# Mutational Profile of Ocular Lymphoma

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## Introduction

Classification system of lymphoma has evolved with heated debates since Thomas Hodgkin first described lymphomas in 1832 [1]. Worldwide consensus has only been made in the last two decades or so when the International Lymphoma Study Group published REAL classification in 1994 [2], which has led to the development of modern WHO classification in 2001 [3]. A multiparameter approach is used in the current consensus classification, which takes into account all available information including clinical features, morphology, immunophenotype, and genetics. The relative importance of each feature differs according to the disease, but genetic abnormalities are gaining importance in disease definition, thanks to recent progress in our understanding of lymphoma genetics. In the following chapter, the genetic abnormalities and molecular profiles of ocular lymphomas will be reviewed.

## Definition of Ocular Lymphoma

Ocular lymphomas can be divided into intraocular lymphomas involving vitreous, retina, and uvea, and ocular adnexal lymphomas involving orbit, conjunctiva, lacrimal gland, and eyelid. The most common type of intraocular lymphomas is the vitreoretinal lymphoma, usually diffuse large B-cell lymphoma (DLBCL) of high-grade malignancy with frequent involvement of the central nervous system (CNS) [4]. PCNSL-O is the preferred term to emphasize that it is an ocular variant or subset of primary CNS lymphoma (PCNSL). Uveal lymphoma is an extremely rare type of intraocular lymphomas and is usually extranodal marginal zone B-cell lymphoma (EMZL) of low-grade malignancy [5]. EMZL is also the most common subtype of ocular adnexal lymphomas, accounting for about two-third of cases [6].

## Mutational Profile of Intraocular Lymphoma

PCNSL-O is considered a variant of primary CNS lymphoma. PCNSL-O is the preferred term to emphasize that it is an ocular variant or subset of primary CNS lymphoma (PCNSL). About 50–80% of PCNSL-O patients develop CNS disease within several years [7, 8]. Conversely, about 15–25% of primary CNS lymphoma

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patients show ocular involvement at the time of diagnosis and about 25% without ocular involvement will eventually develop PCNSL-O [4, 8, 9]. Once CNS is involved, the disease is highly fatal. PCNSL-O is an important cause of masquerade syndrome, as it frequently masquerades as intermediate or posterior uveitis, representing about 2% of all uveitis [10].

The diagnosis of PCNSL-O can be confirmed by cytologic confirmation of malignant lymphoma cells in the vitreous body specimens [11]. However, cytologic examination suffers from low sensitivity due to limited number of tumor cells, mishandling of samples, cytolytic effects of preceding corticosteroid treatment due to misdiagnosis as uveitis, and rapid degeneration of lymphoma cells [11, 12]. Other diagnostic tools including immunophenotyping, gene rearrangement study identifying monoclonality of cells, and cytokine ratio (IL10:IL6 > 1) have been developed, but confirmation of PCNSL-O remains still challenging [4, 11, 13].

Although rare cases of peripheral T-cell involving retina/vitreous have been described [14, 15], nearly all PCNSL-O cases are DLBCL [7, 16]. DLBCL is the most common type of B-cell non-Hodgkin lymphoma worldwide [17], but its extreme heterogeneity in histopathology, immunophenotype, and clinical course under current therapy makes it difficult to classify DLBCL into distinct subtypes. A major advancement in classifying heterogeneous DLBCL was the application of GEP, which remains "the gold standard" for identifying DLBCL subtypes at the current time. The most popular system divides DLBCL into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes based on cell-of-origin [18]. GCB subtypes are thought to arise from normal germinal center B cells, expressing genes that are hallmarks of normal germinal center B cells [18–20]. In contrast, ABC subtypes are thought to arise from post-germinal center B cells, as they lack expression of germinal center B cell-restricted genes, but instead express genes that are induced during mitogenic stimulation of B cells [18–20]. GCB subtypes usually show better prognosis than ABC subtypes. GCB versus ABC model also shows biological relevance; t(14;18)(q32;q21)/*IGH-BCL2* usually occurs in GCB subtypes, while NF-κB activation is more prominent in ABC subtypes [21]. A third subgroup, primary mediastinal B-cell lymphoma (PMBL), has recently been defined by GEP that seemed to arise from thymic B cells [19, 22].

