* mutation are more likely to experience CNS involvement.[64,66] In *CD79B*, the first tyrosine mutation (Y196) is common in the Immunoreceptor Tyrosine-based Activation Motif (ITAM) domain. Mutation in the ITAM region is known to increase B-cell receptor (BCR) signaling activity, which may contribute to the development and progression of lymphomas.[78] Biallelic or monoallelic deletion of *CDKN2A*, a tumor suppressor gene, is found in 67%–100% of VRL cases.[63,66,67] *CDKN2A* is predominantly reported in

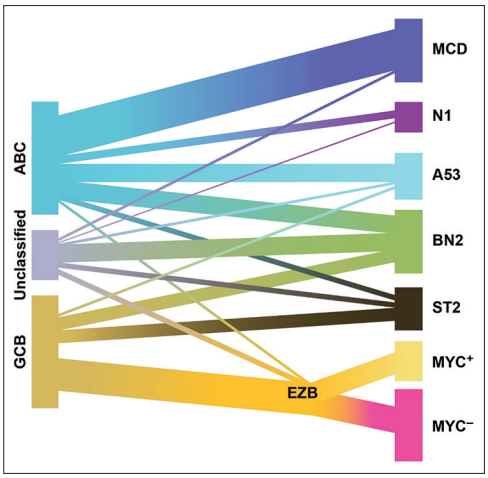

Figure 1: Genetic subtypes of diffuse large b-cell lymphoma based on gene expression profile. Genetic profile of VRL appears to be similar to that of MCD type with frequent *MYD88* and *CD79B* mutations. These findings were reproduced with permission, courtesy of Lee[77]

DLBCL with the ABC subtype.[79] Previous studies show that 44%–100% of VRL patients with *CDKN2A* mutation exhibit CNS involvement.[23,67,70] Other common mutations reported in VRL include *PIM1*,[42,63] *IGLL5*,[42,63] *BTG1*,[42] *BTG2*,[42] *TBL1XR1*,[43] *PTEN*,[67] *and ETV6*.[47] Mutation in *TBL1XR1* is known to impair plasma cell differentiation and bias cell fate toward immature memory B cells.[80] This alteration, in turn, gives rise to ABC-DLBCL derived from memory B cells.[80]

Clinical Presentation and Molecular Features

So far, there have been only a few studies on clinicogenetic association in VRLs. *CD79B* and *BTG2* mutations were associated with high relapse rates in VRL patients with CNS involvement, whereas the *MYD88* mutation was not.[50] Similar results were found in two studies. In an analysis of 17 VRL patients, six patients with *CD79B* mutations developed CNS disease significantly earlier (16.5 months) than 11 patients without the mutations (67 months; $P = 0.0135$).[69] In contrast, patients with the *MYD88* mutation did not show a difference in CNS lymphoma-free survival. In another study of six VRL patients, two patients with CNS progression had *CD79B* mutations, while those without CNS progression did not.[64] A study of cell-free DNA from 23 VRL patients revealed that the *BTG2* mutation was correlated with CNS involvement, while the *CD79B* mutation was correlated with a high initial intraocular IL-10 level. *CARD11* and *AXL* mutations were correlated with earlier ocular onset in CNSL patients.[47] There was no definite correlation of *MYD88*, *CD79B*, *ETV6*, or *PIM1* with progression-free survival. Large studies are needed to verify the effects of mutations on CNS progression in VRL patients.

Genetic studies on CNSL suggest future directions for how genetic analysis can help researchers understand and treat VRL, with or without CNS involvement. In an NGS study of 52 CNSL patients, mutations in *BTG1* and *ETV6*, along with major alterations at 6p21.3, were correlated with accelerated disease progression and an early tumor resistance phenotype.[81] Therapeutically, the Bruton's tyrosine kinase (BTK) inhibitors, such as tirabrutinib and ibrutinib,[82] target the proximal BCR kinase, BTK, which is involved in the pathogenesis of B-cell malignancies.[83] These inhibitors showed favorable responses in CNSL patients with *MYD88* and/or *CD79B* mutations.[43,83] A study of 85 CNSL patients treated with rituximab, high-dose methotrexate, procarbazine, and vincristine revealed that patients with a *CD79B* mutation exhibited prolonged survival, while those with a *MYD88* mutation showed no significant effect.[83] Interestingly, CNSL demonstrated distinct genetic and immunologic features based on Epstein–Barr virus (EBV) status.[82,84] EBV-negative CNSL showed a gene expression profile similar to ABC DLBCL, including mutations in *MYD88*, *CD79B*, and/or *PIM1*, as well as mutations or deletions in *HLA-A*, *HLA-B*, or *HLA-C*. Their phenotype was associated with constitutive NF-κB activation and chronic active B-cell receptor signaling. In contrast, *MYD88*, *CD79B*, and *PIM1* mutations were absent in

