2 Genetics of Uveal Melanoma

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Abstract: Uveal melanomas (UMs) comprise only 3% of all melanomas, but they are the most common primary intraocular malignancy in adults. The disease is associated with high mortality, with the liver being the most common site for secondary tumors. Genetic studies performed over the last 30 years have provided a wealth of information on the changes found in primary posterior UM (ciliary body and choroid), but less is known about the specific alterations of the rarer and the more benign iris melanomas, or the metastatic lesions. Early cytogenetic studies identified consistent chromosomal abnormalities, including monosomy 3 (M3), gain of the long arm of chromosome 8, and changes affecting both arms of chromosomes 1 and 6. More recently, specific genetic mutations have been related to UM. Prominent among these are mutations of guanine nucleotide-binding protein Q polypeptide/guanine nucleotide-binding protein alpha-11 (*GNAQ/GNA11*), which are mutually exclusive and occur in approximately 90% of posterior UMs. Other mutations such as *BRCA1*-associated protein (*BAP1*), splicing factor 3B subunit 1 (*SF3B1*), eukaryotic translation initiation factor 1A, X-linked (*EIF1AX*), and telomerase reverse transcriptase promoter (*TERTp*) have also been associated with UM. There are clear relationships between cytogenetic alterations and prognosis,

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and M3, 8q+ 6p+, and 1p- can be considered as biomarkers. An improved understanding has also been gained regarding the impact of genetic mutations, but ultimately the underlying drivers of the most predictive changes are poorly understood. This review discusses the cytogenetic alterations and gene mutations of UM and the relationship they have, if any, with the outcome.

Key words: Biomarkers; Cytogenetic; Mutations; Uveal melanoma

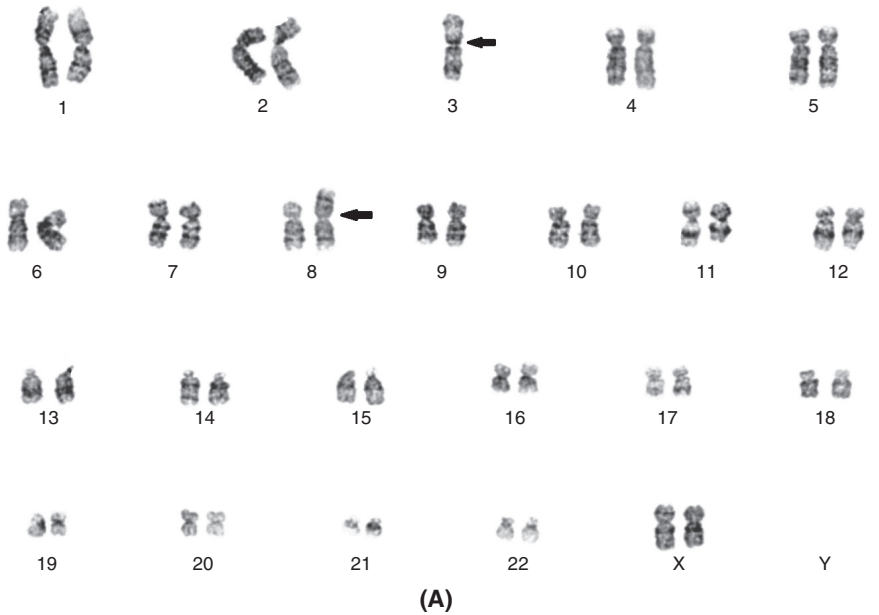
INTRODUCTION

Uveal melanoma (UM) is the most common intraocular malignancy in adults accounting for 80% of all noncutaneous melanomas (1). UM arises from melanocytes within the iris, choroid, and ciliary body collectively termed the uvea or uveal tract, and can be separated into two groups depending on where they are located. Anterior UM arises within the iris, accounting for up to 10% of all UMs. These tumors tend to be benign and are rarely seen to metastasize (2). Posterior UM within the choroid or ciliary body accounts for the remaining 90% of cases and are often highly aggressive and they frequently metastasize. There have been far fewer studies of the genetics of iris melanoma or the metastatic lesions, and they will be reviewed separately after consideration of the genetic changes of posterior (ciliary body and choroid) melanomas. It is also important to bear in mind that UM and cutaneous melanoma (CM) are distinct genetic entities, and they vary not only in their chromosomal changes but also in their mutational signature.

COMMON CHROMOSOME CHANGES IN POSTERIOR UM

The initial investigations exploring the genetic background of UM were almost entirely cytogenetic, and they quickly identified and confirmed that the chromosome changes in UM are not random, and unlike many other solid tumors were relatively few and characteristic in their manner of alteration (3–5). M3, the loss of one copy of chromosome 3, was the most frequent alteration, observed in between 40 and 50% of cases. Also involved was chromosome 8, where simultaneous loss of the short arm (p) and gain of the long arm (q) resulted in the formation of a characteristic isochromosome of 8q (i(8q)). Around 45% of UMs were found to have both M3 and i(8q), with the association most often observed in melanomas with a ciliary body component (Figure 1) (3–15). Some UMs however only show 8q+ without M3.

Other nonrandom abnormalities are gains of 6p and deletions of 1p, found in approximately 40 and 25% of cases, respectively (3, 4, 7–9, 11–15). Deletions of 6q are also observed, and more recent investigations using fluorescence-based methodologies, such as multiplex fluorescence in situ hybridization (MFISH) and array comparative genomic hybridization (aCGH), have shown the combined frequency of changes affecting both arms of chromosome 6 in the order of 60–70%, making chromosome 6 the most altered chromosome in UM (6, 7). The reason why abnormalities of chromosome 6 were under-reported in the earlier cytogenetic



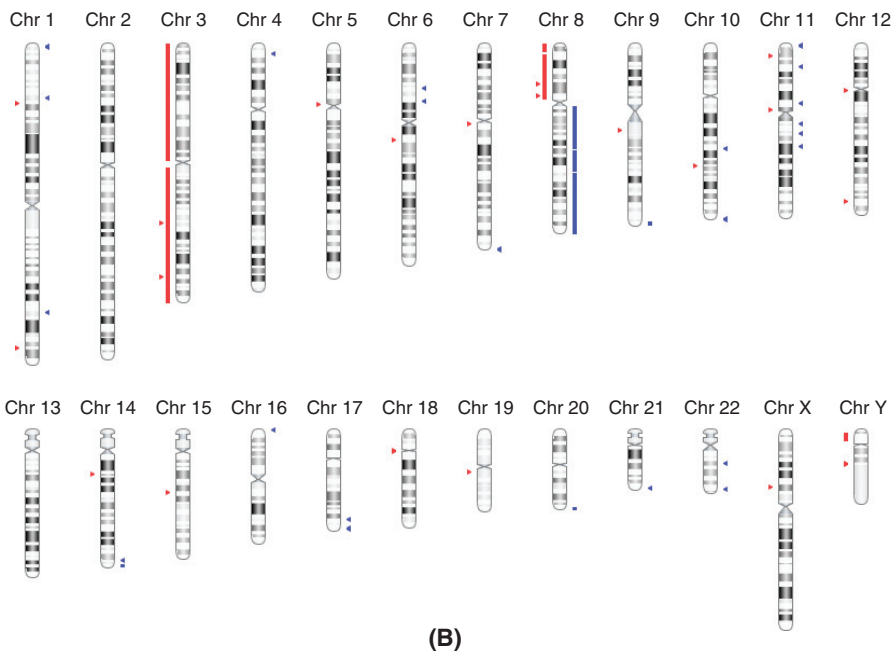


Figure 1 Analysis of chromosome alterations in the same primary uveal melanoma showing the characteristic changes of loss for chromosome 3, or monosomy 3 (M3) and i(8q), as indicated by arrows in the karyotype (a). In the array CGH profile (b), M3 is identified by the red line left of the chromosome ideogram and the i(8q) by the respective loss of 8p (red) and gain of 8q (blue).

