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Genomic and Transcriptomic Tumor Heterogeneity in Bilateral Retinoblastoma

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IMPORTANCE Comprehensive understanding of the genomic and gene-expression differences between retinoblastoma tumors from patients with bilateral disease may help to characterize risk and optimize treatment according to individual tumor characteristics.

OBJECTIVE To compare the genomic features between each eye and a specimen from an orbital relapse in patients with bilateral retinoblastoma.

DESIGN, SETTING, AND PARTICIPANTS In this case, 2 patients with retinoblastoma underwent upfront bilateral enucleation. Tumor samples were subjected to genomic and gene-expression analysis. Primary cell cultures were established from both of the tumors of 1 patient and were used for gene-expression studies.

MAIN OUTCOMES AND MEASURES Whole-exome sequencing was performed on an Illumina platform for fresh tumor samples and DNA arrays (CytoScan or OncoScan) were used for paraffin-embedded samples and cell lines. Gene-expression analysis was performed using Agilent microarrays. Germinal and somatic alterations, copy number alterations, and differential gene expression were assessed.

RESULTS After initial bilateral enucleation, patient 1 showed massive choroidal and laminar optic nerve infiltration, while patient 2 showed choroidal and laminar optic nerve invasion. Patient 1 developed left-eye orbital recurrence and bone marrow metastasis less than 1 year after enucleation. Both ocular tumors showed gains on 1q and 6p but presented other distinct genomic alterations, including an additional gain in 2p harboring the N-myc proto-oncogene (*MYCN*) in the left tumor and orbital recurrence. Similar copy number alterations between the orbital recurrence and the left eye supported the origin of the relapse, with an additional 11q loss only detected in the orbital relapse. Specimens from patient 2 showed common copy number gains and losses, but further evolution rendered a 2p gain spanning *MYCN* in the left tumor. For this patient, microarray expression analysis showed differential expression of the *MYCN* and the forkhead box protein G1 (*FOXG1*) gene pathways between the left and right tumors.

CONCLUSIONS AND RELEVANCE Differential genomic and gene expression features were observed between tumors in 2 patients with bilateral disease, confirming intereye heterogeneity that might be considered if targeted therapies are used in such patients. Chromosomal alteration profile supported the origin of the orbital recurrence from the homolateral eye in 1 patient. Loss in chromosome 11q may have been associated with extraocular relapse in this patient.

Supplemental content

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Bilateral retinoblastoma usually presents with asymmetric tumors, with 1 eye showing more advanced disease than the fellow eye, suggesting that despite having a common germinal *RB1* mutation, other factors may play a role in tumor genesis and progression.[1,2] If the tumor is not diagnosed timely, it may progress in both eyes to advanced disease requiring bilateral enucleation. Upfront bilateral enucleation is seldom performed in high-income countries; thus, when performed, it gives the opportunity of evaluating genomic and gene expression differences that might be present between eyes without the effect of any therapy that could cause clonal selection.[3,4] Herein, we analyzed the genomic and gene expression features between tumors in 2 cases of initially enucleated bilateral retinoblastoma.

Key Points

Question Do both ocular tumors of patients with bilateral retinoblastoma show similar genomic and gene expression features?

Findings In this case report, 2 patients with bilateral retinoblastoma showed eye tumors with distinctive genomic profiles; chromosomal alteration profile supported the origin of the orbital recurrence from the homolateral eye in 1 patient, and in this case, 11q loss may be associated with extraocular relapse. Transcription factor pathways were differentially expressed between the left-eye and right-eye tumors in the second patient.

Meaning These 2 cases suggest genomic and gene expression differences between tumors in patients with bilateral disease and confirm intereye tumor heterogeneity that might be considered with targeted therapies.

Methods

The study was approved by Hospital de Pediatría J.P. Garrahan institutional review board. Written informed consent was obtained from parents or guardians of patients, and all procedures involving human participants were in accordance with the ethical standards and the Declaration of Helsinki. No compensation or incentive was provided to participants of the study.