Table 2: Mutational profile in vitreoretinal lymphoma

Altered genes	Frequency (%)	Possible functions	References
MYD88	53.3–100	NF-kB pathway	Arai *et al.*,[64] Bonzheim *et al.*,[63,65] Raja *et al.*,[42] Lee *et al.*,[66] Pulido *et al.*,[14] Miserocchi *et al.*,[44] Hiemcke-Jiwa *et al.*,[43] Bonzheim *et al.*,[63] Cani *et al.*,[67] Kwak *et al.*,[23] Narasimhan *et al.*,[41] Demirci *et al.*,[38] Chen *et al.*,[62] Wang *et al.*,[68] Taoka *et al.*,[50] Gu *et al.*[47]
CD79B	14–55	NF-kB pathway	Arai *et al.*,[64] Lee *et al.*,[66] Bonzheim *et al.*,[63] Yonese *et al.*,[69] Kwak *et al.*,[23] Gu *et al.*,[47] Chen *et al.*,[62] Wang *et al.*[68]
IGLL5	27–88.9	B cell development	Lee *et al.*,[66] Bonzheim *et al.*,[63] Kwak *et al.*[23]
IRF4	9–60	B cell development	Gu *et al.*,[47] Kwak *et al.*,[23] Wang *et al.*,[68] Chen *et al.*[62]
PIM1	29–90.9	Serine/threonine kinase	Lee *et al.*,[66] Bonzheim *et al.*,[63] Kwak *et al.*,[23] Gu *et al.*,[47] Wang *et al.*,[68] Chen *et al.*,[62] Taoka *et al.*[50]
TBL1XR1	18.2–48	Transcription regulation	Bonzheim *et al.*,[63] Chen *et al.*[62]
ETV6	23–50	Transcription regulation	Choi *et al.*,[46] Kwak *et al.*,[23] Gu *et al.*,[47] Chen *et al.*,[62] Bonzheim *et al.*[63]
CDKN2A	36–100	Tumor suppressor	Lee *et al.*,[66] Bonzheim *et al.*,[63] Cani *et al.*,[67] Kwak *et al.*,[23] Wang *et al.*,[68] Balikov *et al.*,[70] Wang *et al.*[71]
BTG2	9–77.8	Tumor suppressor	Lee *et al.*,[66] Kwak *et al.*,[23] Gu *et al.*,[47] Chen *et al.*[62] Bonzheim *et al.*[63]
BTG1	18–55.6	Tumor suppressor	Lee *et al.*,[66] Kwak *et al.*,[23] Bonzheim *et al.*,[63] Gu *et al.*[47]
PTEN	25	Tumor suppressor	Cani *et al.*[67]

Table 3: Comparison of diagnostic tests for vitreoretinal lymphoma

Diagnostic test	Techniques	Advantages	Limitations
Cytopathology	Cytological examination, B-cell markers (CD20, CD79a, PAX5), T-cell marker (CD3), Ki-67 staining	Gold standard, can use undiluted vitreous to increase yield	Variable diagnostic rates (23%–93.3%), subject to subjective interpretation, fragile lymphoma cells
Immunology	IL-10 and IL-6 analysis (ELISA, cytokine multiplex assays)	High sensitivity (88%–91.7%), easier sample collection (aqueous humor), serial monitoring of disease	May not be applicable to patients with extensive retinal infiltration, sensitivity varies
Flow cytometry	Identifies clonal B cell population, assesses cell size and immunoglobulin light chain expression	Higher sensitivity (60%–82.4%) than cytopathology, detects antigen patterns characteristic of lymphoma	Requires significant number of viable cells (10^5–10^6), may yield false negatives if few lymphoma cells are present
Clonality analysis	IGH and IGK rearrangement analysis for B cell lymphoma, TCR gene rearrangement for T cell lymphoma	Less subjective, rapid turnaround, lower cell requirement	False positives due to low cellularity, may misinterpret scanty cells as pseudo-monoclonality
MYD88 mutation	Detection of MYD88 L265P mutation	High sensitivity (67%–83%), useful for serial monitoring, applicable to aqueous humor and CSF	Requires mutation detection infrastructure
NGS	Targeted panel sequencing, whole-exome sequencing	Identifies actionable genomic alterations, high sensitivity (e.g., MYD88 mutation in 91% of cases)	High cost, requires specialized lab facilities, limited by panel selection
Single cell analysis	Single-cell DNA or RNA sequencing	Profiles transcriptome of individual cells, distinguishes VRL from chronic inflammation	High cost, specialized technology, currently limited application to VRL
Micro RNA analysis	miRNA profiling from vitreous, serum, or CSF samples	Can identify specific miRNA upregulation in VRL, potential noninvasive biomarker	Lack of consensus on miRNA markers, need for standardized protocols