Whether PCNSL-O belongs to GCB or ABC subtypes has been controversial. Frequent findings of t(14;18) in PCNSL-O suggest that PCNSL-O cells originate from GCB with high BCL2 expression [23]. Recent GEP study showed that an expression pattern of PCNSL-O was relatively closer to the GCB subtype than to the ABC subtype [24]. By contrast, $MYD88^{L265P}$ mutation that is frequently seen in PCNSL-O/CNS lymphoma [24–28] is more commonly associated with ABC subtypes than GCB subtypes [18, 29, 30]. The prevalence of $MYD88^{L265P}$ mutation ranges from 0% to 94% in different series of DLBCL patients [30]. It is by far more prevalent in vitreoretinal, CNS, and testicular DLBCL than DLBCL of other locations, suggesting that $MYD88^{L265P}$ is associated with an immune-privileged anatomical compartment [30]. $MYD88^{L265P}$ mutation is detected in the vitreous of 69–87% of PCNSL-O patients [25, 27, 28, 31]. $MYD88^{L265P}$ mutation can also be detected in aqueous humor in minimally invasive manner [32, 33], making it a useful tool for diagnosis and monitoring of disease activity through serial detection of aqueous $MYD88^{L265P}$ mutation [34]. Virtually all mutations in MYD88 including L265P occur in Toll-like receptor (TLR) domain in PCNSL-O [28], which recruit MYD88 protein to the cytoplasmic tail of TLRs to form an active complex that promotes NF-κB and JAK-STAT3 signaling [35].

More recent studies have proposed new genetic subtypes based on shared genomic abnormalities, rather than cell-of-origin. Schmitz and colleagues identified four genetic subtypes that are referred to as MCD (co-occurrence of MYD88 and CD79B mutations), BN2 (BCL6 fusions and NOTCH2 mutation), N1 (NOTCH1 mutations), and EZB (EZH2 mutations and BCL2 translations) [29]. MCD and N1 subtypes were predominantly ABC subtypes and showed poorer outcomes than BN2 and EZB [29]. The