Patients

Patient 1 and patient 2 had bilateral Group E retinoblastoma (**Figure 1**) with no evidence of extraocular extension. Patient 1 underwent upfront bilateral enucleation. Histopathological assessments of both eyes showed massive choroidal invasion and laminar optic nerve involvement. The patient did not receive adjuvant therapy, and after less than a year, a left-orbital and bone marrow relapse occurred. The patient was treated with systemic chemotherapy and died of disease progression.

In patient 2, histopathological evaluations showed the right eye with massive choroidal, intrascleral, and postlaminar optic nerve involvement, while the left eye had focal choroidal and prelaminar optic nerve tumor extension. The patient received adjuvant chemotherapy[5] and remains alive and disease free.

Genomic Studies and Gene Expression Analysis

Genome studies for copy number alterations (CNA) and loss-of-heterozygosity analysis were performed with OncoScan CNV Assay (Thermo Fisher) or SureSelect Clinical Research Exome version 2 (Agilent Technologies), followed by sequencing on an Illumina HiSeq 4000 instrument (Illumina Inc), depending on the availability of fresh or formalin-fixed, paraffin-embedded samples. The analysis of CNAs and somatic and germline variants was performed as described in the eMethods in the Supplement. Two-color, microarray-based gene-expression analysis was performed according to manufacturer's recommendations (eMethods in the Supplement). Data were collected from August 2016 to October 2017.

Patient-Derived Cell Cultures

Low-passage retinoblastoma cell cultures were obtained from fresh samples[6] from both eyes of patient 2 and named HPG-RBT-12L and HPG-RBT-12R. A CytoScan HD Assay (Thermo Fisher) was used for CNA analysis of both cell cultures and compared with the genomic profiles of the matched tumors for qualitative similarities in the presence or absence of segment gains and losses (eMethods in the Supplement).

Data Analysis

Data were analyzed from November 2017 to January 2019. A detailed description is in the eMethods in the Supplement. Briefly, genomic variant analysis from whole exome sequencing was performed by IntegraGen according to their pipeline (http://www.integragen-genomics.com/bioinformatics-and-bioanalysis) and manual review was done with Alamut Visual version 2.10 (Interactive Biosoftware). Copy number alterations were evaluated by reprocessing sequencing files with the Burrows-Wheeler Aligner for alignment, Sambamba for duplicates removal, and the Genome Alteration Print method for ploidy and copy number profiles. The CNA analysis for DNA array files was performed with Chromosome Analysis Software (Thermo Fisher). Final processing in both cases was done in R/Bioconductor version 3.5 (R Project for Statistical Computing). Expression data analysis was performed in R/Bioconductor version 3.5 (R Project for Statistical Computing), the InnateDB database, Pathway Recognition Algorithm using Data Integration on Genomic Models (PARADIGM), and MultiExperiment Viewer software MeV version 4.9 (MEV). Significance for differentially expressed genes was set at $P < .001$ and fold change at 2 or greater.

Results

Genomic differences between eyes were present in patient 1, while the orbital relapse resembled the homolateral eye. Patient 1 showed a previously reported germline heterozygous deletion of the retinoblastoma protein (*RB1*) gene (Leiden Open Variation Database; RB1_00509). A CNA analysis showed that only gains at chromosomes 1q and 6p were present in both ocular tumors, despite differences in the absolute copy numbers. Chromosome 13q showed a normal copy number in the right tumor, while in the left tumor it was in loss of heterozygosity,