ELISA=Enzyme-linked immunosorbent assay, IGH=Immunoglobulin heavy chain, IGK=Immunoglobulin light chain, NGS=Next-generation sequencing, VRL=Vitreoretinal lymphoma, CSF=Cerebrospinal fluids, miRNA=Micro-RNA, IL=Interleukin, TCR=T-cell receptor

all EBV-associated CNSL patients, who are generally immunosuppressed and have a more dismal outcome. EBV-associated CNSL showed preservation of HLA class I or II, indicating preserved antigen processing function despite the patients' immunocompromised state.[82,84] Genetic classification of VRL and CNSL would help researchers understand molecular heterogeneity and provide a framework for targeted treatment.

Conclusion

A summary table comparing diagnostic tests for VRL is shown in Table 3. The molecular diagnosis of VRL has advanced considerably through the use of innovative genetic profiling and diagnostic tools. The identification of frequent mutations, such as those in *MYD88* and *CD79B*, has significantly enhanced the specificity and sensitivity of diagnostic procedures, allowing for more precise therapeutic interventions. Moreover, the use of NGS and liquid biopsies from vitreous samples has emerged as a pivotal development, expanding our understanding and management of VRL. These molecular insights not only deepen our understanding of the pathogenesis of VRL but also pave the way for the development of targeted therapeutic strategies, potentially improving patient outcomes in a condition that frequently presents complex clinical challenges.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