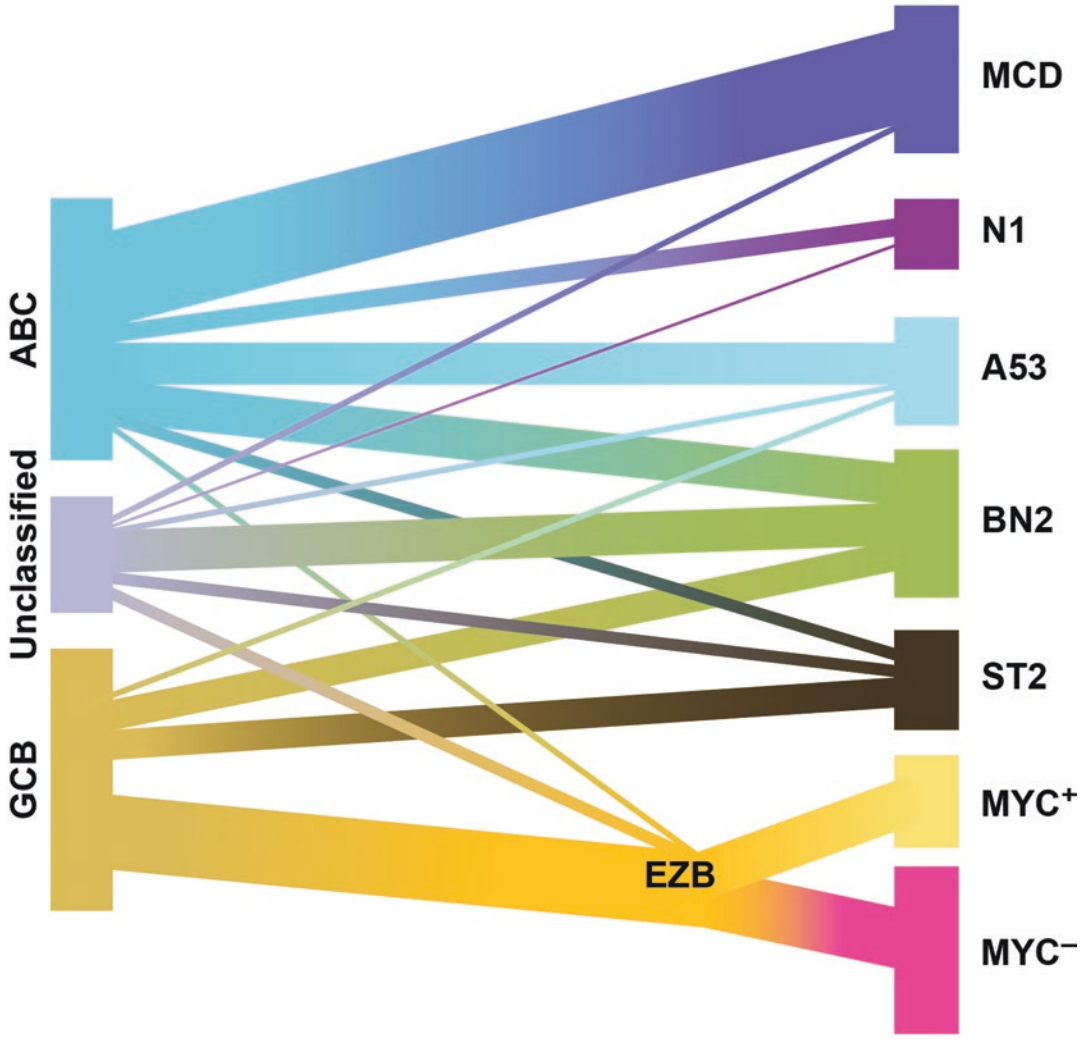


**Fig. 4.1** Genetic subtypes of diffuse large B-cell lymphoma based on gene expression profile (modified from source: Cancer Cell *37*, 551–568, April 13, 2020). Genetic profile of PCNSL-O appears to be similar to that of MCD type with frequent *MYD88* and *CD79B* mutations

same group recently added A53 (TP53 mutations and deletions) and ST2 (SGK1 and TET2 mutated) subtypes to the previous ones [36] (Fig. 4.1). A recent whole exome sequencing (WES) study found mutations of MYD88 and CD79B in 100% and 22.2% of PCNSL-O patients, respectively, and the mutational profile was in general similar to that of MCD subtype [28]. Similarly, a recent targeted next generation sequencing study also found high frequency of MYD88 (74%) and CD79B (55%) mutations and similar mutational spectrum to MCD subtype [37]. Other frequently mutated genes include PIM1, IGLL5, BTG1, BTG2, TBL1XR1, ETV6 [28, 37] (Table 4.1). MYD88 mutation appears to be more commonly found in PCNSL-O than CNS lymphoma, while CD79B mutation may be more commonly associated with CNS lymphoma [28]. Interestingly, CD79B mutation appears to be associated with early CNS progression in PCNSL-O patients [24, 39]. CD79B mutations frequently occur in the first tyrosine residue of immunoreceptor tyrosine-based activation motifs (ITAMs) domain (Y196), which cause active

**Table 4.1** Mutational profile in vitreoretinal lymphoma

| Altered genes | Frequency (%) | Possible functions | References |
|---|---|---|---|
| MYD88 | 57.1–100 | NF-κB pathway | [24, 25, 27, 28, 31–33, 37, 38] |
| CD79B | 22.2–55 | NF-κB pathway | [24, 28, 37, 39] |
| IGLL5 | 52–88.9 | B-cell development | [28, 37] |
| PIM1 | 71–88.9 | Serine/threonine kinase | [28, 37] |
| TBL1XR1 | 48 | Transcription regulation | [34] |
| ETV6 | 45 | Transcription regulation | [34] |
| CDKN2A | 66.7–100 | Tumor suppressor | [28, 37, 38] |
| BTG2 | 77.8 | Tumor suppressor | [28] |
| BTG1 | 55.6 | Tumor suppressor | [28] |
| PTEN | 25 | Tumor suppressor | [38] |

B-cell receptor signaling and NF-κB activation [39]. Biallelic or monoallelic deletion of the tumor suppressor CDKN2A is also a frequent finding in PCNSL-O ranging from 66.7% to 100% [28, 37, 38].

Primary uveal lymphomas are typically EMZL [5]. The genotype or mutational profile has not been studied much due to rarity of the disease, but their morphological and immunophenotypical features seem to be similar to EMZL of other locations [40]. Chromosomal translocation t(11;18)(q21;1q21) (BIRC3/MALT1) has been observed in one study [40].

## Mutational Profile of Ocular Adnexal Lymphoma

EMZL is the most common subtype of ocular adnexal lymphoma [6]. When involving an overlying epithelium such as the conjunctiva or acini of the lacrimal gland, the term "mucosa-associated lymphatic tissue (MALT)" lymphomas are often used instead. But many studies also use the term MALT lymphomas for diseases involving orbital compartment where no epithelium is present. In this chapter, the term EMZL will be used, which would be a more accurate term referring to lymphomas arising in all parts of ocular adnexa. Follicular lymphoma (10–15%), DLBCL (8–13%), and rare mantle cell lymphoma (1–5%) constitute the rest [6, 41]. EMZL and follicular lymphoma generally show better prognosis than DLBCL and mantle cell lymphoma.