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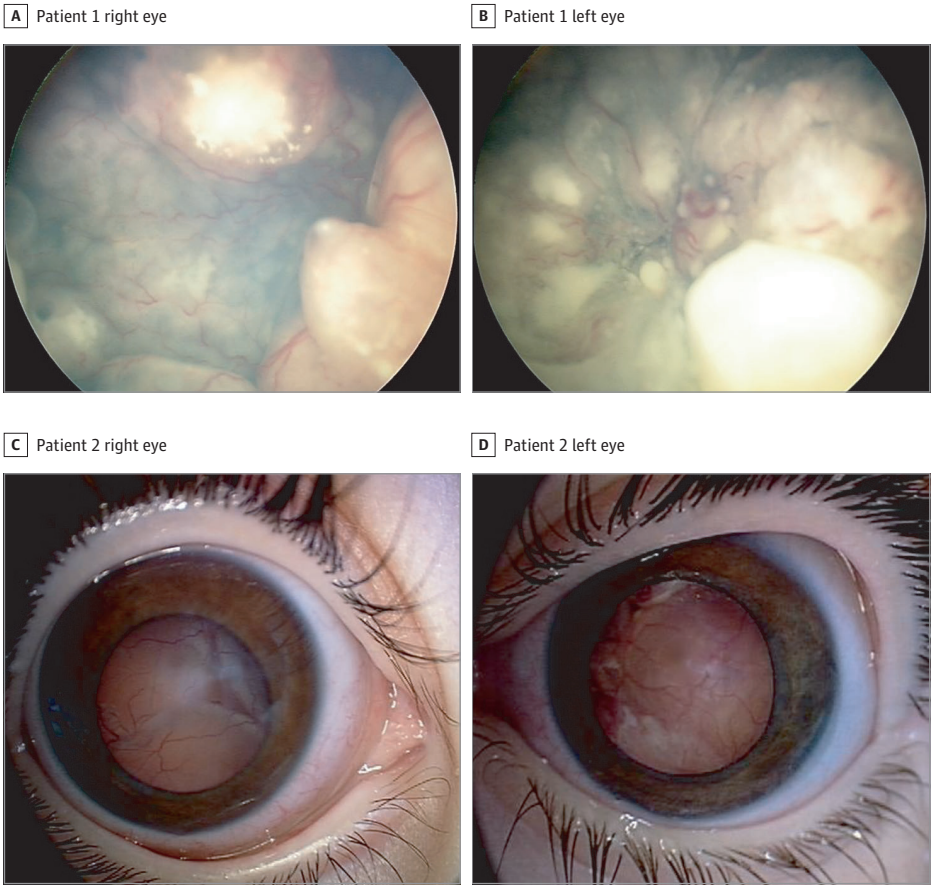
Figure 1. Images at Presentation



A and B, Patient 1's right and left eyes at presentation. C and D, Clinical presentation of the right and left eyes of patient 2.

with a concomitant gain of the mutated allele. The second hit could not be identified for the right-eye tumor. Additionally, a gain in 20q and a deletion of chromosome 16 were present exclusively in the right eye, while the left tumor showed additional gains in 2p (harboring the N-myc proto-oncogene [*MYCN*]), 15q, and 22q11.1, and a loss in 9p21 (**Figure 2**A and B; eTable 1 in the Supplement). Tumor from the left orbital recurrence showed CNAs that closely resembled those found in the left intraocular tumor but showed an additional 11q loss and difference in the absolute copy number of 6p (Figure 2C).

The ocular tumors of patient 2 also showed genomic differences. For patient 2, a germline and heterozygous mutation in *RB1* c.1421G>T (p.(Ser474Ile)) was detected. Among the somatic alterations (eTable 2 in the Supplement), a pathogenic mutation in the BCL6 corepressor (*BCOR*) gene in an allele frequency of 6% was identified only in the left tumor (ClinVar; RCV000538294.1).

Both intraocular tumors showed similar CNA profiles sharing gains in 1q, 6p, and 14q11.2, a 13q loss that includes *RB1* in loss of heterozygosity (considered the second hit), and a subclonal loss at 8p23 (**Figure 3**A and B). Differences included a focal clonal gain of *MYCN* as part of a subclonal gain in 2p, exclusively found in the left tumor, and the allelic ratio in 6p gain. Deletions in 13q showed different boundaries between eyes, and the telomeric end of the right tumor was in copy-neutral loss of heterozygosity. Altogether, in addition to *RB1* alterations, proposed by Alfred G. Knudson, Jr, MD,[2] and required for retinoblastoma initiation, additional genetic changes are summarized in eTable 3 in the Supplement, and a hypothesis for tumor evolution in both patients is depicted in eFigure 1 in the Supplement.

