Published in final edited form as:

Ocul Immunol Inflamm. 2012 August ; 20(4): 244–254. doi:10.3109/09273948.2012.702843.

Genetics of Primary Intraocular Tumors

Nisha Nagarkatti-Gude, MD, PhD¹, Yujuan Wang, MD, PhD^{2,3}, Mohammad Javed Ali, MD, FRCS⁴, Santosh G. Honavar, MD, FACS⁴, Martine J. Jager, MD¹, and Chi-Chao Chan, MD²

¹Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands

²Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA ³Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China ⁴Ocular Oncology Services, L.V. Prasad Eye Institute, Hyderabad, India

Abstract

Primary intraocular neoplasms are tumors that originate within the eye. The most common malignant primary intraocular tumor in adults is uveal melanoma and the second is primary intraocular lymphoma or vitreoretinal (intraocular) lymphoma. The most common malignant intraocular tumor in children is retinoblastoma. Genetics plays a vital role in the diagnosis and detection of ocular tumors. In uveal melanoma, monosomy 3 is the most common genetic alteration and somatic mutations of *BAP1*, a tumor suppressor gene, have been reported in nearly 50% of primary uveal melanomas. The retinoblastoma gene *RBI* is the prototype tumor suppressor gene—mutations in *RBI* alleles lead to inactivated RB protein and the development of retinoblastoma. *Immunoglobulin heavy chain (IgH)* or *T-cell receptor (TCR)* gene rearrangement is observed in B-cell or T-cell primary vitreoretinal lymphoma, respectively. Other factors related to the genetics of these three common malignancies in the eye are discussed and reviewed.

Keywords

Choroidal malignant melanoma; primary intraocular lymphoma; primary vitreoretinal lymphoma; retinoblastoma; uveal melanoma

Intraocular tumors are composed of two types: primary, which originate in the eye, and secondary, which metastasize to the eye. Genetic contributions to intraocular tumor development include the determination of both hereditary predispositions to tumor formation and tumor-driven alterations in gene expression, which are revealed by molecular profiling of malignant tissue. This review discusses the genetics of three primary intraocular tumors: uveal melanoma, the most common intraocular malignancy in adults; primary vitreoretinal lymphoma, a masquerade syndrome of uveitis and the second most common intraocular tumor in adults; and retinoblastoma, the most common intraocular tumor of childhood.

© 2012 Informa Healthcare USA, Inc.

Correspondence: Chi-Chao Chan, MD, 10 Center Drive, 10/10N103, NIH/NEI, Bethesda, MD 20892-1857, USA. chanc@nei.nih.gov.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Drs. Nagarkatti-Gude, Wang, and Ali are shared first authors.

UVEAL MELANOMA

Uveal melanoma (UM, Figure 1) is the most common primary intraocular tumor in adults, with an estimated worldwide incidence between 5.3 and 8.6 cases per million.^{1,2} This malignant tumor arises from melanocytes in the choroid, ciliary body, or iris. While relatively rare, UM can be devastating and, notably, up to 50% of patients may die from metastatic disease despite improvements in both our understanding of the pathophysiology of this condition and treatment modalities.³ Involvement of protooncogenes in UM cells has recently been investigated and evidence of constitutive activation of the mitogen-activated protein kinase (MAPK) pathway has been found. Constitutive activation of GNAQ, a stimulatory α q subunit of heterotrimeric G proteins ($G\alpha\beta\gamma$), is equivalent to oncogenic activation of the MAPK cascade and is observed in approximately 50% of uveal melanomas.⁴

UM occurs primarily in a sporadic manner. However, UM clustering in families has been observed,⁵ suggesting that heritable susceptibility may contribute to UM pathogenesis. The identification of germline mutations in cutaneous melanoma (CM) has only strengthened the hypothesis that germline mutations may also exist for UM since the tumors share a common origin in the melanocyte. The presence of patients with early-onset UM, bilateral UM, both UM and CM, or a family history of multiple UM and/or CM further suggests that a genetic predisposition may exist. Identifying candidate genes is useful in obtaining a better understanding of the pathogenesis of UM and may also help in the establishment of screening or genetic counseling guidelines for susceptible patients and their families. Candidate genes include those responsible for familial forms of CM, while other studies have focused on genes associated with neoplasms that may occur simultaneously with UM, such as those involved in certain forms of breast cancer. Finally, genetic profiling of UM has led to the discovery of several somatic mutations in genes such as *BAP1* and chromosomal anomalies that play a role in pathogenesis and prognosis.^{6,7} As immune responses against melanoma antigens may play a role in either preventing the growth of primary tumors or the development of metastases, several studies have analyzed the distribution of immune-response genes, encoding human leukocyte antigen (HLA) and killer-cell immunoglobulin-like receptor (KIR).^{8,9}

Melanocytes in UM

Uveal and cutaneous melanocytes have a common neural crest origin and both melanomas occur in clusters in a small subset of families, suggesting shared common melanoma candidate genes. It should be noted, however, that while UM and CM are both neurocristopathies, there are distinct differences between the two conditions—for example, environmental factors such as ultraviolet (UV) light exposure are strongly associated with CM but the link to UM is still unclear.¹⁰ Compared to CM, relatively little is known about the etiology of UM. Various groups have studied whether factors that affect the development of CM such as UV radiation or atypical nevi also represent risk factors for UM. While melanin pigment protects against UV radiation, levels of melanin are at least partially controlled via the interaction between α -melanocyte-stimulating hormone (α -MSH) and the melanocortin-1 receptor (MC1R). Certain mutations in *MC1R* have been shown to affect the risk of CM and were also studied in UM. One large study consisting of 350 UM patients and 133 controls detected eight *MC1R* variants (V60L, D84E, V92M, R151C, I155T, R160H, R163Q, and D294H), but found no significant difference in the frequencies of these variants between those with or without UM.¹¹ These results have been confirmed in other studies, which demonstrate that MC1R variants do not play a significant role in susceptibility to develop UM.^{12,13}

Phenotypic host features such as blond or red hair, fair skin, light iris color, skin freckling, presence of cutaneous nevi, and sensitivity to sunlight are important in the development of CM, presumably because these features correspond to an altered response or increased susceptibility to UV light. So, do these features also predispose one to UM? Many observational, case-control studies have attempted to deduce which phenotypic features contribute to UM susceptibility; however, only light eye color has consistently been linked to UM. A recent meta-analysis of 132 reports examining host factors and the development of UM found light iris color, fair skin color, and inability to tan to be significant risk factors.¹⁴ While these traits are heritable, the genetics, for example, of eye color are complex and influenced by more than one gene. It has been demonstrated that the *HERC2/OCA2* genes are most responsible for blue and brown eye color inheritance and also contribute to hair and skin tone¹⁵; however, other genes such as *IRF4*, *SLC2A4*, *SLC45A2*, *TYR*, and *TYRP1* also play a role in eye color.^{16,17} It is hypothesized that the increased risk of UM in people with gray or blue eye color may be caused by greater light transmission due to less melanosomes and/or pigment in the iris or to similarly decreased amounts of choroidal melanin, which means less choroidal protection.¹⁸ Therefore, current studies suggest that the *MC1R* variants are not primarily responsible for UM susceptibility; however, heritable phenotypic features dictated by melanin appear to affect the development of this condition.

CDKN2A/ARF and CDK4

In cases of familial CM, primarily two genes have been shown to be involved: (1) *CDKN2A/alternate reading frames (ARF)* and (2) *CDK4*. The *CDKN2A/ARF* gene is located on chromosome 9q21¹⁹ and is the major gene known to confer high-susceptibility to CM,²⁰ as confirmed by linkage, loss of heterozygosity, and cytogenetic studies.^{19,21-23} *CDKN2A* encodes two distinct proteins from alternatively spliced transcripts: p16 and p14ARF.²⁴ The p14ARF causes cell cycle arrest via p53, whereas p16 causes cells to arrest in G1 by inhibition of CDK4-mediated phosphorylation of retinoblastoma protein.²⁵ Of note, 20–40% of familial cases of CM are related to *CDKN2A* mutations disrupting p16,^{26,27} while *ARF* and *CDK4* germline mutations are far less common.^{28,29} Somatic changes and allelic imbalance at this locus have been demonstrated in sporadic cases of UM,³⁰ and in 30% of UM, expression of p16 is reduced via promoter hypermethylation,³¹ which only strengthens the hypothesis that germline mutations may also exist in *CDKN2A*.

