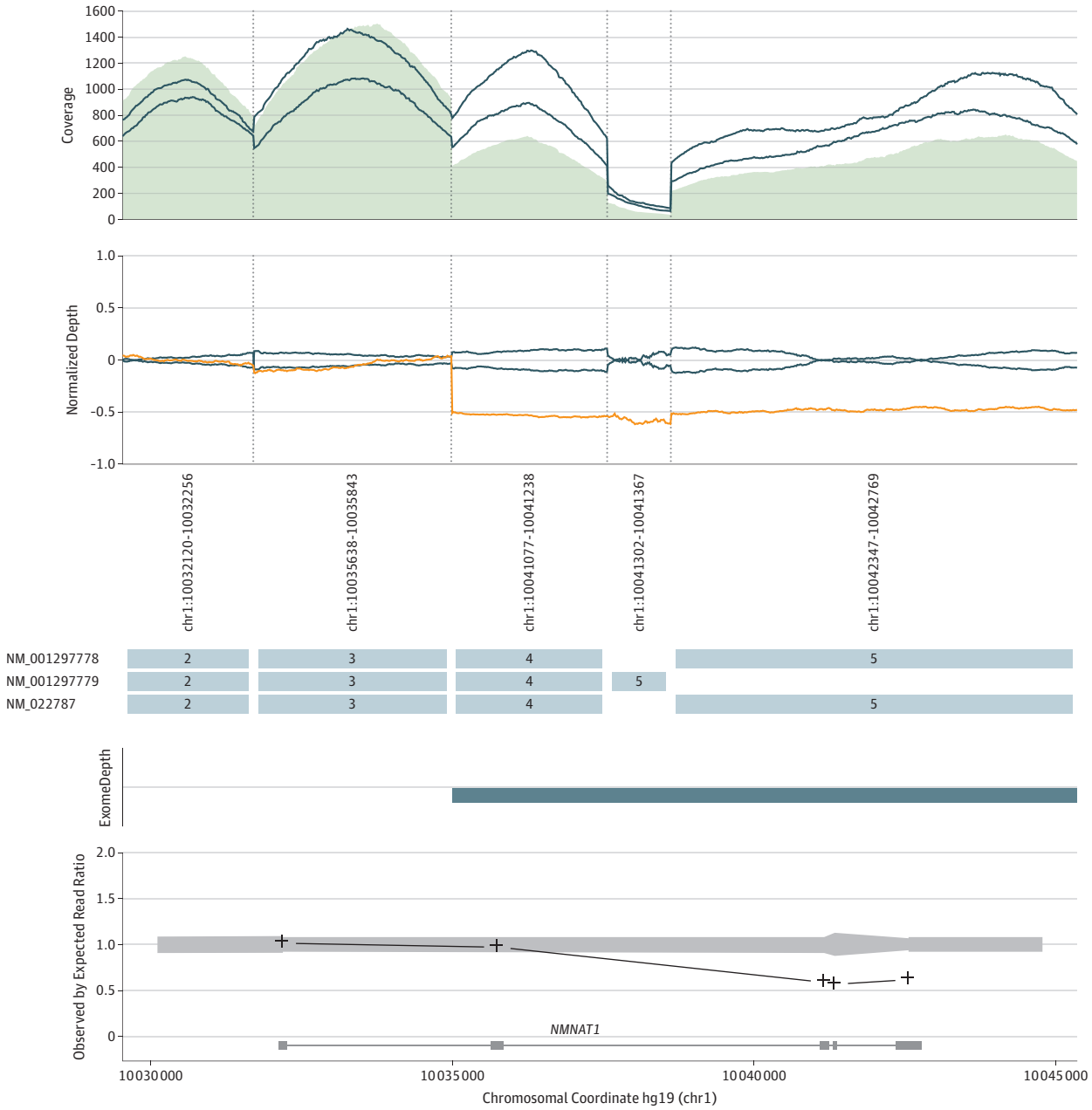
Missed Heterozygous Deletion in Study of Next-Generation Sequencing for Molecular Diagnosis in Patients With Infantile Nystagmus Syndrome

To the Editor In our article "Accuracy of Next-Generation Sequencing for Molecular Diagnosis in Patients With Infantile Nystagmus Syndrome,"[1] we originally reported that patient 8 had a homozygous mutation (c.709C>T) in *NMNAT1*. The patient's father was a heterozygous carrier for the c.709C>T mutation, but the mother was not. We suspected that this could be from uniparental disomy or maternal mosaicism. After further analysis using our customized algorithm to detect copy number variation, we noted that we missed a heterozygous deletion of exons 4 and 5 (**Figure**). Because the c.709C>T mutation was located in the deleted region, we could confirm the pseudohomozygosity and conclude that the patient had compound heterozygosity for hemizygous c.709C>T and heterozygous deletion of exons 4 and 5. The deletion of exons 4 and 5 in *NMNAT1* was inherited from the mother.