studies is that, unlike the gross whole arm changes affecting 1p, M3, and 8q+, alterations of chromosome 6 are often more covert with subtle rearrangements only disclosed through the use of MFISH or aCGH. Other nonrandom changes present in approximately 10–20% of tumors affect chromosomes 9, 10, and 11, while correlated with M3 and i(8q) are deletions of 16q and gain of 21 (8, 10–15). Although changes of all chromosomes have been reported in UM, the relative simplicity of karyotypic alterations, in comparison with other solid tumors, has allowed for a rapid and clear correlation to be observed between specific aberrations and clinical outcomes.

MUTATIONS ASSOCIATED WITH POSTERIOR UM

There have been a number of mutations associated with posterior UM and with the increasing use of rapid high throughput analysis, such as next-generation sequencing, it is likely that more genes will be identified with mutations of relevance to UM. The frequencies at which these mutations occur vary, and their role and importance for UM for the most part remains to be determined. Overall, even deep sequencing studies have shown that UM is a malignancy with a low mutation rate (16). The most common mutations detected however are ubiquitous among posterior UM and involve the guanosine nucleotide-binding protein Q polypeptide (*GNAQ*) and its paralogue, guanosine nucleotide-binding protein alpha-11 (*GNA11*).

GNAQ and GNA11

Mutations of *GNAQ* and *GNA11* are not found in CM, but in posterior UM, mainly targeting codon 209, resulting in an amino acid change from a glutamine to a proline or leucine within the Ras-like domain. Point mutations at codon 209 in either *GNAQ* or *GNA11* are mutually exclusive and have been found to occur in up to 90% of UMs (17–20). There are also rarer mutations that target codon 183 which are present in around 5% of cases, although these usually only occur in the absence of codon 209 mutations (19). *GNAQ* and *GNA11* code for heterotrimeric G_q-proteins containing three subunits, α, β, and γ that facilitate the coupling of transmembrane receptors to intracellular pathways; under normal circumstances, the binding of a ligand to the receptor activates G_q-proteins. When guanonine-5'diphosphate (GDP) is bound to the α subunit, then the G-protein is in an inactive state; however, when guanonine-5'triphosphate (GTP) binds, the β-γ complex is released and in turn activates phospholipase C (PLC). PLC triggers a kinase cascade, resulting in the transcription of pro-proliferative and anti-apoptotic genes, including the upregulation of a key growth regulatory pathway, the mitogen-activated protein kinase (MAPK) pathway (21–23). Mutations at codon 209 of *GNAQ* and *GNA11* target the Ras-like domain of the alpha-q subunit, and the loss of glutamine (essential for intrinsic GTP hydrolysis activity) results in GTP being irreversibly bound to the α subunit and hence constitutive activation of the G_q-protein (17, 18, 20). How these mutations advance UM is still under consideration, but mutations to codon 183 are thought to be less effective in activating the MAPK pathway in comparison to mutations occurring at codon 209. In one instance, mutations of *GNA11* at both codon

209 and codon 183 were found in the same lesion (19). Although in cancer the MAPK pathway is reported as the most consistently upregulated pathway (24–26), the true significance of mutations leading to its upregulation in UM need to be clarified. As activating mutations to *GNAQ* or *GNA11* have been found to be present at all stages of UM progression (including benign lesions), they are thought to be an early, if not initiating, event in UM (17, 27).

BAP1

Harbour and colleagues were the first to describe the inactivation of the Breast Cancer 1 *(BRCA1)*- associated protein 1 (*BAP1*) gene in more than 80% of metastatic UMs, suggesting that this may be a UM tumor suppression gene (28). This gene is located on chromosome 3p21.1 and therefore a copy is often deleted in UM due to the frequent occurrence of M3. The *BAP1* gene encodes for a nuclear localized deubiquitinase with an N-terminal ubiquitin carboxyl hydrolase domain and C-terminal nuclear localization signal domain. Mutations in the *BAP1* gene can prematurely terminate BAP1 protein and also affect the ubiquitin carboxyl-terminal hydrolase domain altering its deubiquitinase activity (29). The BAP1 protein interacts with various proteins, including the tumor suppressor gene *BRCA1*, and thus BAP1 protein plays essential roles in maintaining genome stability, epigenetic modification, transcription regulation, and in the response to DNA damage. Mutations of *BAP1* (unlike those of *GNAQ/GNA11*) are not restricted to melanocytic lesions, and reports in other cancers, as well as UM, have suggested that the action of *BAP1* is wide ranging, directly affecting proliferation by stalling cells in S phase and downregulating the E2F transcription factor (30, 31). Other studies suggest BAP1 protein dysregulation has implications in pluripotency (32). Furthermore, *BAP1* may represent the first clearly identified predisposing gene among hereditary forms of UM. There are many reports of familial UM, often with no clearly identified genetic link (33–36). Germ line mutations among younger patients with UM, and a correlation with *BAP1* mutations in families where there has been a predisposition for renal cancers and mesothelioma, suggest that *BAP1* may indeed be a predisposing gene among a certain class of hereditary UM patients (37–39).

SF3B1

Mutations of the splicing factor 3B subunit 1 (*SF3B1*) gene have been found in 10–20% of UM cases but virtually exclusively in the subset of UM without M3 (40–42). In CM, mutations in *SF3B1* are rare, occurring in only 1% of patients (43), but like *GNAQ/GNA11*, *SF3B1* mutations have been reported in other forms of melanoma (44, 45). *SF3B1* gene is located at chromosome 2q33 and encodes for a subunit of a large complex responsible for processing precursor mRNA (spliceosome), where it ensures correct splicing by retaining pre-mRNA to define the site for splicing (46). Mutations of *SF3B1* can therefore lead to alternative splicing events for multiple genes, with different mutations in UM and other cancers, producing alternate splice variants of a number of genes. For example, in leukemia, and breast and pancreatic cancer, a hotspot at codon 700 is reported (47–50), but for UM and mucosal melanomas mutations at codon 625 of exon 14 predominate (44). The full biological significance of this aberrant splicing of multiple genes

remains to be determined (40, 51, 52), but in leukemia mutations to *SF3B1* alter the DNA damage response, leading to an increase in DNA damage (53).