A *CDKN2A* germline mutation at exon 2 (199 GA) leading to CDKN2A Gly67Ser and ARF Arg81Gln was identified in one family wherein the proband was diagnosed with UM at the age of 47 and the proband's sister and daughter had CM.²⁹ Another germline mutation in exon 1 of *CDKN2A* has also been reported in an individual originally diagnosed with UM at the age of 59 but with no family history of UM or CM.³² Studies by Wang et al., Singh et al., and Soufir et al. failed to demonstrate any germline mutations of this gene in their sample populations, which included cases of familial UM with or without CM, concurrent UM/CM, or bilateral disease.³³⁻³⁵ It should be noted that these were small studies—in fact, the major limitation of most of these studies to date is the small sample size. Another limitation of many of these studies is that screening has been conducted via single-stranded conformational polymorphism (SSCP) analysis, which is estimated to detect only 65% of point mutations.³⁶

The gene regions coding for p14ARF and *CDK4* are less frequently mutated, even in familial cases of CM. Only one study has found a germline sequence variant in the gene region coding for p14ARF, but was unable to ascertain whether the identified variant is pathogenic.³⁷ This mutation was detected in a proband with UM and the proband's mother who also had UM, but no other family members were available for testing.³⁷ Of note, *CDK4* germline mutations in familial CM have been identified only in exon 2, which codes for the p16 binding site but thus far this mutation has yet to be found in patients with UM.

BAP1

BRCA1 (breast cancer 1, early onset) associated protein-1 (BAP1) is a deubiquitinating enzyme with the gene located on 3p12. *BAP1* is hypothesized to be a tumor suppressor gene and somatic mutations in this gene have been associated not only with UM⁷ but also with breast and lung cancers.^{38,39} In UM, monosomy 3 is both the most common genetic alteration and is associated with tumor aggressiveness. Somatic mutations in *BAP1* were identified in 47% of primary UM and were more common in UM with monosomy 3.⁷ Thus, recent studies have focused on investigating whether germline mutations in the *BAP1* gene occur in patients with UM, especially in those with a strong hereditary risk of cancer.

One study identified a single patient with a germline *BAP1* mutation; however, no family history was available.⁷ A more recent study carried out mutational screening via direct sequencing and found that out of 53 patients with a high risk of hereditary cancer, one patient had a germline truncating mutation in *BAP1*.⁴⁰ Several family members of this patient were identified as having this mutation and had developed tumors, including UM, lung adenocarcinoma, and meningioma. Moreover, decreased BAP1 expression was observed in these tumors.⁴⁰ Currently, it appears that germline mutations in *BAP1* are responsible for only a small subset of hereditary UM; thus, the search for other contributory genes continues.

BRCA1/2

It was established in the 1990s that germline mutations of *BRCA1/BRCA2* genes correlate with an increased risk of breast and ovarian cancer. The protein products of these genes are often involved in processes such as DNA repair; thus, mutations may lead to increased risk of other cancers as well. Furthermore, BAP1 is involved in the BRCA pathway and its suppression results in a phenotype consistent with that observed in BRCA1 deficiency. This observation strengthens the hypothesis that germline mutations in *BRCA* genes may be associated with UM.

Studies have largely attempted to retrospectively examine whether patients with known *BRCA1/BRCA2* germline mutations have a history of UM. One study found 2 cases of UM from 468 *BRCA* germline mutation carriers; interestingly, one case was a *BRCA1* mutation and the other was a *BRCA2* mutation.⁴¹ Moran et al. report that in a cohort of 490 families with germline *BRCA1/BRCA2* mutations, 2 carriers of pathogenic *BRCA2* mutations had confirmed cases of UM.⁴² Both of these studies suggest that increased risk of UM may be associated with germline *BRCA* mutations, particularly in *BRCA2*. However, Buecher et al. and Hearle et al. both studied patients with UM and a personal and/or family history of breast or ovarian cancer and found no deleterious germline mutations in *BRCA* genes in these populations—albeit the sample sizes in these studies were relatively small.^{32,43}

Neurofibromatosis Type 1

Neurofibromatosis (NF1; von Recklinghausen syndrome) is an autosomal dominant condition associated with a mutation in *NF1*. NF1 is thought to be a neurocristopathy. As uveal melanocytic cells also originate from the neural crest and several cases exist wherein patients with NF1 also develop UM, it has been proposed that an association exists between these two conditions. One paper concluded that since the prevalence of NF1 is 1 in 3000 and UM is 1 in 13,500, statistically 7 individuals with NF1 in the United States would also have UM by chance alone.⁴⁴ Prior to 2000, only 18 cases of UM in patients with NF1 have been reported.⁴⁴ One study examined the status of the *NF1* tumor suppressor locus in UM and demonstrated *NF1* deletions and decreased expression of neurofibromin in 38 samples of UM. This study demonstrated a role for the *NF1* gene in the pathogenesis of UM; however, whether or not germline *NF1* mutations predispose to UM remains unclear.⁴⁵

Immunogenetics: Human leukocyte antigen

Human leukocyte antigen (HLA) molecules play a significant role in immune recognition. In many tumors, the downregulation of HLA enables the tumor to escape immune surveillance by cytotoxic T cells. However, generally, NK cells via killer-cell immunoglobulin-like receptors (KIRs) specifically target and kill cells with reduced HLA expression and, thus, play a role in fighting tumor cells. In UM, a low HLA class I expression on primary tumors is associated with a decreased risk of metastases, presumably due to NK cell involvement.⁴⁶ Several HLA alleles have been shown to correlate with the development of CM, including HLA-B40, -DR4, and -DR5.^{47,48} In UM, this relationship has also been investigated. Studies have indicated that certain HLA alleles confer either susceptibility to or protection from UM,⁴⁹⁻⁵¹ and another report documented an association between HLA-B40 and metastatic death from UM.⁵² The most recent large-scale study examined which HLA alleles were related to the development of UM or associated with any specific clinical or tumor characteristics in 235 Dutch UM patients and 2440 healthy Dutch blood donors.⁸ The study showed that HLA antigens do not contribute to an increased genetic predisposition to UM,⁸ confirming earlier studies.⁵³ An association may exist between the HLA-B44 allele and decreased survival (Kaplan-Meier analysis/log rank test, $p = .012$), the HLA-DR13 allele and large tumors ($p = .012$), the HLA-B60 allele and ciliary body involvement ($p = .03$), and the HLA-B35 allele and pure spindle cell type ($p = .006$).⁸ However, one has to take into account the large numbers of comparisons in this study, which limits the significance of the findings. KIR and HLA genotypes have been shown to not differ between UM patients and healthy control subjects; however, individuals with genotypes that provide ligands for both KIR2DL1 and KIR2DL2/3 (C1/C2), rather than for either individually, have better outcomes.⁹ These results not only are important in predicting susceptibility and outcomes, but may lead to new immunotherapeutic strategies via the NK cell.

In summary, the presence of UM patient subsets with (1) bilateral UM, (2) early onset UM, (3) personal or family history of CM, (4) family history of UM, or (5) personal history of another neoplasm suggests a genetic predisposition to UM may exist. Current studies are aimed at the identification of candidate susceptibility genes that may play a role in UM, as this condition is associated with significant morbidity and mortality. Most studies have approached this task by examining known germline mutations associated with other conditions such as CM or breast cancer in the context of UM and UM-prone families or by studying whether known somatic mutations in UM may exist in the germline. As of yet, the contribution of these known germline mutations to the pathogenesis of UM is minimal and occurs in only a small proportion of cases. However, the ongoing search to characterize germline alterations in at-risk families is highly warranted. The ability to identify “at-risk” individuals would be extremely useful not only in cancer surveillance and genetic counseling of family members, but also in better understanding the pathogenesis of this condition.

