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Cytogenetic Abnormalities in Uveal Melanoma Based on Tumor Features and Size in 1059 Patients

The 2016 W. Richard Green Lecture

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Purpose: To determine the risks for altered cytogenetic profile based on melanoma features and size.
Design: Retrospective case series.
Participants: A total of 1059 patients with uveal melanoma.
Methods: Fine-needle aspiration biopsy (FNAB) of tumor for DNA amplification and whole genome array–based assay.
Main Outcome Measures: Risk for cytogenetic abnormalities based on features and size: small (≤3 mm thickness), medium (>3–<8 mm), and large (≥8 mm).
Results: Of 1059 patients with uveal melanoma sampled for status of chromosomes 3, 6, and 8, comparison (normal [disomy] chromosomes 3, 6, and 8 vs. any 3, 6, or 8 abnormality) revealed differences in mean age (55 vs. 58 years, $P = 0.018$), ocular melanocytosis (1% vs. 5%, $P = 0.027$), mean visual acuity (VA) (20/30 vs. 20/50, $P = 0.011$), poor VA (≤20/200) (9% vs. 15%, $P = 0.041$), ciliary body location (5% vs. 11%, $P < 0.001$), extramacular location (73% vs. 87%, $P < 0.001$), increased mean distance to optic disc (3.3 vs. 5.0 mm, $P < 0.001$) and foveola (3.1 vs. 4.7 mm, $P < 0.001$), and increased mean basal diameter (9.8 vs. 12.6 mm, $P < 0.001$) and thickness (3.8 vs. 5.9 mm, $P < 0.001$). Tumors classified as small, medium, and large showed abnormalities with loss of disomy of chromosomes 3 (35%/52%/65%), 6 (15%/34%/51%), and 8 (19%/41%/69%), respectively. By comparison (medium/large vs. small melanoma), the odds ratio (OR) included complete monosomy 3 (3.09, $P < 0.001$), partial monosomy 3 (1.44, $P = 0.053$), 6p gain (3.78, $P < 0.001$), 6q gain (1.37, $P = 0.537$), 6p loss (2.52, $P = 0.410$), 6q loss (12.61, $P < 0.001$), 8p gain (6.16, $P < 0.001$), 8p loss (6.04, $P < 0.001$), and 8q gain (4.87, $P < 0.001$). For chromosome 3 monosomy, the OR was highest for ciliary body location (8.17, $P < 0.001$), tumor thickness ≥8 mm (2.70, $P < 0.001$), tumor base ≥10 mm (2.59, $P < 0.001$), and age ≥60 years (1.83, $P < 0.001$). For chromosome 8p loss, the OR was highest for ciliary body location (53.91, $P = 0.008$), ocular melanocytosis (3.95, $P = 0.038$), and thickness ≥8 mm (5.14, $P < 0.001$), whereas for 8q gain, the OR was highest for ciliary body location (102.87, $P = 0.001$), thickness >8 mm (4.44, $P < 0.001$), and ocular melanocytosis (2.75, $P = 0.049$).
Conclusions: Increasing melanoma size demonstrates greater cytogenetic alterations. Alterations in chromosome 8 show unique correlation with melanocytosis. This suggests that prompt management of small melanoma might reduce chromosomal instability and could improve overall patient survival. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

Genetic testing has become the standard of care in the management of uveal melanoma. Most ocular oncologists use fine-needle aspiration biopsy (FNAB) to sample melanoma for genetic profile using an RNA-based or DNA-based technique.[1–6] This profile allows for stratification of uveal melanoma into low or high risk for metastatic disease and plays into decisions regarding frequency of systemic monitoring, consideration of adjuvant systemic therapy to minimize risk for metastasis, and addressing the psychologic needs of the patient.[7–9]

Most patients want to know the genetic profile of their malignancy. In one analysis studying desire for prognostic testing, Beran et al[7] found that 97% of 99 individuals indicated that they wanted testing, but emphasized that supportive counseling should be available. Those with favorable results were more satisfied than those with unfavorable results.[7] Cook et al[8] found a similar approval rate of 97% of 298 individuals for cytogenetic prognostication, and no patient indicated regret or harm. A low-risk result often relieves the patient with "peace of

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Table 1. Uveal Melanoma Cytogenetics and Clinical Features: Patient Demographics at Presentation (n = 1059)