Primary cell cultures derived from patient 2 resembled the genetic features of the matched-ocular tumors. Similar CNAs to the ocular tumors were detected for the matched-cell models (Figure 3C and D; eTable 4 in the Supplement). Observed differences may correspond to changes in clonality (ie, a subclonal gain of 2p only in the left tumor that became clonal in HPG-RBT-12L cells). Unsupervised hierarchical clustering of the whole-gene expression data set showed that cell lines grouped together with their corresponding tumor of origin (eFigure 2 in the Supplement). The comparisons of right vs left tumors and HPG-RBT-12R cells vs HPG-RBT-12L cells showed 997 and 1186 differentially expressed genes (DEGs; $P < .001$; eFigure 2 in the Supplement) while tumor vs matching cell line comparison resulted in almost no DEGs (eFigure 2 in the Supplement). Gene ontology enrichment analysis performed with the common DEGs upregulated in the left tumor and HPG-RBT-12Lcells (eFigure 2 in the Supplement) rendered the term *DNA-binding transcription factors* to indicate the most significantly enriched element. Specifically, *MYCN* was significantly upregulated in both specimens. A hierarchical clus-

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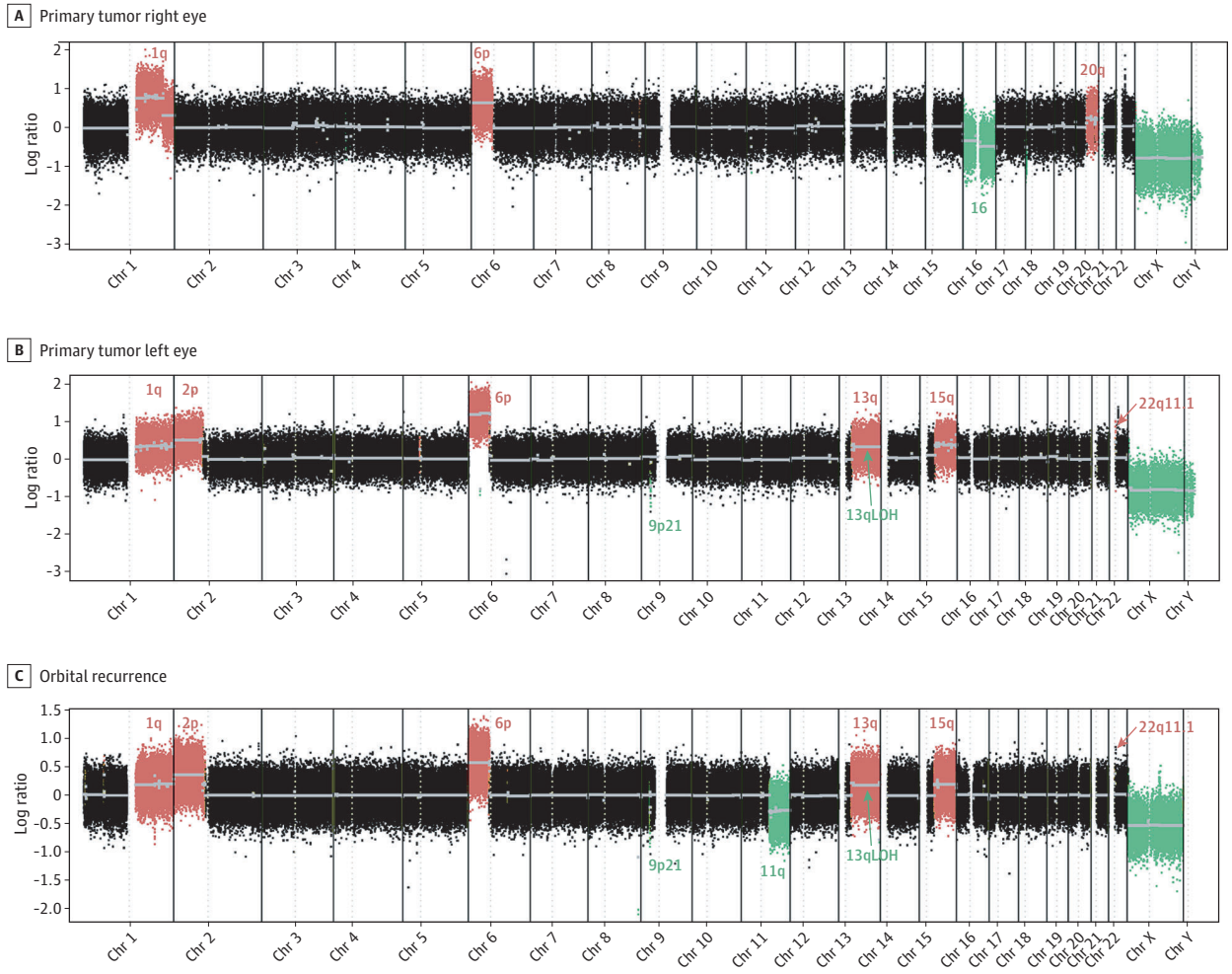
Figure 2. Chromosomal Copy Number Alterations of Patient 1