RETINOBLASTOMA

Retinoblastoma (Figure 2) is the most common intraocular malignancy in children, with an incidence ranging from 1 in 15,000 to 1 in 18,000 live births.⁵⁴ It is second only to uveal melanoma in the frequency of occurrence of malignant intraocular tumors. There is no racial or gender predisposition in the incidence of retinoblastoma. Retinoblastoma is bilateral in 25-35% of cases.⁵⁵ The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months.⁵⁵

Origin and Inheritance

The cellular origin of retinoblastoma has been intensely debated. Possibilities include neuroretinal stem cells, progenitor cells, newly committed postmitotic cells, and differentiated glial cells.⁵⁶⁻⁵⁹ Retinal progenitors and postmitotic cells appear to be the most likely contenders but additional studies are needed to definitively prove the exact origin.

The identification of the inheritance of retinoblastoma and its molecular and biochemical basis proved to be a major landmark in cancer biology. The foundations of this work were laid by Knudson in 1971,⁶⁰ when he proposed the “two-hit hypothesis” according to which, in a case of hereditary disease, one allele is mutated in the germline and the other at the cellular level. In the nonhereditary disease, both alleles are mutated at the cellular level.⁶¹ The inheritance is autosomal dominant with a high penetrance (90% or more).⁶² Knudson’s hypothesis was confirmed by the discovery of the *RB1* gene on chromosome 13, region 14, in 1986 by Dryja et al.⁶³ Sparks et al. discovered a close linkage between *RB1* and the *esterase D* gene (*EsD*).⁶⁴

RB1 Gene

The *RB1* gene, located on chromosome 13q14.2, is a tumor suppressor gene that contains 27 exons distributed over 200 kb of DNA. The gene encodes the retinoblastoma protein (pRb, RB, or RB1), composed of 928 amino acids.⁶⁵ This protein interacts with E2F sites, which are present in many genes involved in cell differentiation, apoptosis, and cell cycle regulations.⁶⁶ Following its attachment to E2F, the protein blocks its transactivation domain and suppresses transcription by inhibiting surrounding enhancers on the promoter region.^{67,68} Thus, it exerts strong control over the cell cycle regulatory mechanisms by inhibiting cell division through S-phase entry blockage.⁶⁹ The pRb protein is itself regulated by phosphorylation mechanisms with the help of cyclin-dependent kinases or CDKs.^{70,71} The paradoxical combination of anti-proliferative and anti-apoptotic functions of the pRb protein was explained on the basis of different mechanisms of actions.⁶⁵

Retinoblastoma is caused by the bi-allelic inactivation of the retinoblastoma susceptibility gene *RB1*. Cytogenetic deletions noted in retinoblastoma have assigned the genetic locus of the disease to q14 of chromosome 13 linked with polymorphic marker gene enzyme esterase D.⁷² More than 900 mutations have been reported in the *RB1* gene, thus reflecting its mutational heterogeneity.⁷³ Germline RB mutations are distributed throughout the gene and are known to occur at the CpG dinucleotides.⁷⁴ *RB1* mutations are found in the second malignant neoplasms seen in retinoblastoma as well as in the sporadic tumors of lungs, breast, and many others.⁷⁵⁻⁷⁷ In other cancers where *RB1* mutations are not seen, pRb protein has been found to be inactivated, highlighting the significant role it plays as a tumor suppressor in cancer biology.⁷⁸ It is not surprising, therefore, that RB pathways in the uveal melanoma and melanoma metastasis are generating great interest.^{65,79}

Detection of the *RB1* mutations has been an ongoing challenge for numerous reasons, which include the large size of the gene, mosaicism, mutational heterogeneity, and the presence of mutations in noncoding regions.⁶² Nonetheless, with the use of multiple approaches like quantitative multiplex PCR, sequencing, denaturing high-performance liquid chromatography (DHPLC), and quantitative multiplex PCR for short fluorescent segments (QMPSF), the detection rates have been as high as 89-92%.⁸⁰⁻⁸² Parsam et al. described a comprehensive and economical approach to detecting *RB1* mutations in an effort to make this clinically more feasible.⁸² The same group later described novel effects of the *RB1* gene on splicing and suggested RNA analysis as a possible adjunct to mutational screening of genomic DNA in retinoblastoma.⁶²

Clinical Implication of the RB1 Gene

Ali et al. attempted to correlate the mutations with the severity of the disease at presentation and found that the size of the *RB1* gene deletion positively correlated with advanced stages at diagnosis, a higher chance of enucleation, and a higher incidence of aggressive histopathological features and metastasis as compared to splice or nonsense mutations.⁸³ Gallie et al. showed that precise identification of the *RB1* gene mutation helped in better management of subsequent siblings and relatives at risk.⁸⁴ This concept calls for newer modalities for early diagnosis and early management so that the priority shifts from eye salvage to vision salvage. Xu et al. showed how precise identification of the mutation helped in preimplantation diagnosis during in vitro fertilization (IVF), thereby successfully selecting against mutational carriers.⁸⁵

The future holds promise for retinoblastoma cancer genetics in terms of preimplantation genetic diagnosis. Development of genetically engineered mouse models have resulted in new insights into retinoblastoma biology and opened up new avenues to test novel treatments.^{86,87} Targeted chemotherapy to specifically activate p53-induced cell death in retinoblastoma cells using nutlin-3a inhibitor to interfere with the MDMX-p53 and MDM2-p53 interactions has led to effective synergistic killing of retinoblastoma cells.^{88,89}

PRIMARY VITREORETINAL LYMPHOMA

Ocular lymphoma is classified based on the tissues it affects: intraocular, orbital, and adnexal. Intraocular lymphoma can be further subdivided into three distinct conditions known as primary vitreoretinal lymphoma (PVRL, also named primary intraocular lymphoma, Figure 3), primary uveal (choroid is common, ciliary body and iris are rare) lymphoma, and secondary metastatic intraocular lymphoma.^{90,91} PVRL, a subtype of primary central nervous system lymphoma (PCNSL), is the most common intraocular lymphoma and initially affects the vitreous, retina, subretina, and optic nerve.⁹⁰ The majority of PVRL cases consist of diffuse large B-cell lymphoma (DLBCL) of non-Hodgkin lymphoma (NHL), although rare cases of T-cell lymphoma have been reported.^{90,92} Primary uveal lymphoma is a type of extranodal marginal zone B-cell lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) and affects the uveal tract.⁹³ Secondary intraocular lymphoma is caused by metastasis of systemic lymphoma cells via blood circulation and primarily affects the uvea, particularly the choroid,⁹⁴ and, in rare instances, the retina and vitreous.⁹⁵

Although there is a report on NHL and family history of lymphatic, hematologic, and other cancers that find a slight increase of brain and other nervous system (odds ratio = 0.80, 95% confidence intervals = 0.38-1.68),⁹⁶ the family history of primary ocular lymphomas has not been well documented due to the rarity of these tumors and the inconsistent reports between family histories of NHL.⁹⁷⁻⁹⁹ Recent studies have reported genetic variation in chromosome 6p21.32 associated with DLBCL susceptibility.^{100, 101} However, the major genetic factors of developing lymphoma are currently unknown.