References

1. Melli B, Gentile P, Nicoli D, Farnetti E, Croci S, Gozzi F, *et al.* Primary vitreoretinal lymphoma: Current diagnostic laboratory tests and new emerging molecular tools. Curr Oncol 2022;29:6908-21.
2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB, Berti E, *et al.* The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-48.
3. Takase H, Arai A, Iwasaki Y, Imai A, Nagao T, Kawagishi M, *et al.* Challenges in the diagnosis and management of vitreoretinal lymphoma – Clinical and basic approaches. Prog Retin Eye Res 2022;90:101053.
4. Tanaka R, Kaburaki T, Taoka K, Karakawa A, Tsuji H, Nishikawa M, *et al.* More Accurate diagnosis of vitreoretinal lymphoma using a combination of diagnostic test results: A prospective observational study. Ocul Immunol Inflamm 2022;30:1354-60.
5. Santos MC, Jiang A, Li AS, Rao PK, Wilson B, Harocopos GJ. Vitreoretinal lymphoma: Optimizing diagnostic yield and accuracy. Am J Ophthalmol 2022;236:120-9.
6. Davis JL. Intraocular lymphoma: A clinical perspective. Eye (Lond) 2013;27:153-62.
7. Kimura K, Usui Y, Goto H, Japanese Intraocular Lymphoma Study Group. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. Jpn J Ophthalmol 2012;56:383-9.
8. Sugita S, Takase H, Sugamoto Y, Arai A, Miura O, Mochizuki M. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol 2009;53:209-14.
9. Raparia K, Chang CC, Chévez-Barrios P. Intraocular lymphoma: Diagnostic approach and immunophenotypic findings in vitrectomy specimens. Arch Pathol Lab Med 2009;133:1233-7.
10. Tan WJ, Wang MM, Ricciardi-Castagnoli P, Chan AS, Lim TS. Cytologic and molecular diagnostics for vitreoretinal lymphoma: Current approaches and emerging single-cell analyses. Front Mol Biosci 2020;7:611017.
11. Fend F, Ferreri AJ, Coupland SE. How we diagnose and treat vitreoretinal lymphoma. Br J Haematol 2016;173:680-92.
12. Kase S, Namba K, Kanno-Okada H, Onozawa M, Hidaka D, Iwata D, *et al.* Immunohistochemical and immunocytochemical analyses in patients with vitreoretinal lymphoma. Ocul Immunol Inflamm 2020;28:147-55.
13. Kuo DE, Wei MM, Knickelbein JE, Armbrust KR, Yeung IY, Lee AY, *et al.* Logistic regression classification of primary vitreoretinal lymphoma versus uveitis by interleukin 6 and interleukin 10 levels. Ophthalmology 2020;127:956-62.
14. Pulido JS, Johnston PB, Nowakowski GS, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: A review. Int J Retina Vitreous 2018;4:18.
15. Costopoulos M, Touitou V, Golmard JL, Darugar A, Fisson S, Bonnemye P, *et al.* ISOLD: A new highly sensitive interleukin score for intraocular lymphoma diagnosis. Ophthalmology 2016;123:1626-8.
16. Carbonell D, Mahajan S, Chee SP, Sobolewska B, Agrawal R, Bülow T, *et al.* Consensus recommendations for the diagnosis of vitreoretinal lymphoma. Ocul Immunol Inflamm 2021;29:507-20.
17. Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, *et al.* Primary vitreoretinal lymphoma: A report from an international primary central nervous system lymphoma collaborative group symposium. Oncologist 2011;16:1589-99.
18. Lee J, Kim SW, Kim H, Lee CS, Kim M, Lee SC. Differential diagnosis for vitreoretinal lymphoma with vitreoretinal findings, immunoglobulin clonality tests, and interleukin levels. Retina 2019;39:1165-76.
19. Cassoux N, Merle-Beral H, Lehoang P, Herbort C, Chan CC. Interleukin-10 and intraocular-central nervous system lymphoma. Ophthalmology 2001;108:426-7.
20. Kang H, Tao Y. Clinical utility of cytokine analysis in the diagnosis and efficacy monitoring of vitreoretinal lymphoma. Int J Ophthalmol 2022;15:1893-902.
21. Park YG, Park WK, Kim RY, Kim M, Park YH. Serial changes in the aqueous IL-10 level after intravitreal methotrexate injection as an indicator of primary vitreoretinal lymphoma recurrence.