EIF1AX

Mutations to eukaryotic translation initiation factor 1A, X-linked (*EIF1AX*), a gene located on chromosome Xp22, occur in approximately 13% of posterior UM. In a similar pattern to *SF3B1* mutations, *EIF1AX* mutations are also mainly restricted to UM without M3 (41). Furthermore, mutations of *EIF1AX* appear to be mutually exclusive to *SF3B1* in UM and other melanocytic lesions (41, 54); although reported in thyroid cancer, they only occur in a subset of tumors without V-Raf Murine Sarcoma Viral Oncogene Homolog B1 (*BRAF*) mutations (commonly mutated in CM) (55, 56). It is of interest that *EIF1AX* (similar to *SF3B1*) also encodes for a protein which interacts with mRNA, with a role in initiating translation, through a combination of recognition of target mRNA and stabilization of the ribosome, to prepare mRNA for translation (54, 56). In UM, mutant *EIF1AX* has been confirmed to result in aberrant translation (57), but whether mutations of both *SF3B1* and *EIF1AX* have biological significance due to a generalized deregulation of translation, or a focalized effect targeting the same or similar genes, has not been shown. It is however considered that both *SF3B1* and *EIF1AX* are later events in UM progression, while their mutual exclusivity suggests that they provide alternative evolutionary pathways for disomy-3 (D3) UM, with no numerical abnormalities of chromosome 3 (58).

Other mutations in posterior UM

A number of other mutations have been serially identified in UM, but the incidence is substantially lower than those already discussed, and their relevance may reflect "background noise" rather than driver mutations. Of these, the telomerase reverse transcriptase (*TERT*) gene (located on chromosome 5p15) has been widely reported in many cancers (59–62), but in UM it only has a low mutation frequency of 1% (63, 64). *TERT* has a multifunctional role including, among others, in the maintenance of telomere length, cell-cycle control, and DNA damage response (59, 65–67). Since most studies suggest that UMs have a low mutational burden (68, 69), it is possible that *TERT* mutations are bystanders in UM.

Other mutations occurring in less than 5% of UMs have recently been reported (68, 69). Of these, Cysteinyl Leukotriene Receptor 2 (*CYSLTR2*) and Phospholipase C Beta 4 (*PLCB4*) are mutually exclusive to *GNAQ/GNA11* mutations with presumably the same functional consequences, and they, in combination with others, serve to further classify the mutational signature of UM into potentially four or more subgroups (68). Additional studies are required to clarify the significance of these mutations and whether they complement or drive UM progression.

GENETIC BIOMARKERS OF POSTERIOR UM

Even from early genetic investigations, it was apparent that recurrent alterations in UM could be used to stratify and determine prognosis, with poor prognosis

being survival of 7 years or less (70, 71). Most of the consistent genetic changes/mutations in UM are predictive of outcome to a greater or lesser extent. There is however one notable exception; mutations of *GNAQ/GNA11* (in almost 95% of UM) may vary in their frequency and presence of rare versus common mutations but still have no clear link to patient outcome (17–19, 68). In comparison, simple chromosome changes such as M3 and 8q+ correlate with clinical parameters of poor prognosis such as larger tumor size, epithelioid cell type, and ciliary body involvement (4, 70–72). Both M3 and 8q+ have repeatedly been shown to strongly correlate with a poorer outcome, especially when they occur together in the same tumor (6, 70, 73, 74) and as such form the basis of many biomarker tests. Furthermore, it is clear that the amplification of the long arm of chromosome 8, in the form of an i(8q), is not a static process and within individual UM there will be a level of heterogeneity with some cells showing just a gain of chromosome 8, while others may have one or many more copies of i(8q) (70, 75). Importantly, this drive toward acquiring additional copies of chromosome 8q is linked to not only a poor prognosis but also a significantly shorter survival (6, 70, 74, 76). Deletion of chromosome 1p is also considered a poor prognostic indicator but may be limited as a biomarker to UM where it is associated with M3 (77, 78). As M3 is such a powerful predictor of poor prognosis, it is not altogether surprising that the alternative scenario of D3 is related to improved survival, while much rarer partial deletions of chromosome 3 appear to correlate with an intermediate prognosis (79–81). Finally, there is some ambivalence over the ascribing of prognosis based upon 6p gain. In most UMs, 6p+ is found in tumors with D3 and is therefore indicative of a good outcome (82). Gain of 6p however is not entirely restricted to D3 tumors and can be found as a later change in tumors with M3 and i(8q) (9, 10, 75, 77, 83). Under these circumstances, it is decidedly associated with a poor outcome; therefore, careful consideration of the circumstances must be made if reliance is just placed on gain of 6p alone.

Although mutations of *GNAQ/GNA11* are not predictive, other mutations do confer a prognostic significance, or as a minimum clearly associate with other known indicators of prognosis. As an example, there is some ambivalence over mutations of *BAP1*, which although clearly segregating with M3 in UM, at a frequency of 40–80% and initially reported in over 80% of metastatic tumors, do not themselves seem to predict a poor prognosis (28, 37, 68). The reason may be that mutations of *BAP1* are not restricted to limited hotspots, and recent evidence suggests that they are no more frequent among metastasizing UM compared with nonmetastasizing UM (84). There does seem to be a clear consensus that *BAP1* mutations do show a correlation with reduced expression of BAP1 protein and more specifically that assessment of the protein by immunohistochemistry provides a more robust indication of outcome compared with mutational analysis alone (85).

In general terms, both *SF3B1* and *EIF1AX* mutations can be considered as indicators of a better prognosis, presumably due to their preponderance among D3 UM (42, 63). Mutations of *SF3B1* should however be considered as an indicator of a qualified good prognosis, as approximately 80% of UM with *SF3B1* mutations have been shown to develop later metastasis, despite being D3 (68, 86). The reason why *SF3B1* mutations may identify a later metastatic onset among classically good prognosis D3 UM could be their association with partial gains of 8q, while *EIF1AX* mutations do not (68). The gain of 8q is consistently

predictive of a poorer outcome, but usually when clearly identified in the form of an i(8q), representing whole arm gain of 8q (6, 70). Less is known about the prognostic relationship for partial 8q, partly because few studies have distinguished differences in the manner of acquisition for 8q gain, and where explored, no reduced survival was reported (6), possibly because additional follow-up is required to detect patients who will succumb to late onset metastasis in this subgroup.

In addition to chromosomal and mutational biomarkers, UM can be classified into poor prognostic groups on the basis of expression of a target set of genes (initially 26 but later refined to 15 genes) that delineate UM into low risk (class 1) and high risk (class 2) (87, 88). Using this data set, class 1 UM patients are ascribed a survival of 95% at around 7 years, while class 2 had approximately only a 30% survival. Further stratification of these subgroups can be achieved when expression of preferentially expressed antigen in melanoma (PRAME) is considered, as increased expression in class 1 UM identifies those with a very low rate of metastasis (89).

GENETIC ANALYSIS OF METASTATIC LESIONS OF POSTERIOR UM

Most UM patients who develop metastatic disease will do so in the liver, often to the exclusion of other sites. There have however been comparatively few genetic studies of the lesions themselves, and not surprisingly those reported are mainly hepatic metastases (5, 90–92). Changes found in the metastases mirror those reported for primary UM, with the single most consistent and frequent change being the 8q gain. It is however of interest that *BAP1* mutations and other predictors of poor outcome, such as M3 and 1p-, are not more frequently represented among metastatic lesions. Conversely, 6p gain, considered as an indicator essentially of good prognosis, is also reported in metastatic lesions (90, 93), whereas reports suggest that although *GNAQ/GNA11* are not predictive of prognosis, *GNA11* mutations are more frequent among metastases (94). Of course, some of these observations require further validation once more information on the metastases themselves becomes available.