IgH or TCR Gene rearrangements and Molecular Genetic Profiling

Monoclonality means that all the lymphocytes are derived from a single cell. Monoclonality is a hallmark of lymphomas, as evidenced by the expression of identical cellular surface markers and gene restriction observed in either immunoglobulin heavy/light chain (IgH/IgL) or T-cell receptor (TCR). Gene rearrangements of *IgH* in B-cell lymphoma and *TCR* in T-cell lymphoma are reliable markers for diagnosis and classification of PVRL.⁹² Among the variable regions, genetic rearrangements associated with B- and T-cell lymphoma are most commonly observed in the *complementarity determining region 3 (CDR3)* region of *IgH* and the *TCR γ* region of *TCR*.^{102,103}

Gene expression profiling greatly contributes to the molecular study of DLBCL.^{104,105} Two major molecular subtypes of DLBCL are identified as germinal center B cell (GCB) and activated B cell (ABC).^{104,105} GCB DLBCL expresses many genes characteristic of normal germinal center B cells,¹⁰⁴ but there are several key genetic alterations. These include cancer-related and relevant genes: *B-cell lymphoma 2 (BCL2)* ectopic expression, *MYC* (Myc, a regulator gene that codes for a transcription factor) dysregulation, *phosphatase and tensin homolog (PTEN)* deletion, human *c-Rel* proto-oncogene (*REL*) amplification, phosphoinositide-3-kinase, catalytic, alpha polypeptide (*PIK3CA*) mutation, and a number of mutated chromatin-modifying genes.^{105,106} In contrast, the gene expression pattern in ABC DLBCL is similar to that which is induced during *in vitro* activation of normal peripheral blood B cells.¹⁰⁴ The ABC subtype is characterized by constitutive nuclear factor (NF)- κ B pathway activation due to mutations in *tumor necrosis factor alpha-induced protein 3 (TNFAIP3)*, *caspase recruitment domain family, member 11 (CARD11)*, and *myeloid differentiation factor 88 (MYD88)* genes.^{105,106} In general, patients with the ABC subtype of DLBCL have a considerably poorer prognosis than those with GCB lymphomas.^{105,107}

The *BCL2* t(14;18) translocation is detected in approximately 35% of GCB DLBCL cases.¹⁰⁸ Ectopic *BCL2* expression results when the gene translocates from its normal position at 18q21 to the *IgH* enhancer at 14q32.¹⁰⁹ *BCL2* overexpression has been confirmed as an independent predictor of poor survival in DLBCL patients.¹⁰⁵ One study reported that within a cohort of 72 PVRL patients, 55% exhibited a *BCL2/IgH* gene translocation.¹¹⁰ In this study, patients who are positive for *BCL2* t(14;18) translocation are significantly younger than those who lack the translocation. However, there is no statistical difference in survival or tumor relapse between the PVRL patients with and without the *BCL2/IgH* gene translocation.

Analysis of *IgH variable region (VH)* gene mutation reveals the cell origin and stage of tumor transformation.¹¹¹ Almost all PCNSL harbors a *VH* gene that demonstrates somatic mutation and intracлонаl heterogeneity, suggesting a GCB DLBCL origin.¹¹¹ In contrast, the finding of novel N-glycosylation sites in the tumor *VH* gene would suggest a lack of *VH* intracлонаl heterogeneity. Consequently, PVRL tumors without intracлонаl heterogeneity may stem from ABC DLBCL.¹¹²

BCL6 is required for the formation of normal germinal center B cells and T-cell-dependent antigen responses. *BCL6* is also considered a proto-oncogene; *BCL6* mutations are the most frequently detected genetic alterations in both GCB and ABC DLBCL and high expression of *BCL6* transcripts is detected in PVRL.¹⁰⁵ Chromosomal translocation of *BCL6* at 3q27 is the most characteristic genetic abnormality seen in DLBCL.¹⁰⁵ The translocation usually occurs in a conserved regulatory region spanning the promoter and results in constitutive expression of *BCL6*.¹¹³ Deregulated *BCL6* expression suppresses *p53* transcription, which prevents tumor cell apoptosis and permits lymphoma development.^{113,114}

Since NF- κ B promotes proliferation and survival of lymphocytes, aberrant NF- κ B activation drives lymphoma pathogenesis, particularly in ABC DLBCL and MALT lymphoma.¹¹⁵ Several factors, including *CARD11*, *BCL10*, and *MALT1*, which mediate constitutive NF- κ B activation via the classical pathway, are identified in ABC DLBCL.¹¹⁶ In contrast, genetic rearrangement of *NF- κ B2* is responsible for alternative NF- κ B pathway activation in DLBCL.¹¹⁵ Meanwhile, stabilized API2-MALT1 chimeric proteins, which result from genetic translocations, cause constitutive NF- κ B activation and are found to play an important role in MALT lymphoma.¹¹⁷ The role of *BCL10* is, however, not as prominent, as it was found that in 26 PVRL cases, only 23% were positive for *BCL10* expression.¹¹⁰

The t(14;18)(q32;q21) translocation, involving the *IgH* gene at 14q32 and *MALT1* at 18q21, has been identified as a novel recurrent genetic aberration in MALT lymphomas.¹¹⁵ This translocation links the *MALT1* gene to the *IgH* enhancer, resulting in deregulated *MALT1* expression. A large study showed the presence of *IgH/MALT1* in 6.8% of ocular adnexal MALT lymphoma.¹¹⁸ Higher incidences of the translocation have been reported in MALT lymphomas of the ocular adnexa (3 of 8 cases) and conjunctiva (1 of 3 cases).^{119,120}

CXCL12 and CXCL13

The origin of the lymphoma cells in PVRL and PCNSL is unknown. It is possible that PVRL cells could result from neoplastic transformation in one of the lymphocyte subpopulations from the lymphoid organ.⁹⁰ Alternatively, polyclonal inflammatory proliferations in the CNS might select for an aberrant monoclonal malignant cell population, which may in turn be the source of the malignancy.¹²¹ Because these proliferative lymphoma cells possess homing chemokine receptors such as chemokine (CXC motif) receptor 4 (CXCR4) and CXCR5, they are drawn to the eye (retinal pigment epithelium (RPE) and retina) by the respective ligands chemokine (CXC motif) ligand 12 (CXCL12) and CXCL13 expressed in the RPE.¹²² Additionally, in PCNSL interaction of the adhesion molecules lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule (ICAM-1) may play a role in lymphoma cells homing to the brain.¹²³

IL-10 and TNF- α Polymorphism

IL-10 production contributes to the clinical course of DLBCL. IL-10 elevation in either intraocular or cerebrospinal fluids is highly correlated with B-cell PVRL.^{90,124,125} Three single nucleotide polymorphisms (SNPs) in the *IL-10* promoter at positions -1082, -819, and -592 are reported to influence IL-10 production in vitro.¹²⁶ *IL-10* mRNA has been detected in lymphoma cells of PVRL patients with either high or low vitreal IL-10 levels.¹²⁷ Recently, we also found higher SNP frequency of *IL-10-1082* and a correlation between this SNP and IL-10 levels in the vitreous of PVRL patients.¹²⁸

TNF- α (*rs1799724*) CC genotype has been found to be associated with NHL and DLBCL in both population-based and case-control studies.^{129,130} However, there are no reports on PCNSL or PVRL.

Infectious DNA

Infectious agents have been reported to play causative roles in ocular lymphoma.⁹⁰ Epstein-Barr virus (EBV) is associated with lymphoma and mostly occurs in the course of an underlying immunodeficiency. EBV can directly transform and immortalize normal B cells *in vitro*. Upon examination of lymphoid cells from 21 PVRL cases, we identified EBV DNA in 2 cases, one of which came from a patient who was afflicted with AIDS.¹²⁷ This suggests that EBV may play a role in the induction of PVRL in immunocompromised patients.^{90,127} Other infectious agents that may contribute to PVRL include HHV8 and *Toxoplasma gondii*.⁹⁰

Human T-cell leukemia virus type 1 (HTLV-1) infection is the established cause of adult T-cell leukemia/lymphoma (ATL), an aggressive malignancy of CD4-positive T lymphocytes. Transactivation is the major mechanism involved in the HTLV-1-mediated leukemogenesis.¹³¹ It is dominated by the viral oncoproteins Tax, which drives dissemination of HTLV-1 into T-cell clones, and HTLV-1 basic leucine zipper factor (HBZ), which maintains the HTLV-1-infected clones.¹³² Like other retroviral genomes, the HTLV-1 genome contains *gag*, *pol*, and *env* structural genes that encode important proteins to facilitate replication and infection. Both the HTLV-1 *gag* and *pol* genes have been found in specimens of T-cell ocular lymphoma.^{133,134}

In summary, the majority of PVRL cases consist of a high-grade B-cell malignancy arising most likely from either a late germinal-center or an early postgerminal center B cell.¹³⁵ Significant progress has been made in the understanding of the molecular genetic alterations in ocular lymphoma. Genetic studies have shed light on molecular features that greatly explain the clinical heterogeneity that exists in various lymphomas. Additionally, these studies have explored multiple pathogens, molecules, and pathways involved in ocular lymphoma and revealed the underlying pathogenesis of ocular lymphoma.