This change affects 1 row and 1 footnote in Table 2 of our article.[1] A new reference has been added to the References list and is cited in Table 2.[1] These changes do not affect our conclusions. We have requested correction to the article to address these errors.[2] We confirm there are no other errors in the published article. Table 2 has been corrected online.

Figure. A Heterozygous Deletion of Exons 4 and 5 Was Detected Using the ExomeDepth and Customized Depth Normalizing Software



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Conflict of Interest Disclosures: None reported.

1. Rim JH, Lee ST, Gee HY, et al. Accuracy of next-generation sequencing for molecular diagnosis in patients with infantile nystagmus syndrome. *JAMA Ophthalmol*. 2017;135(12):1376-1385. doi:10.1001/jamaophthalmol.2017.4859

2. Errors in table 2 [published online September 26, 2019]. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2019.3190

Diffuse Uveal Melanocytic Proliferation With Primary Vitreoretinal Lymphoma

To the Editor We congratulate Leskov et al on their excellent imaging documentation[1] of a unilateral case of primary vitreoretinal lymphoma. The authors noted a giraffe skin–like appearance of the right fundus with apparent areas of hyperpigmentation and corresponding hypoautofluorescence that resembles the retinal pigment epithelial (RPE) alterations of bilateral diffuse uveal melanocytic proliferation (BDUMP).

Characteristic features of BDUMP include bilateral multifocal red subretinal patches at the level of the RPE that resemble a giraffe skin, early hyperfluorescence on fluorescein angiography, and diffuse melanocytic infiltration of the choroid.[1] Naysan et al[2] reported multimodal imaging features of BDUMP and demonstrated classic optical coherence tomographic findings of RPE thickening and loss with choroidal infiltration and thickening.

Leskov et al[1] found areas of RPE thickening and thinning on optical coherence tomography, but the findings were unilateral, and the authors specifically stated that neither eye had choroidal thickening. The histopathology image showed atypical lymphocytes without melanocytic proliferation. Given the unilaterality, lack of choroidal thickening, and absence of melanocytic proliferation, the findings in this case are not consistent with a diagnosis of BDUMP but rather RPE alterations and detachments, which are commonly seen in eyes with vitreoretinal lymphoma. The macular appearance is suggestive of a condition called *cloudy vitelliform submaculopathy*, which has previously been described in association with vitreoretinal lymphoma.[3]

Pefkianaki et al[4] have also described BDUMP-like fundus changes with RPE alterations and detachments as the presenting sign of central nervous system lymphoma, but without choroidal findings. The authors[1] noted choroidal thickening to 458 µm by optical coherence tomography without reporting the choroidal thickness of the fellow eye, and a review of the optical coherence tomographic images reveals RPE changes without obvious choroidal infiltration. Huang[5] has also reported BDUMP-like fundus changes in a patient with testicular T-cell lymphoma with ocular involvement after treatment with systemic chemotherapy, whole-body radiation, and intravitreal methotrexate. This report[5] described areas of RPE alterations and atrophy resembling BDUMP, without any choroidal thickening or melanocytic proliferation. These authors[1] have recognized the classic features of vitreoretinal or testicular lymphoma with RPE detachments and alterations and unfortunately mislabeled them as BDUMP. To fulfill the criteria for BDUMP, documented choroidal infiltration with melanocytic proliferation should be observed.

We recently reviewed 168 eyes of 95 patients with vitreoretinal lymphoma seen on the Ocular Oncology Service at Wills Eye Hospital and found extensive RPE changes in 17% of patients. We believe that the pseudo-BDUMP fundus appearance reported by Leskov et al[1] is associated with alterations at the level of the RPE and should be differentiated from true BDUMP.

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1. Leskov I, Lyon AT, Jampol LM. Diffuse uveal melanocytic proliferation with primary vitreoretinal lymphoma. *JAMA Ophthalmol*. 2019;137(7):834-837. doi:10.1001/jamaophthalmol.2019.0905

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5. Huang JJ. Intraocular metastasis of testicular natural killer T-cell lymphoma with diffuse retinal pigment epithelium changes. *Retin Cases Brief Rep*. 2011;5(1):42-45. doi:10.1097/ICB.0b013e3181c333bc

In Reply Dalvin and colleagues state that the findings in the patient we treated[1] who had vitreoretinal lymphoma are not consistent with a diagnosis of diffuse uveal melanocytic proliferation (DUMP). They base this on (1) the absence of documented choroidal thickening, (2) the absence of melanocytic cells in the biopsy, and (3) the unilaterality or asymmetry of the condition.

In the original article by Gass et al[2] defining this condition, the first criterion was the presence of red patches at the level of pigment epithelium and intense hyperfluorescence on fluorescein angiography (termed *giraffe skin*). Both findings were prominent in the case we reported.[1] Gass et al[2] pointed out that this change can be seen prior to the detection of choroidal thickening or melanocytic tumors. They did not have optical coherence tomography.

In the original report,[1] we stated that the choroid was not thickened. In rereviewing the optical coherence tomographic data, we found that it is clear that, at presentation, the choroid