A, Right-eye tumor. B, Left-eye tumor. C, Orbital recurrence. Each dot represents a log ratio of tumor signal compared with the normal reference. Losses and gains in chromosomal regions correspond with negative and positive values, respectively. The y-axis depicts the log ratio, and chromosomal positions are represented in the x-axis (Chr indicates chromosome). The orbital recurrence shows a similar profile to the left eye, with an additional loss at 11q.

tering using genes from 2 previously reported *MYCN* gene signatures[7,8] resulted in the correct segregation of the right and left tumors and cell lines (eFigure 3 in the Supplement).

The *FOXG1* gene was the most pronounced DEG between the left-eye and right-eye tumors and the derived cell lines (eFigure 2 in the Supplement). A hierarchical clustering performed with a previously reported *FOXG1* gene signature revealed 2 distinct clusters of right vs left specimens (eFigure 3 in the Supplement).[9] Both analyses suggested an influence of *MYCN* and *FOXG1* in the differential phenotype of the left tumor of patient 2.

Discussion

Comparative tumor biology studies between eyes simultaneously enucleated at diagnosis in bilateral retinoblastoma have not been reported thus far. We found differences in genomic aberrations and gene-expression profiles, suggesting tumor heterogeneity in 2 patients with initial bilateral enucleation.

Intertumor heterogeneity, including gains in *MYCN*, may be determinants for the evolution of more aggressive tumors as shown in both patients studied. Also, intratumor heterogeneity is suspected by the finding that 6% of the left-eye tumor cells of patient 2 presented a mutation in *BCOR*.[2,4]

Copy number alteration analysis indicated that the origin of the orbital relapse in patient 1 was the homolateral eye. A deletion in 11q was found in the orbital tissue, a known risk factor for neuroblastoma that has also been reported in few intraocular retinoblastomas but not associated with an increased risk of extraocular relapse.[10-13] Moreover, patient 1 showed a *MYCN* gain in both the left eye and orbital relapse, but this was absent in the right eye. The *MYCN* gene is a known driver in solid pediatric tumors, and its amplification has been proposed as a driver of retinoblastoma in cases with wild-type *RB1*[11,14]; however, *MYCN* gains have also been reported in 65% of initially enucleated eyes of patients who are $RB^{-/-}$, and its prognostic implications are not clear.[11]