CONCLUSION

Specific molecules can serve as biomarkers for the diagnosis and classification of intraocular malignancies. Some distinctive molecules closely related to the growth profiles of different tumors can serve as valuable indicators of prognosis and survival analysis. Identification of genetic and molecular profiles associated with intraocular tumors has led to improved knowledge of pathogenesis and offered novel therapeutic strategies. Moreover, genetic studies on specific molecules and pathways could reveal more detailed features of intraocular tumors that provide hints for identifying pivotal molecules that can be targeted therapeutically.

REFERENCES

- [1]. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011; 118(9):1881–1885. [PubMed: 21704381]
- [2]. Virgili G, Gatta G, Ciccolallo L, et al. Incidence of uveal melanoma in Europe. *Ophthalmology*. 2007; 114(12):2309–2315. [PubMed: 17498805]
- [3]. Landreville S, Agapova OA, Harbour JW. Emerging insights into the molecular pathogenesis of uveal melanoma. *Future Oncol*. 2008; 4(5):629–636. [PubMed: 18922120]
- [4]. Patel M, Smyth E, Chapman PB, et al. Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res*. 2011; 17(8):2087–2100. [PubMed: 21444680]
- [5]. Kodjikian L, Nguyen K, Lumbroso L, et al. Familial uveal melanoma: a report on two families and a review of the literature. *Acta Ophthalmol Scand*. 2003; 81(4):389–395. [PubMed: 12859267]
- [6]. Bronkhorst IH, Maat W, Jordanova ES, et al. Effect of heterogeneous distribution of monosomy 3 on prognosis in uveal melanoma. *Arch Pathol Lab Med*. 2011; 135(8):1042–1047. [PubMed: 21809997]
- [7]. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*. 2010; 330(6009):1410–1413. [PubMed: 21051595]
- [8]. Maat W, Haasnoot GW, Claas FH, et al. HLA Class I and II genotype in uveal melanoma: relation to occurrence and prognosis. *Invest Ophthalmol Vis Sci*. 2006; 47(1):3–6. [PubMed: 16384937]
- [9]. Maat W, van der Slik AR, Verhoeven DH, et al. Evidence for natural killer cell-mediated protection from metastasis formation in uveal melanoma patients. *Invest Ophthalmol Vis Sci*. 2009; 50(6):2888–2895. [PubMed: 19234348]
- [10]. Shah CP, Weis E, Lajous M, et al. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. *Ophthalmology*. 2005; 112(9):1599–1607. [PubMed: 16051363]
- [11]. Hearle N, Humphreys J, Damato BE, et al. Role of MC1R variants in uveal melanoma. *Br J Cancer*. 2003; 89(10):1961–1965. [PubMed: 14612910]
- [12]. Metzelaar-Blok JA, ter Huurne JA, Hurks HM, et al. Characterization of melanocortin-1 receptor gene variants in uveal melanoma patients. *Invest Ophthalmol Vis Sci*. 2001; 42(9):1951–1954. [PubMed: 11481256]
- [13]. Houlston RS, Damato BE. Genetic predisposition to ocular melanoma. *Eye (Lond)*. 1999; 13(Pt 1):43–46. [PubMed: 10396383]
- [14]. Weis E, Shah CP, Lajous M, et al. The association between host susceptibility factors and uveal melanoma: a meta-analysis. *Arch Ophthalmol*. 2006; 124(1):54–60. [PubMed: 16401785]

- [15]. Kayser M, Liu F, Janssens AC, et al. Three genome-wide association studies and a linkage analysis identify *HERC2* as a human iris color gene. *Am J Hum Genet.* 2008; 82(2):411–423. [PubMed: 18252221]
- [16]. Liu F, van Duijn K, Vingerling JR, et al. Eye color and the prediction of complex phenotypes from genotypes. *Curr Biol.* 2009; 19(5):R192–R193. [PubMed: 19278628]
- [17]. Branicki W, Liu F, van Duijn K, et al. Model-based prediction of human hair color using DNA variants. *Hum Genet.* 2011; 129(4):443–454. [PubMed: 21197618]
- [18]. Schmidt-Pokrzywniak A, Jockel KH, Bornfeld N, et al. Positive interaction between light iris color and ultraviolet radiation in relation to the risk of uveal melanoma: a case-control study. *Ophthalmology.* 2009; 116(2):340–348. [PubMed: 19091418]
- [19]. Cannon-Albright LA, Goldgar DE, Meyer LJ, et al. Assignment of a locus for familial melanoma, MLM, to chromosome 9p13-p22. *Science.* 1992; 258(5085):1148–1152. [PubMed: 1439824]
- [20]. Kamb A, Shattuck-Eidens D, Eeles R, et al. Analysis of the p16 gene (*CDKN2*) as a candidate for the chromosome 9p melanoma susceptibility locus. *Nat Genet.* 1994; 8(1):23–26. [PubMed: 7987388]
- [21]. Cowan JM, Halaban R, Francke U. Cytogenetic analysis of melanocytes from premalignant nevi and melanomas. *J Natl Cancer Inst.* 1988; 80(14):1159–1164. [PubMed: 3166071]
- [22]. Dracopoli NC, Alhadeff B, Houghton AN, et al. Loss of heterozygosity at autosomal and X-linked loci during tumor progression in a patient with melanoma. *Cancer Res.* 1987; 47(15):3995–4000. [PubMed: 2886213]
- [23]. Petty EM, Gibson LH, Fountain JW, et al. Molecular definition of a chromosome 9p21 germ-line deletion in a woman with multiple melanomas and a plexiform neurofibroma: implications for 9p tumor-suppressor gene(s). *Am J Hum Genet.* 1993; 53(1):96–104. [PubMed: 8317504]
- [24]. Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* 2006; 66(20):9818–9828. [PubMed: 17047042]
- [25]. Serrano M, Gomez-Lahoz E, DePinho RA, et al. Inhibition of ras-induced proliferation and cellular transformation by p16^{INK4}. *Science.* 1995; 267(5195):249–252. [PubMed: 7809631]
- [26]. Soufir N, Avril MF, Chompret A, et al. The French Familial Melanoma Study Group. Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. *Hum Mol Genet.* 1998; 7(2):209–216. [PubMed: 9425228]
- [27]. Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of *CDKN2A* mutations for melanoma. *J Natl Cancer Inst.* 2002; 94(12):894–903. [PubMed: 12072543]
- [28]. Bressac-de-Paillerets B, Avril MF, Chompret A, et al. Genetic and environmental factors in cutaneous malignant melanoma. *Biochimie.* 2002; 84(1):67–74. [PubMed: 11900878]
- [29]. Kannengiesser C, Avril MF, Spatz A, et al. *CDKN2A* as a uveal and cutaneous melanoma susceptibility gene. *Genes Chromosomes Cancer.* 2003; 38(3):265–268. [PubMed: 14506702]
- [30]. Merbs SL, Sidransky D. Analysis of p16 (*CDKN2/MTS-1/INK4A*) alterations in primary sporadic uveal melanoma. *Invest Ophthalmol Vis Sci.* 1999; 40(3):779–783. [PubMed: 10067984]
- [31]. van der Velden PA, Metzelaar-Blok JA, Bergman W, et al. Promoter hypermethylation: a common cause of reduced p16(*INK4a*) expression in uveal melanoma. *Cancer Res.* 2001; 61(13):5303–5306. [PubMed: 11431374]
- [32]. Hearle N, Damato BE, Humphreys J, et al. Contribution of germline mutations in *BRCA2*, *P16(INK4A)*, *P14(ARF)* and *P15* to uveal melanoma. *Invest Ophthalmol Vis Sci.* 2003; 44(2):458–462. [PubMed: 12556369]
- [33]. Wang X, Egan KM, Gragoudas ES, et al. Constitutional alterations in p16 in patients with uveal melanoma. *Melanoma Res.* 1996; 6(6):405–410. [PubMed: 9013477]
- [34]. Singh AD, Croce CM, Wary KK, et al. Familial uveal melanoma: absence of germline mutations involving the cyclin-dependent kinase-4 inhibitor gene (p16). *Ophthalmic Genet.* 1996; 17(1):39–40. [PubMed: 8740697]