Sci Rep 2020;10:15992.
22. Zhuang Z, Zhang Y, Zhang X, Zhang M, Zou D, Zhang L, *et al.* Circulating cell-free DNA and IL-10 from cerebrospinal fluids aid primary vitreoretinal lymphoma diagnosis. Front Oncol 2022;12:955080.
23. Kwak JJ, Lee KS, Lee J, Kim YJ, Choi EY, Byeon SH, *et al.* Next-generation sequencing of vitreoretinal lymphoma by vitreous liquid biopsy: Diagnostic potential and genotype/phenotype correlation. Invest Ophthalmol Vis Sci 2023;64:27.
24. Sehgal A, Pulido JS, Mashayekhi A, Milman T, Deák GG. Diagnosing vitreoretinal lymphomas-an analysis of the sensitivity of existing tools. Cancers (Basel) 2022;14:598.
25. Cantu CA, Green CL, Cummings TJ, Liu B, Dash RC. Flow cytometry immunophenotyping of vitreous specimens does not contribute to diagnosis of lymphoma without supporting morphologic features. Diagn Cytopathol 2019;47:275-81.
26. Davis JL, Viciana AL, Ruiz P. Diagnosis of intraocular lymphoma by flow cytometry. Am J Ophthalmol 1997;124:362-72.
27. Missotten T, Tielemans D, Bromberg JE, van Hagen PM, van Lochem EG, van Dongen JJ, *et al.* Multicolor flowcytometric immunophenotyping is a valuable tool for detection of intraocular lymphoma. Ophthalmology 2013;120:991-6.
28. Shumilov E, Mazzeo P, Zinkernagel MS, Legros M, Porret N, Romagna L, *et al.* Comprehensive laboratory diagnostic workup for patients with suspected intraocular lymphoma including flow cytometry, molecular genetics and cytopathology. Curr Oncol 2022;29:766-76.
29. Tuaillon N, Chan CC. Molecular analysis of primary central nervous system and primary intraocular lymphomas. Curr Mol Med 2001;1:259-72.
30. Allam A, Kabelitz D. TCR trans-rearrangements: Biological significance in antigen recognition versus the role as lymphoma biomarker. J Immunol 2006;176:5707-12.
31. Coupland SE, Anastassiou G, Bornfeld N, Hummel M, Stein H. Primary intraocular lymphoma of T-cell type: Report of a case and review of the literature. Graefes Arch Clin Exp Ophthalmol 2005;243:189-97.
32. Chan CC. Molecular pathology of primary intraocular lymphoma. Trans Am Ophthalmol Soc 2003;101:275-92.
33. Wang Y, Shen D, Wang VM, Sen HN, Chan CC. Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. Int J Mol Sci 2011;12:5684-97.
34. Kokovic I, Jezersek Novakovic B, Novakovic S. Diagnostic value of immunoglobulin κ light chain gene rearrangement analysis in B-cell lymphomas. Int J Oncol 2015;46:953-62.
35. Baehring JM, Androudi S, Longtine JJ, Betensky RA, Sklar J, Foster CS, *et al.* Analysis of clonal immunoglobulin heavy chain rearrangements in ocular lymphoma. Cancer 2005;104:591-7.
36. Frenkel S, Pe'er J, Kaufman R, Maly B, Habot-Wilner Z. The importance of cytokines analysis in the diagnosis of vitreoretinal lymphoma. Acta Ophthalmol 2020;98:e668-73.
37. Jeelall YS, Horikawa K. Oncogenic MYD88 mutation drives Toll pathway to lymphoma. Immunol Cell Biol 2011;89:659-60.
38. Demirci H, Rao RC, Elner VM, Demirci FY, Axenov L, Betz B, *et al.* Aqueous humor-derived MYD88 L265P mutation analysis in vitreoretinal lymphoma: A potential less invasive method for diagnosis and treatment response assessment. Ophthalmol Retina 2023;7:189-95.
39. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, *et al.* Oncogenically active MYD88 mutations in human lymphoma. Nature 2011;470:115-9.
40. Lee JH, Jeong H, Choi JW, Oh H, Kim YS. Clinicopathologic significance of MYD88 L265P mutation in diffuse large B-cell lymphoma: A meta-analysis. Sci Rep 2017;7:1785.
41. Narasimhan S, Joshi M, Parameswaran S, Rishi P, Khetan V, Ganesan S, *et al.* MYD88 L265P mutation in intraocular lymphoma: A potential diagnostic marker. Indian J Ophthalmol 2020;68:2160-5.
