Concomitant Loss of Chromosome 3 and Whole Arm Losses and Gains of Chromosome 1, 6, or 8 in Metastasizing Primary Uveal Melanoma

Yan Aalto,1 Lotta Eriksson,2 Stefan Seregard,2 Olle Larsson,3 and Sakari Knuutila1

PURPOSE. To elucidate the genetic differences between metastasizing and nonmetastasizing primary tumors, uveal melanoma samples were screened for DNA copy number alterations by comparative genomic hybridization (CGH).

METHODS. DNA copy number changes were studied on 14 primary uveal melanomas that had not metastasized, 15 primary uveal melanomas that had metastasized, and on 6 metastases that were available from 6 primary uveal melanomas. CGH is based on quantitation of the fluorescence intensity of differentially labeled DNAs. Tumor DNA labeled with FITC dCTP and dUTP and normal DNA labeled with Texas red dCTP and dUTP were hybridized to normal metaphase chromosomes. The hybridizations were analyzed using an Olympus fluorescence microscope and the ISIS digital image analysis system to identify gain or loss of genetic material.

RESULTS. Primary uveal melanomas that had metastasized and metastases had significantly more changes than primary uveal melanomas that had not metastasized. Comparison between primary nonmetastasizing tumors, metastasizing tumors, and metastases showed that the most common DNA copy number changes were −3 (21%, 75%, 67%, respectively), −6q (7%, 40%, 83%), −1p (0, 33%, 50%), −13q (14%, 13%, 50%), −8p (14%, 27%, 0), +18q (0, 13%, 50%), +8q (14%, 53%, 100%), +6p (29%, 20%, 17%), +1q (0, 7%, 33%), and +16p (0, 7%, 33%).

CONCLUSIONS. Loss of chromosome 3, loss of 6q, and gain of 8q were significantly associated with poor overall survival. In addition, losses of 1p were only found in primary uveal melanomas that had metastasized and in metastases, which suggests that this region may harbor a tumor suppressor gene important in the tumor progression. Finally, loss of chromosome 3 may be associated with isochromosome formation of 1q, 6p, 8q, 16p, 20q, and 22q. (Invest Ophthalmol Vis Sci. 2001;42:313–317)

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Uveal melanoma is the most frequent intraocular tumor in the Western world.1 Despite improvements in primary treatment protocols, more than 50% of the patients still die of late-occurring metastases.2,3 Cytogenetic and molecular genetic studies have revealed that the majority of cases show nonrandom chromosomal aberrations of chromosomes 1, 3, 6, and 8 and that loss of chromosome 3 and gain of 8q are significantly associated with overall survival and the development of metastases.4–8 To gain further insight into the distribution of the chromosomal aberrations between metastasizing and nonmetastasizing primary tumors, we screened uveal melanoma samples for DNA copy number alterations by comparative genomic hybridization (CGH).

MATERIALS AND METHODS

Thirty-five paraffin-embedded tumor specimens were collected during diagnostic procedures from 1970 to 1985 from 31 patients (12 women, 19 men) referred to the Karolinska Hospital. All patients had posterior uveal melanoma managed by enucleation of the eye harboring the tumor. The age of the patients ranged from 23 to 87 years (median, 61 years). The patients were selected to form two groups: survivors (alive 15 years or more after enucleation without signs of metastatic disease) and dead (died of metastatic melanoma). Follow-up time is from enucleation to death from melanoma. Clinical data of the 31 patients are summarized in Table 1. All parts of the study were conducted in compliance with the Declaration of Helsinki.

DNA extraction was performed as described elsewhere9 with slight modifications. In all specimens, the proportion of tumor cells was at least 50%. DNA in peripheral blood specimens from healthy donors was extracted according to standard procedures and used as reference in the CGH analyses.

CGH was performed as described previously.10,11 Tumor DNA and normal reference DNA were labeled by nick translation with fluorescein-isothiocyanate–conjugated dCTP and dUTP (DuPont, Boston, MA) and Texas Red–conjugated dCTP and dUTP (DuPont). The hybridization was analyzed using an Olympus fluorescence microscope mounted to a CCD camera and the ISIS digital image analysis system (MetaSystems, Altlussheim, Germany). Three-color images (green for tumor DNA, red for reference DNA, and blue for chromosome counterstaining) were acquired from 8 to 10 metaphases with strong uniform hybridization. Chromosome regions were interpreted as overrepresented when the green-to-red ratio was higher than 1.17 (gains) and underrepresented when the ratio was lower than 0.85 (losses). A ratio value higher than 1.5 was used to define a high-level amplification.

The Mann-Whitney test was used to compare the number of aberrations and the frequency of individual changes between different tumor types.