- [35]. Soufir N, Bressac-de Paillerets B, Desjardins L, et al. Individuals with presumably hereditary uveal melanoma do not harbour germline mutations in the coding regions of either the P16INK4A, P14ARF or cdk4 genes. *Br J Cancer*. 2000; 82(4):818–822. [PubMed: 10732752]
- [36]. Eng C, Brody LC, Wagner TM, et al. Interpreting epidemiological research: blinded comparison of methods used to estimate the prevalence of inherited mutations in BRCA1. *J Med Genet*. 2001; 38(12):824–833. [PubMed: 11748305]
- [37]. Abdel-Rahman MH, Pilarski R, Massengill JB, et al. Melanoma candidate genes CDKN2A/p16/INK4A, p14ARF, and CDK4 sequencing in patients with uveal melanoma with relative high-risk for hereditary cancer predisposition. *Melanoma Res*. 2011; 21(3):175–179. [PubMed: 21412176]
- [38]. Jensen DE, Proctor M, Marquis ST, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. *Oncogene*. 1998; 16(9):1097–1112. [PubMed: 9528852]
- [39]. Jensen DE, Rauscher FJ 3rd. BAP1, a candidate tumor suppressor protein that interacts with BRCA1. *Ann N Y Acad Sci*. 1999; 886:191–194. [PubMed: 10667217]
- [40]. Abdel-Rahman MH, Pilarski R, Cebulla CM, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. *J Med Genet*. 2011; 48(12):856–859. [PubMed: 21941004]
- [41]. Cruz C, Teule A, Caminal JM, et al. Uveal melanoma and BRCA1/BRCA2 genes: a relationship that needs further investigation. *J Clin Oncol*. 2011; 29(34):e827–e829. [PubMed: 22025144]
- [42]. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. *Fam Cancer*. 2011; 11(2):235–242. [PubMed: 22187320]
- [43]. Buecher B, Gauthier-Villars M, Desjardins L, et al. Contribution of CDKN2A/P16 (INK4A), P14 (ARF), CDK4 and BRCA1/2 germline mutations in individuals with suspected genetic predisposition to uveal melanoma. *Fam Cancer*. 2010; 9(4):663–667. [PubMed: 20842456]
- [44]. Honavar SG, Singh AD, Shields CL, et al. Iris melanoma in a patient with neurofibromatosis. *Surv Ophthalmol*. 2000; 45(3):231–236. [PubMed: 11094247]
- [45]. Foster WJ, Fuller CE, Perry A, et al. Status of the NF1 tumor suppressor locus in uveal melanoma. *Arch Ophthalmol*. 2003; 121(9):1311–1315. [PubMed: 12963615]
- [46]. Jager MJ, Hurks HM, Levitskaya J, et al. HLA expression in uveal melanoma: there is no rule without some exception. *Hum Immunol*. 2002; 63(6):444–451. [PubMed: 12039519]
- [47]. Pollack MS, Livingston PO. HLA and DR antigen frequencies in melanoma patients: possible relation to disease prognosis. *Tissue Antigens*. 1985; 26(4):262–265. [PubMed: 3878014]
- [48]. Mendez R, Aptsiauri N, Del Campo A, et al. HLA and melanoma: multiple alterations in HLA class I and II expression in human melanoma cell lines from ESTDAB cell bank. *Cancer Immunol Immunother*. 2009; 58(9):1507–1515. [PubMed: 19340423]
- [49]. Ignatov RK, Terent'eva LS, Shul'gina NS. Distribution of the HLA antigen system in melanoblastoma of the uvea. *Oftalmol Zh*. 1977; 32(4):289–294. [PubMed: 896116]
- [50]. Martinetti M, Tafi A, De Paoli F, et al. Immunogenetic heterogeneity of uveal melanoma. *Cancer Detect Prev*. 1988; 12(1-6):145–148. [PubMed: 3180122]
- [51]. Dieckhues B, Junemann G, Kuchle HJ, et al. HLA-antigens in eye diseases (author's transl). *Klin Monbl Augenheilkd*. 1979; 175(5):681–685. [PubMed: 547095]
- [52]. Jager MJ, Volker-Dieben HJ, de Wolff-Rouendaal D, et al. Possible relation between HLA and ABO type and prognosis of uveal melanoma. *Doc Ophthalmol*. 1992; 82(1-2):43–47. [PubMed: 1305026]
- [53]. Metzelaar-Blok JA, Hurks HM, Naipal A, et al. Normal HLA class I, II, and MICA gene distribution in uveal melanoma. *Mol Vis*. 2005; 11:1166–1172. [PubMed: 16379028]
- [54]. Young, JL.; Smith, MA.; Roffers, SD., et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER Program. NIH; 1999.
- [55]. Bishop JO, Madson EC. Retinoblastoma. Review of the current status. *Surv Ophthalmol*. 1975; 19(6):342–366. [PubMed: 1145423]
- [56]. Dyer MA, Bremner R. The search for the retinoblastoma cell of origin. *Nat Rev Cancer*. 2005; 5(2):91–101. [PubMed: 15685194]