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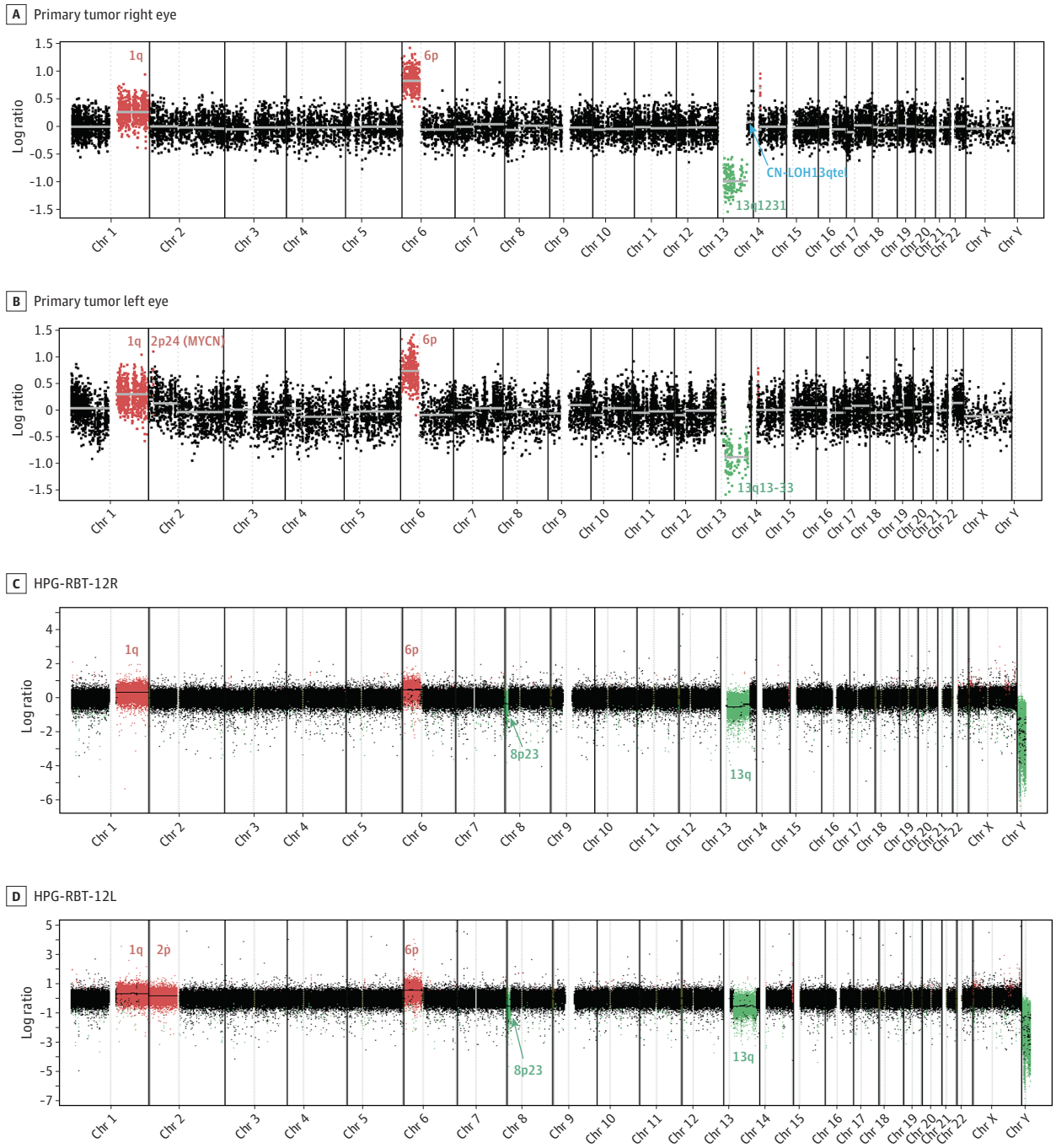
Figure 3. Copy Number Alterations in Samples From Patient 2



A, Right-eye tumors. B, Left-eye tumors. C and D, Matched primary cell lines. Similar chromosomal alterations were detected between eye tumors, except for a 2p gain encompassing the *MYCN* gene locus. The chromosomal profiles of both HPG-RBT-12R (C) and HPG-RBT-12L (D) cells were similar to the matched original tumors, with no additional alterations. Chr indicates chromosome.

In addition to a differential gene expression profile of the *MYCN* pathway between eye tumors in patient 2, we also report an upregulated gene expression of *FOXG1* pathway in the absence of a copy number gain of this gene. The *FOXG1* gene is involved in telencephalon development, and it has been proposed to play a role in glioblastoma and medulloblastoma, despite no reports in retinoblastoma.[9,15]

Limitations

The limitation of this series is its small sample size. Our findings cannot be generalized until they are confirmed in larger studies.

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Conclusions

The present study shows intereye and intratumor heterogeneity in 2 patients with simultaneously enucleated bilateral retinoblastoma and suggests each affected eye might be considered individually for potential targeted therapies based on specific genetic and differential gene expression features. In 1 patient, the orbital relapse showed an 11q loss absent in the homolateral eye that could be associated with extraocular relapse.

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Supervision: Ottaviani, Fandiño, Podhajcer, Chantada, Llera, Schaiquevich.

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