THE SEQUENCE OF GENETIC PROGRESSION IN POSTERIOR UM

The constitutive activation of the MAPK pathway through mutation has been identified as an early event in many cancers (17, 95, 96). As most posterior UMs have activating mutations of *GNAQ/GNA11*, it is clearly an early, if not initiating, event. Studies have however reported that melanocytic nevi, melanocytomas, and blue nevi also have mutations of GNAQ/GNA11, and in these benign lesions it is purported to associate with an intermediate state with potential to transform and become malignant (97). In relation to posterior UM, the findings of studies on

choroidal nevi (98) and anterior iris UM are perhaps more pertinent (see below). As iris melanomas are, in the majority of cases, manifestly benign, the presence of *GNAQ/GNA11* mutations suggest that in UM they are initiating events, increasing proliferation by upregulating the MAPK pathway, but not necessarily inducing transformation to malignancy. As such, *GNAQ/GNA11* mutations act as a rung on a ladder toward malignancy but other changes are also necessary to proceed.

At the forefront of these additional alterations is M3, with many cytogenetic/molecular studies identifying it as an early and sometimes the only other change in addition to *GNAQ/GNA11* (99). Equally, 6p+ when associated with D3 tumors appears to fulfill the same role in providing the next step in tumor progression (82). Mutations of *BAP1* in M3 UM, and *SF3B1* and *EIF1AX* in D3 UM, are closely linked to the cytogenetic changes of M3 and 6p+, respectively. There are few studies that have made detailed comparisons, so information on the timing of these events is limited. *BAP1* mutations are however reported as subsequent to M3 (68), and as mutations of both *SF3B1* and *EIF1AX* are reported as being related to 6p+ in UM, it can be assumed that they are secondary to that of 6p gain (69, 86). In terms of gross abnormalities, there is almost universal agreement that 8q gain is a later event and its high frequency among metastatic lesions acts as confirmation of the relationship with advanced UM (70, 77, 82, 83, 99, 100). The proposed sequence with relationship to outcome and clinical parameters is presented in Figure 2.

IRIS MELANOMAS

There have been far fewer genetic studies performed on iris melanomas compared to their posterior counterparts, but from the information so far gleaned they appear to represent somewhat a halfway house between posterior UM and CM (101–106). In this respect, iris melanomas are reported as sharing changes with posterior UM such as deletions of 1p, M3, and chromosome 6 alterations (both p and q). Evidence however suggests that iris melanomas also have abnormalities of other chromosomes rarely affected in posterior UM, such as changes of chromosome 9p, an alteration more often related to CM (105), and rearrangements affecting chromosome 18 (105, 106). Equally, iris melanomas are reported as sharing mutations with posterior UM and also CM, with studies identifying mutations of both *GNAQ/GNA11* and *BRAF* in iris melanomas (105, 107). Furthermore, a surprisingly high frequency of *EIF1AX* mutations has been reported for iris melanomas (108). Mutations have not yet been documented for *SF3B1*, and it is likely that the small sample size for most of these reports means that the rarer mutations may still be detectable in iris melanomas, once more are sequenced. It is premature to predict how these mutations and chromosome changes impact on iris melanoma development; however, it was observed that *BRAF* mutations in 9 of the 19 tumors sequenced were more likely to associate with tumor recurrence (107), while in contrast the relatively high frequency of the good prognostic mutations of *EIF1AX* is perhaps symptomatic of the benign nature of most iris melanomas, or vice versa.

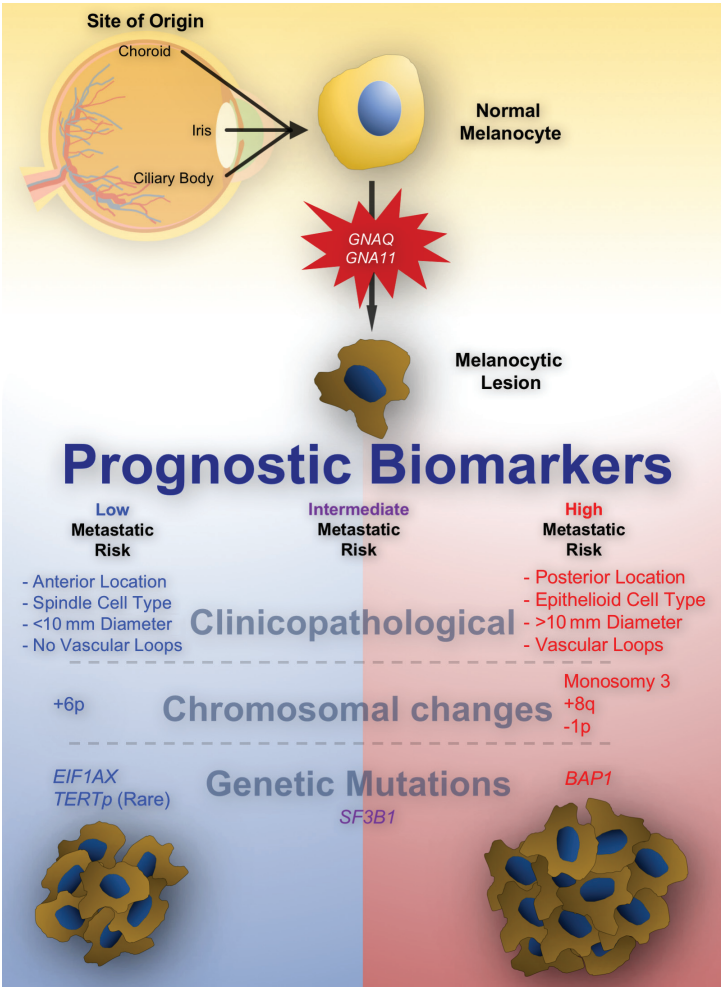


Figure 2 Correlation of clinicopathological, chromosomal, and genetic biomarkers with prognosis in uveal melanoma and putative sequence of events. There are well-defined clinical, chromosomal, and genetic biomarkers identified in UM that contribute to prognosis in UM. Mutations to *GNAQ* and its paralogue *GNA11* have been identified as an early change in UM and are not associated with prognosis but may represent an initiating event. Poor prognosis is associated with a posterior location, epithelioid cell type, monosomy 3, isochromosome 8q, and loss of 1p. Recent studies have also identified that mutations to *BAP1* are indicative of a poor prognosis, whereas mutations to *EIF1AX*, although considered a later event in UM progression, are in fact associated with low metastatic risk. Mutations to *SF3B1* are also thought to occur late in UM progression and are associated with an intermediate prognosis in patients without monosomy 3, who otherwise would have had a good prognosis.