- [57]. Pardal R, Clarke MF, Morrison SJ. Applying the principles of stem-cell biology to cancer. *Nat Rev Cancer*. 2003; 3(12):895–902. [PubMed: 14737120]
- [58]. MacPherson D, Sage J, Kim T, et al. Cell type-specific effects of Rb deletion in the murine retina. *Genes Dev*. 2004; 18(14):1681–1694. [PubMed: 15231717]
- [59]. Coles BL, Angenieux B, Inoue T, et al. Facile isolation and the characterization of human retinal stem cells. *Proc Natl Acad Sci U S A*. 2004; 101(44):15772–15777. [PubMed: 15505221]
- [60]. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971; 68(4):820–823. [PubMed: 5279523]
- [61]. Knudson, AG, Jr. *Clinical Ophthalmic Oncology*. Elseviers; Philadelphia, USA: 2007. Retinoblastoma and cancer genetics.
- [62]. Parsam VL, Ali MJ, Honavar SG, et al. Splicing aberrations caused by constitutional RB1 gene mutations in retinoblastoma. *J Biosci*. 2011; 36(2):281–287. [PubMed: 21654082]
- [63]. Fung YK, Murphree AL, T'Ang A, et al. Structural evidence for the authenticity of the human retinoblastoma gene. *Science*. 1987; 236(4809):1657–1661. [PubMed: 2885916]
- [64]. Sparkes RS, Sparkes MC, Wilson MG, et al. Regional assignment of genes for human esterase D and retinoblastoma to chromosome band 13q14. *Science*. 1980; 208(4447):1042–1044. [PubMed: 7375916]
- [65]. Harbour JW. Eye cancer: unique insights into oncogenesis: the Cogan Lecture. *Invest Ophthalmol Vis Sci*. 2006; 47(5):1736–1745. [PubMed: 16638975]
- [66]. Flemington EK, Speck SH, Kaelin WG Jr. E2F-1-mediated transactivation is inhibited by complex formation with the retinoblastoma susceptibility gene product. *Proc Natl Acad Sci U S A*. 1993; 90(15):6914–6918. [PubMed: 8346196]
- [67]. Helin K, Harlow E, Fattaey A. Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. *Mol Cell Biol*. 1993; 13(10):6501–6508. [PubMed: 8413249]
- [68]. Weintraub SJ, Prater CA, Dean DC. Retinoblastoma protein switches the E2F site from positive to negative element. *Nature*. 1992; 358(6383):259–261. [PubMed: 1321348]
- [69]. Goodrich DW, Wang NP, Qian YW, et al. The retinoblastoma gene product regulates progression through the G1 phase of the cell cycle. *Cell*. 1991; 67(2):293–302. [PubMed: 1655277]
- [70]. Chen PL, Scully P, Shew JY, et al. Phosphorylation of the retinoblastoma gene product is modulated during the cell cycle and cellular differentiation. *Cell*. 1989; 58(6):1193–1198. [PubMed: 2673546]
- [71]. Lundberg AS, Weinberg RA. Functional inactivation of the retinoblastoma protein requires sequential modification by at least two distinct cyclin-cdk complexes. *Mol Cell Biol*. 1998; 18(2):753–761. [PubMed: 9447971]
- [72]. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature*. 1986; 323(6089):643–646. [PubMed: 2877398]
- [73]. Valverde JR, Alonso J, Palacios I, et al. RB1 gene mutation up-date, a meta-analysis based on 932 reported mutations available in a searchable database. *BMC Genet*. 2005; 6:53. [PubMed: 16269091]
- [74]. Harbour JW. Overview of RB gene mutations in patients with retinoblastoma: implications for clinical genetic screening. *Ophthalmology*. 1998; 105(8):1442–1447. [PubMed: 9709755]
- [75]. Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in patients with retinoblastoma: a review of the literature. *Ophthalmic Genet*. 1997; 18(1):27–34. [PubMed: 9134547]
- [76]. T'Ang A, Varley JM, Chakraborty S, et al. Structural rearrangement of the retinoblastoma gene in human breast carcinoma. *Science*. 1988; 242(4876):263–266. [PubMed: 3175651]
- [77]. Bookstein R, Rio P, Madreperla SA, et al. Promoter deletion and loss of retinoblastoma gene expression in human prostate carcinoma. *Proc Natl Acad Sci U S A*. 1990; 87(19):7762–7766. [PubMed: 2217208]
- [78]. Sherr CJ. Cancer cell cycles. *Science*. 1996; 274(5293):1672–1677. [PubMed: 8939849]
- [79]. Harbour JW, Worley L, Ma D, et al. Transducible peptide therapy for uveal melanoma and retinoblastoma. *Arch Ophthalmol*. 2002; 120(10):1341–1346. [PubMed: 12365913]

- [80]. Houdayer C, Gauthier-Villars M, Lauge A, et al. Comprehensive screening for constitutional RB1 mutations by DHPLC and QMPSF. *Hum Mutat.* 2004; 23(2):193–202. [PubMed: 14722923]
- [81]. Richter S, Vandezande K, Chen N, et al. Sensitive and efficient detection of RB1 gene mutations enhances care for families with retinoblastoma. *Am J Hum Genet.* 2003; 72(2):253–269. [PubMed: 12541220]
- [82]. Parsam VL, Kannabiran C, Honavar S, et al. A comprehensive, sensitive and economical approach for the detection of mutations in the RB1 gene in retinoblastoma. *J Genet.* 2009; 88(4): 517–527. [PubMed: 20090211]
- [83]. Ali M, Parsam V, Honavar S, et al. RB1 gene mutations in retinoblastoma and its clinical correlation. *Saudi J Ophthalmol.* 2010; 24:119–123.
- [84]. Gallie BL, Gardiner J, Toi A, et al. Retinoblastoma treatment in premature infants diagnosed prenatally by ultrasound and molecular diagnosis. *Am J Hum Genet.* 1999; (Suppl):65, A62.
- [85]. Xu K, Rosenwaks Z, Beaverson K, et al. Preimplantation genetic diagnosis for retinoblastoma: the first reported liveborn. *Am J Ophthalmol.* 2004; 137(1):18–23. [PubMed: 14700639]
- [86]. Windle JJ, Albert DM, O'Brien JM, et al. Retinoblastoma in transgenic mice. *Nature.* 1990; 343(6259):665–669. [PubMed: 1689463]
- [87]. Zhang J, Schweers B, Dyer MA. The first knockout mouse model of retinoblastoma. *Cell Cycle.* 2004; 3(7):952–959. [PubMed: 15190215]
- [88]. Laurie NA, Donovan SL, Shih CS, et al. Inactivation of the p53 pathway in retinoblastoma. *Nature.* 2006; 444(7115):61–66. [PubMed: 17080083]
- [89]. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med.* 2004; 10(8): 789–799. [PubMed: 15286780]
- [90]. Chan, CC.; Gonzales, JA. Primary Intraocular Lymphoma. World Scientific; Singapore: 2007.
- [91]. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. *Oncologist.* 2011; 16(11):1589–1599. [PubMed: 22045784]
- [92]. Wang Y, Shen D, Wang VM, et al. Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. *Int J Mol Sci.* 2011; 12(9):5684–5697. [PubMed: 22016619]
- [93]. Coupland SE, Foss HD, Hidayat AA, et al. Extranodal marginal zone B cell lymphomas of the uvea: an analysis of 13 cases. *J Pathol.* 2002; 197(3):333–340. [PubMed: 12115879]
- [94]. Chan CC, Buggage RR, Nussenblatt RB. Intraocular lymphoma. *Curr Opin Ophthalmol.* 2002; 13(6):411–418. [PubMed: 12441846]
- [95]. Cao X, Shen D, Callanan DG, et al. Diagnosis of systemic metastatic retinal lymphoma. *Acta Ophthalmol.* 2011; 89(2):e149–e154. [PubMed: 19958292]
- [96]. Chatterjee N, Hartge P, Cerhan JR, et al. Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. *Cancer Epidemiol Biomarkers Prev.* 2004; 13(9): 1415–1421. [PubMed: 15342441]
- [97]. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. *Int J Cancer.* 2007; 120(Suppl 12):1–39. [PubMed: 17405121]
- [98]. Goldin LR, Bjorkholm M, Kristinsson SY, et al. Highly increased familial risks for specific lymphoma subtypes. *Br J Haematol.* 2009; 146(1):91–94. [PubMed: 19438470]
- [99]. Dias C, Isenberg DA. Susceptibility of patients with rheumatic diseases to B-cell non-Hodgkin lymphoma. *Nat Rev Rheumatol.* 2011; 7(6):360–368. [PubMed: 21637317]
- [100]. Smedby KE, Foo JN, Skibola CF, et al. GWAS of follicular lymphoma reveals allelic heterogeneity at 6p21.32 and suggests shared genetic susceptibility with diffuse large B-cell lymphoma. *PLoS Genet.* 2011; 7(4):e1001378. [PubMed: 21533074]
- [101]. Wang SS, Menashe I, Cerhan JR, et al. Variations in chromosomes 9 and 6p21.3 with risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev.* 2011; 20(1):42–49. [PubMed: 21148756]
- [102]. Coupland SE, Anastassiou G, Bornfeld N, et al. Primary intraocular lymphoma of T-cell type: report of a case and review of the literature. *Graefes Arch Clin Exp Ophthalmol.* 2005; 243(3): 189–197. [PubMed: 15806372]