	Chromosomes 3, 6, 8 Tested, Disomy for all Chromosomes (D368) n = 189 (%)	Only Chromosome 3 Tested, Disomy for Chromosome 3 (D3) n = 237 (%)	With Any Chromosome Abnormality (ND) n = 633 (%)	*P* Value* ND versus D368/D3
Mean age, yrs (median, range)	55 (58, 10–83)	55 (55, 13–88)	58 (59, 14–95)	0.018†
Gender				0.598
Male	97 (51)	110 (46)	310 (49)	
Female	92 (49)	127 (54)	323 (51)	
Race				0.843
White	182 (96)	231 (97)	613 (97)	
African-American	0 (0)	0 (0)	2 (<1)	
Hispanic	5 (3)	6 (3)	15 (2)	
Asian	1 (<1)	0 (0)	1 (<1)	
Others	1 (<1)	0 (0)	2 (<1)	
Affected eye				0.647
Right	100 (53)	127 (54)	319 (50)	
Left	89 (47)	110 (46)	314 (50)	
Ocular melanocytosis	2 (1)	15 (6)	30 (5)	0.027
Mean VA (median)	20/30 (20/25)	20/40 (20/30)	20/50 (20/30)	0.011†
Poor VA	17 (9)	24 (10)	94 (15)	0.041

D3 = disomy of chromosome 3; D368 = disomy of chromosomes 3, 6, and 8; ND = not disomy (implying at least 1 chromosomal abnormality on 3, 6, or 8); VA = visual acuity.
Poor VA is Snellen VA ≤20/200.
*Chi-square test, paired comparisons are by Fisher exact test comparing ND with D368 and D3.
†Analysis of variance followed by post hoc tests using Bonferroni correction.

Table 2. Uveal Melanoma Cytogenetics and Clinical Features: Tumor Features at Presentation (n = 1059)

	Chromosomes 3, 6, 8 Tested, Disomy for all Chromosomes (D368) n = 189 (%)	Only Chromosome 3 Tested, Disomy for Chromosome 3 (D3) n = 237 (%)	With Any Chromosome Abnormality (ND) n = 633 (%)	*P* Value* ND versus D368/D3
Tumor epicenter				<0.001
Choroid	170 (90)	225 (95)	543 (86)	
Ciliary body	9 (5)	7 (3)	69 (11)	
Iris	10 (5)	5 (2)	21 (3)	
Tumor quadrant				<0.001
Macula	50 (27)	66 (28)	83 (13)	
Inferior	38 (20)	37 (16)	165 (26)	
Temporal	31 (16)	45 (19)	149 (24)	
Superior	38 (20)	50 (21)	130 (21)	
Nasal	27 (14)	34 (14)	100 (16)	
Diffuse	5 (3)	5 (2)	6 (1)	
Anterior margin				<0.001
Macula	19 (10)	15 (6)	16 (3)	
Macula to equator	91 (48)	117 (49)	180 (28)	
Equator to ora	46 (24)	78 (33)	205 (32)	
Ciliary body	20 (11)	20 (8)	186 (29)	
Iris	13 (7)	7 (3)	46 (7)	
Posterior margin				<0.001
Macula	119 (63)	150 (63)	305 (48)	
Macula to equator	54 (29)	77 (33)	270 (43)	
Equator to ora	4 (2)	4 (2)	29 (5)	
Ciliary body	4 (2)	3 (1)	11 (2)	
Iris	8 (4)	3 (1)	18 (3)	
Mean distance to optic nerve, mm (median, range)	3.3 (3, 0–15)	3.3 (3, 0–18)	5.0 (4, 0–20)	<0.001†
Mean distance to foveola, mm (median, range)	3.1 (2, 0–13)	3.2 (2, 0–15)	4.7 (3, 0–21)	<0.001†
Mean largest basal diameter, mm (median, range)	9.8 (9, 4–21)	10.0 (10, 3–20)	12.6 (12, 3–24)	<0.001†
Mean thickness, mm (median, range)	3.8 (3.1, 1.2–10.7)	4.1 (3.4, 0.7–11.6)	5.9 (5.0, 0.7–20.4)	<0.001†
Documented growth	33 (17)	55 (23)	78 (12)	<0.001

D3 = disomy of chromosome 3; D368 = disomy of chromosomes 3, 6, and 8; ND = not disomy (implying at least 1 chromosomal abnormality on 3, 6, or 8).
*Chi-square.
†Analysis of variance.