CONCLUSION

Since genetic studies have become engaged in improving the understanding of the basis of UM, related chromosome changes and genetic mutations have been identified that can be usefully employed as biomarkers to predict prognosis. Whatever methodology is applied, the use of genetic biomarkers is now the most reliable method for detecting outcome, but no single method is infallible. The challenge now is to improve our understanding and to extrapolate how these quintessential alterations act as drivers, and most importantly how their behavior can be counteracted. In this respect, it is highly likely that future studies will be able to fine-tune the relationship between individual genetic mutations and their role in UM. Understanding how gross chromosomal changes, such as those of 1p, M3, 6p+ and 8q+, serve to drive, or differentiate, UM behavior is entirely another ball game. Furthermore, a virtually undescribed landscape that could impact on such changes is emerging, with recent studies suggesting that the well-described genetic biomarkers of UM are only a signpost for epigenetic modulators capable of dividing the broad brush genetic classes into further subgroups, with an impact not yet fully comprehended (68, 69, 109). The genetic landscape of UM, although not as obviously unstable as many cancers, is not however featureless and seemingly is far more complex than first thought.

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REFERENCES

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: Trends in incidence, treatment, and survival. Ophthalmology. 2011;118(9):1881–5. http://dx.doi.org/10.1016/j.ophtha.2011.01.040
2. Shields CL, Kaliki S, Furuta M, Mashayekhi A, Shields JA. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8,033 cases. Retina. 2012;32(7):1363–72. http://dx.doi.org/10.1097/IAE.0b013e31824d09a8
3. Sisley K, Rennie IG, Cottam DW, Potter AM, Potter CW, Rees RC. Cytogenetic findings in six posterior uveal melanomas: Involvement of chromosomes 3, 6, and 8. Genes Chromosomes Cancer. 1990;2(3):205–9. http://dx.doi.org/10.1002/gcc.2870020307
4. Sisley K, Cottam DW, Rennie IG, Parsons MA, Potter AM, Potter CW, et al. Non-random abnormalities of chromosomes 3, 6, and 8 associated with posterior uveal melanoma. Genes Chromosomes Cancer. 1992;5(3):197–200. http://dx.doi.org/10.1002/gcc.2870050304
5. Rey JA, Bello MJ, de Campos J, Ramos MC, Benítez J. Cytogenetic findings in a human malignant melanoma metastatic to the brain. Cancer Genet Cytogenet. 1985;16(2):179–83. http://dx.doi.org/10.1016/0165-4608(85)90013-5

6. Hammond DW, Al-Shammari NS, Danson S, Jacques R, Rennie IG, Sisley K. High-resolution array CGH analysis identifies regional deletions and amplifications of chromosome 8 in uveal melanoma. Invest Ophthalmol Vis Sci. 2015;56(6):3460–6. http://dx.doi.org/10.1167/iovs.14-16215
7. Sisley K, Tattersall N, Dyson M, Smith K, Mudhar HS, Rennie IG. Multiplex fluorescence in situ hybridization identifies novel rearrangements of chromosomes 6, 15, and 18 in primary uveal melanoma. Exp Eye Res. 2006;83(3):554–9. http://dx.doi.org/10.1016/j.exer.2006.02.007
8. Prescher G, Bornfeld N, Friedrichs W, Seeber S, Becher R. Cytogenetics of twelve cases of uveal melanoma and patterns of nonrandom anomalies and isochromosome formation. Cancer Genet Cytogenet. 1995;80(1):40–6. http://dx.doi.org/10.1016/0165-4608(94)00165-8
9. Prescher G, Bornfeld N, Becher R. Nonrandom chromosomal abnormalities in primary uveal melanoma. J Natl Cancer Inst. 1990;82(22):1765–9. http://dx.doi.org/10.1093/jnci/82.22.1765
10. Horsman DE, White VA. Cytogenetic analysis of uveal melanoma consistent occurrence of monosomy 3 and trisomy 8q. Cancer. 1993;71(3):811–19. http://dx.doi.org/10.1002/1097-0142(19930201)71:3%3C811::AID-CNCR2820710325%3E3.0.CO;2-F
11. Singh AD, Boghosian-Sell L, Wary KK, Shields CL, De Potter P, Donoso LA, et al. Cytogenetic findings in primary uveal melanoma. Cancer Genet Cytogenet. 1994;72(2):109–15. http://dx.doi.org/10.1016/0165-4608(94)90125-2
12. Gordon KB, Thompson CT, Char DH, O'Brien JM, Kroll S, Ghazvini S, et al. Comparative genomic hybridization in the detection of DNA copy number abnormalities in uveal melanoma. Cancer Res. 1994;54(17):4764–8.
13. Speicher MR, Prescher G, du Manoir S, Jauch A, Horsthemke B, Bornfeld N, et al. Chromosomal gains and losses in uveal melanomas detected by comparative genomic hybridization. Cancer Res. 1994;54(14):3817–23.
14. Naus NC, van Drunen E, de Klein A, Luyten GP, Paridaens DA, Alers JC, et al. Characterization of complex chromosomal abnormalities in uveal melanoma by fluorescence in situ hybridization, spectral karyotyping, and comparative genomic hybridization. Genes Chromosomes Cancer. 2001;30(3):267–73. http://dx.doi.org/10.1002/1098-2264(2000)9999:9999%3C::AID-GCC1088%3E3.0.CO;2-7
15. Kilic E, van Gils W, Lodder E, Beverloo HB, van Til ME, Mooy CM, et al. Clinical and cytogenetic analyses in uveal melanoma. Invest Ophthalmol Vis Sci. 2006;47(9):3703–7. http://dx.doi.org/10.1167/iovs.06-0101
16. Johansson P, Aoude LG, Wadt K, Glasson WJ, Warrier SK, Hewitt AW, et al. Deep sequencing of uveal melanoma identifies a recurrent mutation in PLCB4. Oncotarget. 2016;7(4):4624. http://dx.doi.org/10.18632/oncotarget.6614
17. Onken MD, Worley LA, Long MD, Duan S, Council ML, Bowcock AM, et al. Oncogenic mutations in GNAQ occur early in uveal melanoma. Invest Ophthalmol Vis Sci. 2008;49(12):5230–4. http://dx.doi.org/10.1167/iovs.08-2145
18. Van Raamsdonk CD, Bezrookove V, Green G, Bauer J, Gaugler L, O'Brien JM, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature. 2009;457(7229):599–602. http://dx.doi.org/10.1038/nature07586
19. Van Raamsdonk CD, Griewank KG, Crosby MB, Garrido MC, Vemula S, Wiesner T, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med. 2010;363(23):2191–9. http://dx.doi.org/10.1056/NEJMoa1000584
20. Sisley K, Doherty R, Cross NA. What hope for the future? GNAQ and uveal melanoma. Br J Ophthalmol. 2011;95(5):620–3. http://dx.doi.org/10.1136/bjo.2010.182097
21. Radhika V, Dhanasekaran N. Transforming G proteins. Oncogene. 2001;20(13):1607. http://dx.doi.org/10.1038/sj.onc.1204274
22. Goldsmith Z, Dhanasekaran D. G protein regulation of MAPK networks. Oncogene. 2007;26(22):3122. http://dx.doi.org/10.1038/sj.onc.1210407
23. Feng X, Degese MS, Iglesias-Bartolome R, Vaque JP, Molinolo AA, Rodrigues M, et al. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. Cancer Cell. 2014;25(6):831–45. http://dx.doi.org/10.1016/j.ccr.2014.04.016

24. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007;26(22):3279. http://dx.doi.org/10.1038/sj.onc.1210421
25. Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer. 2003;3(1):11. http://dx.doi.org/10.1038/nrc969
26. Kim EK, Choi E-J. Pathological roles of MAPK signaling pathways in human diseases. Biochim Biophys Acta. 2010;1802(4):396–405. http://dx.doi.org/10.1016/j.bbadis.2009.12.009
27. Bauer J, Kilic E, Vaarwater J, Bastian BC, Garbe C, de Klein A. Oncogenic GNAQ mutations are not correlated with disease-free survival in uveal melanoma. Br J Cancer. 2009;101(5):813. http://dx.doi.org/10.1038/sj.bjc.6605226
28. Harbour JW, Onken MD, Roberson ED, Duan S, Cao L, Worley LA, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010;330(6009):1410–13. http://dx.doi.org/10.1126/science.1194472
29. Jensen DE, Proctor M, Marquis ST, Gardner HP, Ha SI, Chodosh LA, 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):1097–112. http://dx.doi.org/10.1038/sj.onc.1201861
30. Pan H, Jia R, Zhang L, Xu S, Wu Q, Song X, et al. BAP1 regulates cell cycle progression through E2F1 target genes and mediates transcriptional silencing via H2A monoubiquitination in uveal melanoma cells. Int J Biochem Cell Biol. 2015;60:176–84. http://dx.doi.org/10.1016/j.biocel.2015.01.001
31. Bott M, Brevet M, Taylor BS, Shimizu S, Ito T, Wang L, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21. 1 losses in malignant pleural mesothelioma. Nature genetics. 2011;43(7):668–72. http://dx.doi.org/10.1038/ng.855
32. Moon S, Lee Y-K, Lee S-W, Um S-J. Suppressive role of OGT-mediated O-GlcNAcylation of BAP1 in retinoic acid signaling. Biochem Biophys Res Commun. 2017;492(1):89–95. http://dx.doi.org/10.1016/j.bbrc.2017.08.029
33. Singh AD, Shields CL, De Potter P, Shields JA, Trock B, Cater J, et al. Familial uveal melanoma: Clinical observations on 56 patients. Arch Ophthalmol. 1996;114(4):392–9. http://dx.doi.org/10.1001/archopht.1996.01100130388005
34. Singh AD, Croce CM, Wary KK, Shields JA, Donoso LA, Shields CL, 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. http://dx.doi.org/10.3109/13816819609057868
35. Smith JH, Padnick-Silver L, Newlin A, Rhodes K, Rubinstein WS. Genetic study of familial uveal melanoma: Association of uveal and cutaneous melanoma with cutaneous and ocular nevi. Ophthalmology. 2007;114(4):774–9. http://dx.doi.org/10.1016/j.ophtha.2006.08.041
36. Singh AD, Wang MX, Donoso LA, Shields CL, De Potter P, Shields JA, et al. Familial uveal melanoma, III: Is the occurrence of familial uveal melanoma coincidental? Arch Ophthalmol. 1996;114(9):1101–4. http://dx.doi.org/10.1001/archopht.1996.01100140303008
37. Abdel-Rahman MH, Pilarski R, Cebulla CM, Massengill JB, Christopher BN, Boru G, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. J Med Genet. 2011;48(12):856–9. http://dx.doi.org/10.1136/jmedgenet-2011-100156
38. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43(10):1022–5. http://dx.doi.org/10.1038/ng.912
39. Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois-d'Enghien C, et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am J Hum Genet. 2013;92(6):974–80. http://dx.doi.org/10.1016/j.ajhg.2013.04.012
40. Furney SJ, Pedersen M, Gentien D, Dumont AG, Rapinat A, Desjardins L, et al. SF3B1 mutations are associated with alternative splicing in uveal melanoma. Cancer Discov. 2013;3(10):1122–9. http://dx.doi.org/10.1158/2159-8290.CD-13-0330
41. Martin M, Masshofer L, Temming P, Rahmann S, Metz C, Bornfeld N, et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat Genet. 2013;45(8):933–6. http://dx.doi.org/10.1038/ng.2674
42. Harbour JW, Roberson ED, Anbunathan H, Onken MD, Worley LA, Bowcock AM. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. Nat Genet. 2013;45(2):133–5. http://dx.doi.org/10.1038/ng.2523

43. Kong Y, Krauthammer M, Halaban R. Rare SF3B1 R625 mutations in cutaneous melanoma. Melanoma Res. 2014;24(4):332–4. http://dx.doi.org/10.1097/CMR.0000000000000071
44. Hintzsche JD, Gorden NT, Amato CM, Kim J, Wuensch KE, Robinson SE, et al. Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. Melanoma Res. 2017;27(3):189–99. http://dx.doi.org/10.1097/CMR.0000000000000345
45. Schilling B, Bielefeld N, Sucker A, Hillen U, Zimmer L, Schadendorf D, et al. Lack of SF3B1 R625 mutations in cutaneous melanoma. Diagn Pathol. 2013;8(1):87. http://dx.doi.org/10.1186/1746-1596-8-87
46. Alsafadi S, Houy A, Battistella A, Popova T, Wassef M, Henry E, et al. Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage. Nat Commun. 2016;7:10615. http://dx.doi.org/10.1038/ncomms10615
47. Malcovati L, Papaemmanuil E, Bowen DT, Boultwood J, Della Porta MG, Pascutto C, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood. 2011;118(24):6239–46. http://dx.doi.org/10.1182/blood-2011-09-377275
48. Wang L, Lawrence MS, Wan Y, Stojanov P, Sougnez C, Stevenson K, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med. 2011;365(26):2497–506. http://dx.doi.org/10.1056/NEJMoa1109016
49. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491(7424):399–405. http://dx.doi.org/10.1038/nature11547
50. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70. http://dx.doi.org/10.1038/nature11412
51. DeBoever C, Ghia EM, Shepard PJ, Rassenti L, Barrett CL, Jepsen K, et al. Transcriptome sequencing reveals potential mechanism of cryptic 3'splice site selection in SF3B1-mutated cancers. PLoS Comput Biol. 2015;11(3):e1004105. http://dx.doi.org/10.1371/journal.pcbi.1004105
52. Jin S, Su H, Tran N-T, Song J, Lu SS, Li Y, et al. Splicing factor SF3B1K700E mutant dysregulates erythroid differentiation via aberrant alternative splicing of transcription factor TAL1. PLoS One. 2017;12(5):e0175523. http://dx.doi.org/10.1371/journal.pone.0175523
53. Te Raa G, Derks I, Navrkalova V, Skowronska A, Moerland P, Van Laar J, et al. The impact of SF3B1 mutations in CLL on the DNA-damage response. Leukemia. 2015;29(5):1133. http://dx.doi.org/10.1038/leu.2014.318
54. Küsters-Vandevelde HV, Creytens D, Van Engen-van Grunsven AC, Jeunink M, Winnepenninckx V, Groenen PJ, et al. SF3B1 and EIF1AX mutations occur in primary leptomeningeal melanocytic neoplasms; yet another similarity to uveal melanomas. Acta Neuropathol Commun. 2016;4(1):5. http://dx.doi.org/10.1186/s40478-016-0272-0
55. Yoo S-K, Lee S, Kim S-J, Jee H-G, Kim B-A, Cho H, et al. Comprehensive analysis of the transcriptional and mutational landscape of follicular and papillary thyroid cancers. PLoS Genet. 2016;12(8):e1006239. http://dx.doi.org/10.1371/journal.pgen.1006239
56. Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, et al. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159(3):676–90. http://dx.doi.org/10.1016/j.cell.2014.09.050
57. Johnson CP, Kim IK, Esmaeli B, Amin-Mansour A, Treacy DJ, Carter SL, et al. Systematic genomic and translational efficiency studies of uveal melanoma. PLoS One. 2017;12(6):e0178189. http://dx.doi.org/10.1371/journal.pone.0178189
58. Decatur CL, Ong E, Garg N, Anbunathan H, Bowcock AM, Field MG, et al. Driver mutations in uveal melanoma: Associations with gene expression profile and patient outcomes. JAMA Ophthalmol. 2016;134(7):728–33. http://dx.doi.org/10.1001/jamaophthalmol.2016.0903
59. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013;339(6122):957–9. http://dx.doi.org/10.1126/science.1229259
60. Bojesen SE, Pooley KA, Johnatty SE, Beesley J, Michailidou K, Tyrer JP, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet. 2013;45(4):371–84. http://dx.doi.org/10.1038/ng.2566

61. Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009;41(2):221–7. http://dx.doi.org/10.1038/ng.296
62. Blasco MA. Telomeres and human disease: Ageing, cancer and beyond. Nat Rev Genet. 2005;6(8):611–22. http://dx.doi.org/10.1038/nrg1656
63. Dono M, Angelini G, Cecconi M, Amaro A, Esposito AI, Mirisola V, et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: Detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. Br J Cancer. 2014;110(4):1058–65. http://dx.doi.org/10.1038/bjc.2013.804
64. Koopmans AE, Ober K, Dubbink HJ, Paridaens D, Naus NC, Belunek S, et al. Prevalence and implications of TERT promoter mutation in uveal and conjunctival melanoma and in benign and premalignant conjunctival melanocytic lesions. Invest Ophthalmol Vis Sci. 2014;55(9):6024–30. http://dx.doi.org/10.1167/iovs.14-14901
65. Cesare AJ, Reddel RR. Alternative lengthening of telomeres: Models, mechanisms and implications. Nat Rev Genet. 2010;11(5):319–30. http://dx.doi.org/10.1038/nrg2763
66. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. Eur J Cancer. 1997;33(5):787–91. http://dx.doi.org/10.1016/S0959-8049(97)00062-2
67. Wu XQ, Huang C, He X, Tian YY, Zhou DX, He Y, et al. Feedback regulation of telomerase reverse transcriptase: New insight into the evolving field of telomerase in cancer. Cell Signal. 2013;25(12):2462–8. http://dx.doi.org/10.1016/j.cellsig.2013.08.009
68. Robertson AG, Shih J, Yau C, Gibb EA, Oba J, Mungall KL, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell. 2017;32(2):204–20.e15.
69. Royer-Bertrand B, Torsello M, Rimoldi D, El Zaoui I, Cisarova K, Pescini-Gobert R, et al. Comprehensive genetic landscape of uveal melanoma by whole-genome sequencing. Am J Hum Genet. 2016;99(5):1190–8. http://dx.doi.org/10.1016/j.ajhg.2016.09.008
70. Sisley K, Rennie IG, Parsons MA, Jacques R, Hammond DW, Bell SM, et al. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis. Genes Chromosomes Cancer. 1997;19(1):22–8. http://dx.doi.org/10.1002/(SICI)1098-2264(199705)19:1%3C22::AID-GCC4%3E3.0.CO;2-2
71. Bornfeld N, Prescher G, Becher R, Hirche H, Jöckel K, Horsthemke B. Prognostic implications of monosomy 3 in uveal melanoma. Lancet. 1996;347(9010):1222–5. http://dx.doi.org/10.1016/S0140-6736(96)90736-9
72. Singh A, Shields C, Shields J. Prognostic factors in uveal melanoma. Melanoma Res. 2001;11(3):255–63. http://dx.doi.org/10.1097/00008390-200106000-00007
73. Patel KA, Edmondson ND, Talbot F, Parsons MA, Rennie IG, Sisley K. Prediction of prognosis in patients with uveal melanoma using fluorescence in situ hybridisation. Br J Ophthalmol. 2001;85(12):1440–4. http://dx.doi.org/10.1136/bjo.85.12.1440
74. Versluis M, de Lange MJ, van Pelt SI, Ruivenkamp CA, Kroes WG, Cao J, et al. Digital PCR validates 8q dosage as prognostic tool in uveal melanoma. PLoS One. 2015;10(3):e0116371. http://dx.doi.org/10.1371/journal.pone.0116371
75. Sisley K, Parsons M, Garnham J, Potter A, Curtis D, Rees R, et al. Association of specific chromosome alterations with tumour phenotype in posterior uveal melanoma. Br J Cancer. 2000;82(2):330–8.
76. van den Bosch T, van Beek JG, Vaarwater J, Verdijk RM, Naus NC, Paridaens D, et al. Higher percentage of FISH-determined monosomy 3 and 8q amplification in uveal melanoma cells relate to poor patient prognosis. Invest Ophthalmol Vis Sci. 2012;53(6):2668–74. http://dx.doi.org/10.1167/iovs.11-8697
77. Aalto Y, Eriksson L, Seregard S, Larsson O, Knuutila S. Concomitant loss of chromosome 3 and whole arm losses and gains of chromosome 1, 6, or 8 in metastasizing primary uveal melanoma. Invest Ophthalmol Vis Sci. 2001;42(2):313–17.
78. Kilic E, Naus NC, van Gils W, Klaver CC, van Til ME, Verbiest MM, et al. Concurrent loss of chromosome arm 1p and chromosome 3 predicts a decreased disease-free survival in uveal melanoma patients. Invest Ophthalmol Vis Sci. 2005;46(7):2253–7. http://dx.doi.org/10.1167/iovs.04-1460
79. Parrella P, Fazio VM, Gallo AP, Sidransky D, Merbs SL. Fine mapping of chromosome 3 in uveal melanoma. Cancer Res. 2003;63(23):8507–10.