- [103]. Chan CC. Primary intraocular lymphoma: clinical features, diagnosis, and treatment. *Clin Lymphoma*. 2003; 4(1):30–31. [PubMed: 12837151]
- [104]. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000; 403(6769):503–511. [PubMed: 10676951]
- [105]. Schneider C, Pasqualucci L, Dalla-Favera R. Molecular pathogenesis of diffuse large B-cell lymphoma. *Semin Diagn Pathol*. 2011; 28(2):167–177. [PubMed: 21842702]
- [106]. Hartmann EM, Ott G, Rosenwald A. Molecular biology and genetics of lymphomas. *Hematol Oncol Clin North Am*. 2008; 22(5):807–823. vii. [PubMed: 18954738]
- [107]. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002; 346(25):1937–1947. [PubMed: 12075054]
- [108]. Iqbal J, Meyer PN, Smith L, et al. BCL2 predicts survival in germinal center B-cell-like diffuse large B-Cell lymphoma treated with CHOP-like therapy and rituximab. *Clin Cancer Res*. 2011 Epub 2011/2009/2022.
- [109]. Ngan BY, Chen-Levy Z, Weiss LM, et al. Expression in non-Hodgkin's lymphoma of the bcl-2 protein associated with the t(14;18) chromosomal translocation. *N Engl J Med*. 1988; 318(25):1638–1644. [PubMed: 3287162]
- [110]. Wallace DJ, Shen D, Reed GF, 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(7):2750–2756. [PubMed: 16799010]
- [111]. Lossos IS, Alizadeh AA, Eisen MB, et al. Ongoing immunoglobulin somatic mutation in germinal center B cell-like but not in activated B cell-like diffuse large cell lymphomas. *Proc Natl Acad Sci U S A*. 2000; 97(18):10209–10213. [PubMed: 10954754]
- [112]. Malumbres R, Davis J, Ruiz P, et al. Somatic mutated immunoglobulin IGHV@ genes without intraclonal heterogeneity indicate a postgerminal centre origin of primary intraocular diffuse large B-cell lymphomas. *Br J Haematol*. 2007; 138(6):749–755. [PubMed: 17760806]
- [113]. Chen W, Iida S, Louie DC, et al. Heterologous promoters fused to BCL6 by chromosomal translocations affecting band 3q27 cause its deregulated expression during B-cell differentiation. *Blood*. 1998; 91(2):603–607. [PubMed: 9427715]
- [114]. Phan RT, Dalla-Favera R. The BCL6 proto-oncogene suppresses p53 expression in germinal-centre B cells. *Nature*. 2004; 432(7017):635–639. [PubMed: 15577913]
- [115]. Demchenko YN, Kuehl WM. A critical role for the NFkB pathway in multiple myeloma. *Oncotarget*. 2010; 1(1):59–68. [PubMed: 20890394]
- [116]. Ngo VN, Davis RE, Lamy L, et al. A loss-of-function RNA interference screen for molecular targets in cancer. *Nature*. 2006; 441(7089):106–110. [PubMed: 16572121]
- [117]. Izumiyama K, Nakagawa M, Yonezumi M, et al. Stability and subcellular localization of API2-MALT1 chimeric protein involved in t(11;18) (q21;q21) MALT lymphoma. *Oncogene*. 2003; 22(50):8085–8092. [PubMed: 14603249]
- [118]. Ye H, Gong L, Liu H, et al. MALT lymphoma with t(14;18) (q32;q21)/IGH-MALT1 is characterized by strong cytoplasmic MALT1 and BCL10 expression. *J Pathol*. 2005; 205(3):293–301. [PubMed: 15682443]
- [119]. Murga Penas EM, Hinz K, Roser K, et al. Translocations t(11;18)(q21;q21) and t(14;18)(q32;q21) are the main chromosomal abnormalities involving MLT/MALT1 in MALT lymphomas. *Leukemia*. 2003; 17(11):2225–2229. [PubMed: 12931213]
- [120]. Streubel B, Lamprecht A, Dierlamm J, et al. T(14;18) (q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood*. 2003; 101(6):2335–2339. [PubMed: 12406890]
- [121]. Buggage RR, Chan CC, Nussenblatt RB. Ocular manifestations of central nervous system lymphoma. *Curr Opin Oncol*. 2001; 13(3):137–142. [PubMed: 11307054]
- [122]. Chan CC, Shen D, Hackett JJ, et al. Expression of chemokine receptors, CXCR4 and CXCR5, and chemokines, BLC and SDF-1, in the eyes of patients with primary intraocular lymphoma. *Ophthalmology*. 2003; 110(2):421–426. [PubMed: 12578791]

- [123]. Bashir R, Coakham H, Hochberg F. Expression of LFA-1/ ICAM-1 in CNS lymphomas: possible mechanism for lymphoma homing into the brain. *J Neurooncol.* 1992; 12(2):103–110. [PubMed: 1348529]
- [124]. Chan CC, Whitcup SM, Solomon D, et al. Interleukin-10 in the vitreous of patients with primary intraocular lymphoma. *Am J Ophthalmol.* 1995; 120(5):671–673. [PubMed: 7485372]
- [125]. Whitcup SM, Stark-Vancs V, Wittes RE, et al. Association of interleukin 10 in the vitreous and cerebrospinal fluid and primary central nervous system lymphoma. *Arch Ophthalmol.* 1997; 115(9):1157–1160. [PubMed: 9298057]
- [126]. Turner DM, Williams DM, Sankaran D, et al. An investigation of polymorphism in the interleukin-10 gene promoter. *Eur J Immunogenet.* 1997; 24(1):1–8. [PubMed: 9043871]
- [127]. Chan CC. Molecular pathology of primary intraocular lymphoma. *Trans Am Ophthalmol Soc.* 2003; 101:275–292. [PubMed: 14971583]
- [128]. Ramkumar HL, Shen DF, Tuo J, et al. IL-10-1082 SNP and IL-10 in primary CNS and vitreoretinal lymphomas. *Graefes Arch Clin Exp Ophthalmol.* May 25.2012 Epub ahead of print.
- [129]. Chen Y, Zheng T, Lan Q, et al. Cytokine polymorphisms in Th1/Th2 pathway genes, body mass index, and risk of non-Hodgkin lymphoma. *Blood.* 2011; 117(2):585–590. [PubMed: 20952689]
- [130]. Wang SS, Cozen W, Cerhan JR, et al. Immune mechanisms in non-Hodgkin lymphoma: joint effects of the TNF G308A and IL10 T3575A polymorphisms with non-Hodgkin lymphoma risk factors. *Cancer Res.* 2007; 67(10):5042–5054. [PubMed: 17510437]
- [131]. Jarrett RF. Viruses and lymphoma/leukaemia. *J Pathol.* 2006; 208(2):176–186. [PubMed: 16362996]
- [132]. Bangham CR, Toulza F. Adult T cell leukemia/lymphoma: FoxP3(+) cells and the cell-mediated immune response to HTLV-1. *Adv Cancer Res.* 2011; 111:163–182. [PubMed: 21704832]
- [133]. Liu MM, Furusato E, Cao X, et al. Ocular manifestations and pathology of adult T-cell leukemia/lymphoma associated with human T-lymphotropic virus type 1. *Rare Tumors.* 2010; 2(4):e63. [PubMed: 21234255]
- [134]. Buggage RR, Smith JA, Shen D, et al. Conjunctival T-cell lymphoma caused by human T-cell lymphotropic virus infection. *Am J Ophthalmol.* 2001; 131(3):381–383. [PubMed: 11239876]
- [135]. Coupland SE, Chan CC, Smith J. Pathophysiology of retinal lymphoma. *Ocul Immunol Inflamm.* 2009; 17(4):227–237. [PubMed: 19657975]

FIGURE 1.
Clinical photograph of choroidal melanoma. A large choroidal melanoma appears as a dome-shaped, lightly pigmented mass under the retina.

FIGURE 2. Clinical and macroscopic photograph of retinoblastoma. (A) Leukocoria, a white pupillary reflex, and exotropia of the right eye are the most common signs of a child with retinoblastoma. (B) Gross section of an enucleated eye with retinoblastoma shows tumor nodules infiltrating most of the retina and pars plana.

FIGURE 3. Clinical photograph of PVRL. (A) Many cellular clumps and free cells are seen in the vitreous of a patient with PVRL. (B) Multiple subretinal and retinal infiltrates in a PVRL patient.