42. Raja H, Salomão DR, Viswanatha DS, Pulido JS. Prevalence of myd88 l265p mutation in histologically proven, diffuse large B-cell vitreoretinal lymphoma. Retina 2016;36:624-8.
43. Hiemcke-Jiwa LS, Ten Dam-van Loon NH, Leguit RJ, Nierkens S, Ossewaarde-van Norel J, de Boer JH, *et al.* Potential diagnosis of vitreoretinal lymphoma by detection of myd88 mutation in aqueous humor with ultrasensitive droplet digital polymerase chain reaction. JAMA Ophthalmol 2018;136:1098-104.
44. Miserocchi E, Ferreri AJ, Giuffrè C, Cangi MG, Francaviglia I, Calimeri T, *et al.* MYD88 L265P mutation detection in the aqueous humor of patients with vitreoretinal lymphoma. Retina 2019;39:679-84.
45. Marchese A, Di Biase C, Cicinelli MV, Menean M, Ferrari G, Bandello F, *et al.* Anterior segment involvement in vitreoretinal lymphoma: Clinical manifestations, molecular findings and *in vivo* confocal microscopy. Br J Ophthalmol 2024;108:1168-71.
46. Choi S, Shin S, Lee ST, Lee J, Lee JS, Kim B, *et al.* Serial detection of MYD88 L265P mutation in the aqueous humor of a patient with vitreoretinal lymphoma for disease monitoring. Ocul Immunol Inflamm 2021;29:485-9.
47. Gu J, Jiang T, Liu S, Ping B, Li R, Chen W, *et al.* Cell-Free DNA sequencing of intraocular fluid as liquid biopsy in the diagnosis of vitreoretinal lymphoma. Front Oncol 2022;12:932674.
48. Yamada S, Ishida Y, Matsuno A, Yamazaki K. Primary diffuse large B-cell lymphomas of central nervous system exhibit remarkably high prevalence of oncogenic MYD88 and CD79B mutations. Leuk Lymphoma 2015;56:2141-5.
49. Braggio E, Van Wier S, Ojha J, McPhail E, Asmann YW, Egan J, *et al.* Genome-wide analysis uncovers novel recurrent alterations in primary central nervous system lymphomas. Clin Cancer Res 2015;21:3986-94.
50. Taoka K, Shimura-Nukina A, Honda A, Masamoto Y, Kurokawa M. Gene panels for intraocular lymphoma can overcome diagnostic difficulties and enable precision medicine. Blood 2023;142:5030.
51. Tan WJ, Wang MM, Castagnoli PR, Tang T, Chan AS, Lim TS. Single B-cell genomic analyses differentiate vitreoretinal lymphoma from chronic inflammation. Ophthalmology 2021;128:1079-90.
52. Ruan H, Wang Z, Zhai Y, Xu Y, Pi L, Zheng J, *et al.* Single-cell transcriptome analysis of diffuse large B cells in cerebrospinal fluid of central nervous system lymphoma. iScience 2021;24:102972.
53. Wei B, Liu Z, Fan Y, Wang S, Dong C, Rao W, *et al.* Analysis of cellular heterogeneity in immune microenvironment of primary central nervous system lymphoma by single-cell sequencing. Front Oncol 2021;11:683007.
54. Liu J. Control of protein synthesis and mRNA degradation by microRNAs. Curr Opin Cell Biol 2008;20:214-21.
55. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, *et al.* Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A 2004;101:2999-3004.
56. Tuo J, Shen D, Yang HH, Chan CC. Distinct microRNA-155 expression in the vitreous of patients with primary vitreoretinal lymphoma and uveitis. Am J Ophthalmol 2014;157:728-34.
57. Baraniskin A, Kuhnhenn J, Schlegel U, Schmiegel W, Hahn S, Schroers R. MicroRNAs in cerebrospinal fluid as biomarker for disease course monitoring in primary central nervous system lymphoma. J Neurooncol 2012;109:239-44.
58. Kakkassery V, Schroers R, Coupland SE, Wunderlich MI, Schargus M, Heinz C, *et al.* Vitreous microRNA levels as diagnostic biomarkers for vitreoretinal lymphoma. Blood 2017;129:3130-3.
59. Minezaki T, Usui Y, Asakage M, Takanashi M, Shimizu H,