RESULTS

Twenty-nine of 35 tumors showed DNA copy number changes (mean, 3.2 aberrations/tumor; range, 0–14; Table 1, Figs. 1 and 2).
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* Cell type: 1, spindle; 2, mixed; 3, epithelioid; 4, necrosis.
† Location: 1, posterior choroid; 2, anterior choroid; 3, ciliare.
‡ Tumor diameter (mm).
§ Tumor thickness (mm).
¶ Grade of invasion (1–3): level 1, invasion <⅓ of sclera; level 2, >⅓ of sclera; level 3, extrabulbar growth.
‖ Dead of tumor (1, yes; 0, no).
# Dead of any cause (1, yes; 0, no).
** High-level amplifications in bold.
FIGURE 1. Summary of gains and losses of DNA copy number changes detected by CGH in 35 uveal melanomas. Gains are shown on the right side of the chromosome diagrams and losses on the left side. Each line illustrates the affected region of the chromosome in a single tumor sample. Solid lines, the affected regions in metastasizing primary tumors and metastases; dotted lines, the affected regions in nonmetastasizing primary tumors; bold lines, the high-level amplifications.

FIGURE 2. CGH analysis of uveal melanoma (case 29). Fluorescence ratio image with three overlapping layers: green (FITC) for tumor DNA, red (Texas Red) for reference DNA, and blue (DAPI) for chromosome counterstaining on a metaphase lymphocyte preparation from a normal female. Arrows, the most prominent changes (cf. Table 1): loss of chromosome 3 (green-to-red ratio < 0.85), amplification of 8q (> 1.5), and loss of 8p.
The most common losses in nonmetastasizing tumors, metastasizing tumors, and metastases affected chromosome 3 (21%, 73%, 67%, respectively). Other frequent losses involved 6q (7%, 40%, 83%), 1p (0, 33%, 33%), 13q (14%, 13%, 50%), 8p (14%, 27%, 0), and 18 (7%, 13%, 33%) with minimal overlapping regions at 6q14-q23, 1p31, 13q14-31, and 8p12-pter. The most frequent gains involved 8q (14%, 53%, 100%), 6p (29%, 17%, 0), 1q (0, 7%, 33%), 16p (0, 7%, 33%), 16q (1, 7%, 33%), and 22 (0, 7%, 33%), with minimal overlapping regions at 8q24.1-pter, 6p22-pter, 1p, 20q, and 22. High-level copy number increases were also found at 8q (14%, 27%, 0), and 18 (7%, 40%, 83%), 1p (0, 33%, 33%), 13q (14%, 13%, 50%), 8p (1, 7%, 33%), and 22 (0, 7%, 33%). Other frequent losses involved 6q (14%, 27%, 0), and 18 (7%, 40%, 83%), 1p (0, 33%, 33%), 13q (1, 7%, 33%), 8p (0, 7%, 33%), and 22 (0, 7%, 33%)

The differences between nonmetastasizing tumors, metastasizing tumors, and metastases are summarized in Table 2. The mean number of DNA copy number changes was significantly higher in the metastasizing tumors and in metastases than in the nonmetastasizing tumors (P < 0.05). There was no significant difference in DNA copy number changes between metastasizing tumors and metastases.

### Discussion

In this CGH study we show that several consistent chromosomal imbalances are present in uveal melanomas and that the frequency of DNA copy number changes is significantly higher in metastasizing primary tumors and metastases than in nonmetastasizing primary tumors. Losses of 3, 6q, 1p, and 8p and the most recurrent gains, 8q and 6p, were also seen, albeit less frequently, in nonmetastasizing tumors. Losses of 1p were only present in metastasizing tumors and metastases. No association between clinicopathologic parameters (e.g., cell type, tumor size and location) and DNA sequence copy number changes was found in this study.

Our database that covers the findings reported in close to 300 publications (http://www.helsinki.fi/~lgl www/CMG.html; provided by the University of Helsinki) supports the notion that loss of whole chromosome 3 is a unique genetic change in uveal melanoma. In other tumor types, loss of chromosome 3 involves mostly the short arm.12 The candidate genes in 3p are VHL (von Hippel-Lindau) at 3p25-p26, FHIT (fragile histidine triad) at 3p14.2, DNA mismatch repair gene MLH1 at 3p21.3-p23, and DNA repair gene XPC at 3p25.12 The long arm of chromosome 3 is not known to harbor any known tumor suppressor gene.