80. Tschentscher F, Hüsing J, Hölter T, Kruse E, Dresen IG, Jöckel K-H, et al. Tumor classification based on gene expression profiling shows that uveal melanomas with and without monosomy 3 represent two distinct entities. Cancer Res. 2003;63(10):2578–84.
81. Abdel-Rahman MH, Christopher BN, Faramawi MF, Said-Ahmed K, Cole C, McFaddin A, et al. Frequency, molecular pathology and potential clinical significance of partial chromosome 3 aberrations in uveal melanoma. Mod Pathol. 2011;24(7):954–62. http://dx.doi.org/10.1038/modpathol.2011.51
82. Parrella P, Sidransky D, Merbs SL. Allelotype of posterior uveal melanoma. Cancer Res. 1999;59(13):3032–7.
83. Sisley K. Tumors of the eye. In: Heim S, Mitelman F, editors. Cancer cytogenetics: Chromosomal and molecular genetic aberrations of tumor cells. 4th ed. Chichester: John Wiley and Sons; 2015. p. 538–54.
84. Staby KM, Gravdal K, Mørk SJ, Heegaard S, Vintermyr OK, Krohn J. Prognostic impact of chromosomal aberrations and GNAQ, GNA11 and BAP1 mutations in uveal melanoma. Acta Ophthalmol. 2017;96:31–8. http://dx.doi.org/10.1111/aos.13452.
85. Kalirai H, Dodson A, Faqir S, Damato B, Coupland S. Lack of BAP1 protein expression in uveal melanoma is associated with increased metastatic risk and has utility in routine prognostic testing. Br J Cancer. 2014;111(7):1373–80. http://dx.doi.org/10.1038/bjc.2014.417
86. Yavuzyigitoglu S, Koopmans AE, Verdijk RM, Vaarwater J, Eussen B, Van Bodegom A, et al. Uveal melanomas with SF3B1 mutations: A distinct subclass associated with late-onset metastases. Ophthalmology. 2016;123(5):1118–28. http://dx.doi.org/10.1016/j.ophtha.2016.01.023
87. Onken MD, Worley LA, Ehlers JP, Harbour JW. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. Cancer Res. 2004;64(20):7205–9. http://dx.doi.org/10.1158/0008-5472.CAN-04-1750
88. Harbour JW. A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile. In: Thurin M, Marincola F, editors. Molecular diagnostics for melanoma: Methods and protocols. Totowa: Humana Press; 2014. p. 427– 40.
89. Field MG, Decatur CL, Kurtenbach S, Gezgin G, van der Velden PA, Jager MJ, et al. PRAME as an independent biomarker for metastasis in uveal melanoma. Clin Cancer Res. 2016;22(5):1234–42. http://dx.doi.org/10.1158/1078-0432.CCR-15-2071
90. Van Beek JG, Koopmans AE, Vaarwater J, Verdijk RM, de Klein A, Naus NC, et al. Metastatic disease in uveal melanoma: Importance of a genetic profile? Melanoma Res. 2015;25(5):447–9. http://dx.doi.org/10.1097/CMR.0000000000000176
91. Trolet J, Hupé P, Huon I, Lebigot I, Decraene C, Delattre O, et al. Genomic profiling and identification of high-risk uveal melanoma by array CGH analysis of primary tumors and liver metastases. Invest Ophthalmol Vis Sci. 2009;50(6):2572–80. http://dx.doi.org/10.1167/iovs.08-2296
92. McCarthy C, Kalirai H, Lake SL, Dodson A, Damato BE, Coupland SE. Insights into genetic alterations of liver metastases from uveal melanoma. Pigment Cell Melanoma Res. 2016;29(1):60–7. http://dx.doi.org/10.1111/pcmr.12433
93. Yonekawa Y, Kim IK. Epidemiology and management of uveal melanoma. Hematol Oncol Clin North Am. 2012;26(6):1169–84. http://dx.doi.org/10.1016/j.hoc.2012.08.004
94. Griewank KG, Van De Nes J, Schilling B, Moll I, Sucker A, Kakavand H, et al. Genetic and clinicopathologic analysis of metastatic uveal melanoma. Mod Pathol. 2014;27(2):175–83. http://dx.doi.org/10.1038/modpathol.2013.138
95. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949–54. http://dx.doi.org/10.1038/nature00766
96. McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta. 2007;1773(8):1263–84. http://dx.doi.org/10.1016/j.bbamcr.2006.10.001
97. Marwaha N, Batanian JR, Coppens JR, Pierson MJ, Richards-Yutz J, Ebrahimzadeh J, et al. Subcutaneous melanocytoma mimicking a lipoma: A rare presentation of a rare neoplasm with histological, immunohistochemical, cytogenetic and molecular characterization. J Cutan Pathol. 2016;43(12):1186–96. http://dx.doi.org/10.1111/cup.12808

98. Vader M, Madigan M, Versluis M, Suleiman H, Gezgin G, Gruis N, et al. GNAQ and GNA11 mutations and downstream YAP activation in choroidal nevi. Br J Cancer. 2017;117(6):884–7. http://dx.doi.org/10.1038/bjc.2017.259
99. Prescher G, Bornfeld N, Becher R. Two subclones in a case of uveal melanoma: Relevance of monosomy 3 and multiplication of chromosome 8q. Cancer Genet Cytogenet. 1994;77(2):144–6. http://dx.doi.org/10.1016/0165-4608(94)90230-5
100. Ehlers JP, Worley L, Onken MD, Harbour JW. Integrative genomic analysis of aneuploidy in uveal melanoma. Clin Cancer Res. 2008;14(1):115–22. http://dx.doi.org/10.1158/1078-0432.CCR-07-1825
101. Sisley K, Brand C, Parsons MA, Maltby E, Rees RC, Rennie IG. Cytogenetics of iris melanomas: Disparity with other uveal tract melanomas. Cancer Genet Cytogenet. 1998;101(2):128–33. http://dx.doi.org/10.1016/S0165-4608(97)00230-6
102. Krishna Y, Kalirai H, Thornton S, Damato BE, Heimann H, Coupland SE. Genetic findings in treatment-naïve and proton-beam-radiated iris melanomas. Br J Ophthalmol. 2016;100(7):1012–16. http://dx.doi.org/10.1136/bjophthalmol-2015-308301
103. Harbour JW, Wilson D, Finger PT, Worley LA, Onken MD. Gene expressing profiling of iris melanomas. Ophthalmology. 2013;120(1):213. http://dx.doi.org/10.1016/j.ophtha.2012.08.016
104. Shields CL, Kaliki S, Hutchinson A, Nickerson S, Patel J, Kancherla S, et al. Iris nevus growth into melanoma: Analysis of 1611 consecutive eyes: The ABCDEF guide. Ophthalmology. 2013;120(4):766–72. http://dx.doi.org/10.1016/j.ophtha.2012.09.042
105. Mensink H, Vaarwater J, De Keizer RJ, de Wolff-Rouendaal D, Mooy C, De Klein A, et al. Chromosomal aberrations in iris melanomas. Br J Ophthalmol. 2011;95(3):424–8. http://dx.doi.org/10.1136/bjo.2010.181289
106. Fabian ID, Thaung C, AlHarby L, Sisley K, Mudhar HS, Doherty RE, et al. Late solitary extraocular recurrence from previously resected iris melanoma. Am J Ophthalmol. 2017;181:97–105. http://dx.doi.org/10.1016/j.ajo.2017.06.025
107. Henriquez F, Janssen C, Kemp EG, Roberts F. The T1799A BRAF mutation is present in iris melanoma. Invest Ophthalmol Vis Sci. 2007;48(11):4897–900. http://dx.doi.org/10.1167/iovs.07-0440
108. Scholz SL, Mõller I, Reis H, Süßkind D, van de Nes JA, Leonardelli S, et al. Frequent GNAQ, GNA11, and EIF1AX mutations in iris melanoma. Invest Ophthalmol Vis Sci. 2017;58(9):3464–70. http://dx.doi.org/10.1167/iovs.17-21838
109. Triozzi PL, Eng C, Singh AD. Targeted therapy for uveal melanoma. Cancer Treat Rev. 2008;34(3):247–58. http://dx.doi.org/10.1016/j.ctrv.2007.12.002