Nezu N, *et al.* High-throughput microrna profiling of vitreoretinal lymphoma: Vitreous and serum MicroRNA Profiles Distinct from Uveitis. J Clin Med 2020;9:1844.
60. Huang RS, Mihalache A, Popovic MM, Cruz-Pimentel M, Pandya BU, Muni RH, *et al.* Diagnostic methods for primary vitreoretinal lymphoma: A systematic review. Surv Ophthalmol 2024;69:456-64.
61. Zhao XY, Cheng TT, Meng LH, Zhang WF, Chen YX. Clinical features, diagnosis, management and prognosis of primary intraocular lymphoma. Front Oncol 2022;12:808511.
62. Chen X, Hu Y, Su W, Yang S, Wang X, Zhang P, *et al.* diagnostic value of genetic mutation analysis and mutation profiling of cell-free DNA in intraocular fluid for vitreoretinal lymphoma. Cancer Commun (Lond) 2022;42:1217-21.
63. Bonzheim I, Sander P, Salmerón-Villalobos J, Süsskind D, Szurman P, Gekeler F, *et al.* The molecular hallmarks of primary and secondary vitreoretinal lymphoma. Blood Adv 2022;6:1598-607.
64. Arai A, Takase H, Yoshimori M, Yamamoto K, Mochizuki M, Miura O. Gene expression profiling of primary vitreoretinal lymphoma. Cancer Sci 2020;111:1417-21.
65. Bonzheim I, Giese S, Deuter C, Süsskind D, Zierhut M, Waizel M, *et al.* High frequency of MYD88 mutations in vitreoretinal B-cell lymphoma: A valuable tool to improve diagnostic yield of vitreous aspirates. Blood 2015;126:76-9.
66. Lee J, Kim B, Lee H, Park H, Ho Byeon S, Choi JR, *et al.* Whole exome sequencing identifies mutational signatures of vitreoretinal lymphoma. Haematologica 2020;105:e458-60.
67. Cani AK, Hovelson DH, Demirci H, Johnson MW, Tomlins SA, Rao RC. Next generation sequencing of vitreoretinal lymphomas from small-volume intraocular liquid biopsies: New routes to targeted therapies. Oncotarget 2017;8:7989-98.
68. Wang X, Su W, Gao Y, Feng Y, Wang X, Chen X, *et al.* A pilot study of the use of dynamic analysis of cell-free DNA from aqueous humor and vitreous fluid for the diagnosis and treatment monitoring of vitreoretinal lymphomas. Haematologica 2022;107:2154-62.
69. Yonese I, Takase H, Yoshimori M, Onozawa E, Tsuzura A, Miki T, *et al.* CD79B mutations in primary vitreoretinal lymphoma: Diagnostic and prognostic potential. Eur J Haematol 2019;102:191-6.
70. Balikov DA, Hu K, Liu CJ, Betz BL, Chinnaiyan AM, Devisetty LV, *et al.* Comparative molecular analysis of primary central nervous system lymphomas and matched vitreoretinal lymphomas by vitreous liquid biopsy. Int J Mol Sci 2021;22:9992.
71. Wang L, Sato-Otsubo A, Sugita S, Takase H, Mochizuki M, Usui Y, *et al.* High-resolution genomic copy number profiling of primary intraocular lymphoma by single nucleotide polymorphism microarrays. Cancer Sci 2014;105:592-9.
72. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
73. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. Pathology 2018;50:74-87.
74. Wallace DJ, Shen D, Reed GF, Miyanaga M, Mochizuki M, Sen HN, *et al.* Detection of the bcl-2 t (14;18) translocation and proto-oncogene expression in primary intraocular lymphoma. Invest Ophthalmol Vis Sci 2006;47:2750-6.
75. Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ, *et al.* Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med 2018;378:1396-407.
76. Wright GW, Huang DW, Phelan JD, Coulibaly ZA, Roulland S, Young RM, *et al.* A Probabilistic classification tool for genetic subtypes of diffuse large B Cell lymphoma with therapeutic implications. Cancer Cell 2020;37:551-68.e14.
77. Lee CS. Mutational profile of ocular lymphoma. In: Raval VR, Mruthyunjaya P, Singh AD, editors. Ocular and Adnexal Lymphoma. Cham: Springer International Publishing; 2023. p. 23-9.
78. Flümann R, Hansen J, Meinel J, Pfeiffer P, Goldfarb Wittkopf H, Lütz A, *et al.* An inducible Cd79b mutation confers ibrutinib sensitivity in mouse models of Myd88-driven diffuse large B-cell lymphoma. Blood Adv 2024;8:1063-74.
79. Schneider C, Pasqualucci L, Dalla-Favera R. Molecular pathogenesis of diffuse large B-cell lymphoma. Semin Diagn Pathol 2011;28:167-77.
80. Venturutti L, Teater M, Zhai A, Chadburn A, Babiker L, Kim D, *et al.* TBL1XR1 mutations drive extranodal lymphoma by inducing a Pro-tumorigenic memory fate. Cell 2020;182:297-316.e27.
81. Mo SS, Geng H, Cerejo M, Wen KW, Solomon DA, Rubenstein JL. Next-generation sequencing of newly-diagnosed primary CNS lymphoma reveals alterations in BTG1, ETV6, and 6p are associated with chemoresistance and inferior progression-free Survival. Blood 2022;140:3516-7.
82. Roschewski M, Phelan JD. Sorting biologic subtypes of primary CNS lymphoma. Blood 2021;137:1436-7.
83. Yamaguchi J, Ohka F, Lushun C, Motomura K, Aoki K, Takeuchi K, *et al.* CD79B Y196 mutation is a potent predictive marker for favorable response to R-MPV in primary central nervous system lymphoma. Cancer Med 2023;12:7116-26.
84. Gandhi MK, Hoang T, Law SC, Brosda S, O'Rourke K, Tobin JW, *et al.* EBV-associated primary CNS lymphoma occurring after immunosuppression is a distinct immunobiological entity. Blood 2021;137:1468-77.