Previous chromosome banding analyses and loss of heterozygosity studies fit well to our finding that losses of chromosome 3 and gains of chromosome 8 are signs of poor prognosis.4,13–15 Presence of chromosome 6 abnormality has been observed to improve prognosis.9 We found that the frequency of 6p gains in nonmetastasizing primary tumors was higher than in metastasizing primary tumors and metastases, but the difference was not significant (P > 0.05). However, the frequency of chromosome 6q losses in metastasizing primary tumors and metastases was significantly higher than that in nonmetastasizing primary tumors. All seven patients with loss of 6q had died of their tumor.

In the present study all nine patients with gain of 8q had loss of chromosome 3. However, three patients had the loss of 3 but not the gain of 8q. Therefore, the loss of chromosome 3 seems to be an early event in uveal melanoma16 and may lead to increased genomic instability, especially to induction of isochromosome formation, which has been pointed out by Prescher et al.16,17 The association we found between loss of chromosome 3 and isochromosome-like findings of 1q, 6p, 8q, 16p, 20q, and 22q (gain of one arm and loss of the other one; see Fig. 1), agrees with previous CGH analyses of uveal and cutaneous melanomas.7,6,18 The mechanism that causes the induction of isochromosome formation is not known. However, several tumor suppressor loci on chromosome 3 may be involved in the regulation of centromere or mitotic division.

Losses of 1p, with minimal overlapping region at 1p21-p23, were only detected in metastasizing tumors. Loss of chromosomal material of 1p does not occur exclusively in uveal melanoma. Deletion of 1p has been observed in a variety of other solid tumors and has been associated with tumor progression.14 Recently Silsey et al.19 indicated that loss of material of 1p is associated with large ciliary body melanomas.

In conclusion, our results indicate that metastasized primary uveal melanomas and metastases have significantly more copy number changes than nonmetastasized primary uveal melanomas, that losses of chromosome 3, 6q, and 1p, and gains of 8q are prognostically poor signs, and that the loss of chromosome 3 may be associated with isochromosome formation of 1q, 6p, 8q, 16p, 20q, and 22q.

### Table 2. Comparison of DNA Copy Number Gains (+) and Losses (−) between Nonmetastasizing Uveal Melanomas, Metastasizing Uveal Melanomas, and Metastases

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<td>7 (0.5 ± 0.1)</td>
<td>17 (1.1 ± 0.4)</td>
<td>18 (3 ± 1.3)*</td>
</tr>
<tr>
<td>−1p</td>
<td>0</td>
<td>5 (0.3 ± 0.1)</td>
<td>2 (0.3 ± 0.1)</td>
</tr>
<tr>
<td>+1q</td>
<td>0</td>
<td>1 (0.07 ± 0.07)</td>
<td>2 (0.5 ± 0.2)</td>
</tr>
<tr>
<td>−5</td>
<td>3 (0.2 ± 0.1)</td>
<td>11 (0.7 ± 0.1)*</td>
<td>4 (0.7 ± 0.2)</td>
</tr>
<tr>
<td>+6p</td>
<td>4 (0.2 ± 0.1)</td>
<td>3 (0.2 ± 0.1)</td>
<td>1 (0.17 ± 0.17)</td>
</tr>
<tr>
<td>−6q</td>
<td>1 (0.1 ± 0.1)</td>
<td>6 (0.4 ± 0.1)*</td>
<td>5 (0.8 ± 0.2)*</td>
</tr>
<tr>
<td>−8p</td>
<td>2 (0.14 ± 0.1)</td>
<td>4 (0.3 ± 0.1)</td>
<td>0</td>
</tr>
<tr>
<td>+8q</td>
<td>2 (0.14 ± 0.1)</td>
<td>8 (0.5 ± 0.1)*</td>
<td>6 (1 ± 0)*</td>
</tr>
<tr>
<td>High-level amplifications in 8q</td>
<td>2 (0.14 ± 0.1)</td>
<td>3 (0.2 ± 0.1)</td>
<td>2 (0.3 ± 0.2)</td>
</tr>
<tr>
<td>+16p</td>
<td>0</td>
<td>1 (0.07 ± 0.07)</td>
<td>2 (0.3 ± 0.2)</td>
</tr>
<tr>
<td>−16q</td>
<td>1 (0.07 ± 0.07)</td>
<td>1 (0.07 ± 0.07)</td>
<td>0</td>
</tr>
<tr>
<td>+20q</td>
<td>0</td>
<td>1 (0.07 ± 0.07)</td>
<td>2 (0.3 ± 0.2)</td>
</tr>
</tbody>
</table>

Values in parentheses are means ± SEM.

Mann-Whitney test applied to group means. *P < 0.05; compared to nonmetastasizing primary tumors.
Acknowledgment

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References


DNA Copy Number Changes in Uveal Melanoma