Ocular adnexal MALT lymphomas derive from post-germinal center B cells [41]. Chronic infections by *Chlamydia psittaci* have been linked to the pathogenesis of ocular adnexal MALT lymphomas in some geographical regions [42]. Various chromosomal translocations including (1;14)(p22;q32)(BCL10/IgH), t(14;18)(q32;p21)(IgH/MALT1), t(11;18)(q21;1q21)(BIRC3/MALT1), and t(3;14)(p14;q32)(FOXP1/IgH) are frequently seen in EMZL of other locations including lung and stomach, but they are rarely or not detected in ocular adnexal EMZL [43, 44]. In contrast, mutation or deletion in TNFAIP3, a NF-κB negative regulator, is frequently seen in ocular adnexal EMZL, but not commonly seen in EMZL of other sites [43–45]. Constitute activation of NF-κB signaling pathway is a hallmark finding of ocular adnexal EMZL and TNFAIP3 appears to be the major driver gene in terms of frequency and known functional aspects [43, 44, 46, 47]. Mutations of TNFAIP3, along with other frequently mutated genes involved in NF-κB pathway including, MYD88, BCL10, and CD79B may be collectively involved in oncogenesis of ocular adnexal EMZL via NF-κB signaling pathway [43, 48]. Other frequently mutated genes by whole exome or whole genome sequencing include TBL1XR1 and CREBBP [43, 44]. TBL1XR1 can activate transcription factors such as NF-κB and JUN and promote tumor cell survival [44]. CREBBP is an epigenetic regulator, encoding a histone/protein acetyltransferase. Mutations were also reported in other epigenetic regulators KMT2D and KMT2C in ocular adnexal EMZL [43, 46]. These

findings suggest that epigenetic dysregulation is involved in pathogenesis of ocular adnexal EMZL in addition to activated NF-κB pathway [43]. Other frequently mutated genes reported include NOTCH1, NOTCH2, TET2, LRP1B, JAK3, LRP1B, COL12A1, COL1A2, DOCK8, TP53, PRDM1 (Table 4.2) [44, 46, 48].

Molecular studies in ocular adnexal follicular lymphomas and DLBCL are few due to their rarity. Their molecular alterations may follow genotypic patterns of systemic follicular lymphomas and DLBCL. MYD88 mutation is more frequently seen in ocular adnexal DLBCL than in ocular adnexal EMZL [49]. Mutations in epigenetic modulators, EZH2 and ARID1A were both common in ocular adnexal DLBCL and ocular adnexal follicular lymphoma in one study [49]. Mutations in histone methyltransferases KMT2B in ocular adnexal follicular lymphoma and KMT3B in ocular adnexal DLBCL were also seen [49]. Other frequently seen mutations include CDKN2A, PTEN, ATM, NF1, NRAS in ocular adnexal DLBCL, and HRAS in follicular lymphoma [49].

**Table 4.2** Mutational profile of ocular adnexal extranodal marginal zone B-cell lymphoma

| Altered genes | Frequency (%) | Functions | References |
|---|---|---|---|
| TNFAIP3 | 27–54 | NF-κB pathway | [43, 44, 46–48] |
| MYD88 | 4–25 | NF-κB pathway | [43, 46–49] |
| BCL10 | 4–6 | NF-κB pathway | [43, 48] |
| CD79B | 2–4 | NF-κB pathway | [43, 48] |
| TBL1XR1 | 6–19 | Transcription regulation | [43, 44, 47] |
| CREBBP | 13–25 | Epigenetic regulation | [43, 44, 46] |
| KMT2D | 6–22 | Epigenetic regulation | [43, 46, 48] |
| KMT2C | 25 | Epigenetic regulation | [46] |
| TET2 | 15 | Epigenetic regulation | [46] |
| NOTCH1 | 2–8 | B-cell differentiation | [43, 47–49] |
| NOTCH2 | 8–15 | B-cell differentiation | [46, 48] |
| DOCK8 | 6 | B-cell differentiation | [44] |
| JAK3 | 11 | JAK/STAT pathway | [44] |
| COL12A1 | 7 | Cell adhesion | [44] |
| COL1A2 | 6 | Cell adhesion | [44] |
| LRP1B | 6–25 | Tumor suppressor | [43, 46] |
| TP53 | 8 | Tumor suppressor | [48] |

## Conclusions

Lymphoma is one of the most heterogeneous groups of malignancies with complicated classification systems. The heterogeneity in lymphoma owes primarily to the complex features of development and differentiation of B-cell and T-cell lymphocytes. Recent progress in our understanding of pathogenesis and clinical course of lymphomas was made with GEP studies that even changed how we classify lymphomas (e.g. GCB and ABC subtypes in DLBCL). Mutational profiles of ocular lymphomas seemed to be different from lymphomas of the "same subtype" occurring at other sites. Mutational profile of vitreoretinal DLBCL is characterized by the high, if not the highest, frequency of MYD88 mutation among DLBCLs, possibly in association with ocular immune privilege and it does not seem to simply fit into either GCB and ABC subtypes. Chromosomal translocations are frequently seen in EMZL of other sites, but not in ocular adnexal EMZL. By contrast, somatic mutations, especially TNFAIP3 mutation, are frequently detected in ocular adnexal EMZL, while they are less commonly seen in EMZL of other sites. Further genetic studies are warranted, especially in other rare subtypes of ocular lymphomas, that will advance our understanding and management of ocular lymphomas.

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