

OOG collaborative study on ATRX loss in Conjunctival melanoma prognosis

Dear colleagues,

The Dutch Conjunctival Melanoma Centers would like to invite you for a collaboration regarding a study in which the role of ATRX loss is evaluated as a prognostic factor in conjunctival melanoma patients.

Prognostication of CM relies on histopathologic parameters such as Breslow thickness and mutations in secondary driver genes, such as *TERT* promoter are strongly correlated with a shorter survival (1-3). Other molecular studies of CM patients showed recurrent ATRX loss in about 25% of cases (3, 4). Preliminary data from the ROMS cohort indicated an association of both *TERT* promoter mutation and ATRX loss with metastatic disease (5, presented at the 57th OOG meeting in Berlin). A larger cohort study with a uniform approach towards analyzing ATRX loss, *TERT* promoter mutation status over a longer follow-up period is needed to establish the role of ATRX loss in CM. Validation in clinically well-typed patient cohorts with mutation data would strengthen these findings.

Aim of this study

To evaluate the role of ATRX loss regarding prognosis in conjunctival melanoma patients.

Patients and methods

Adult conjunctival melanoma patients of which molecular data is evaluated or tumour material available for immunohistochemistry and genetic sequencing and a follow-up period of at least 10 years.

If applicable, we would like to receive the following data

- Clinical data: age of onset, gender, presence of metastasis, disease free survival, overall survival, treatment
- Genetic data:
 - Mutation status of *BRAF*, *NRAS*, *cKit*, if possible *NF1* and *TERT* promoter
- Histopathological data:
 - Breslow thickness
 - ATRX immunohistochemistry

All data will be collected in a secured digital environment.

ATRX immunostaining may be performed at your own laboratory or can be performed centrally upon receipt of blank slides

Ethical considerations

This study will adhere to the principles of the Declaration of Helsinki.

Reporting

The results will be published in an international, peer reviewed journal. Authors will include researchers involved in this project and members of the Ophthalmic Oncology Group who provided

valid cases for this study, listed in the order of patients enrolled. Initiators of the study will appear as first and last authors.

Financing

Funding requested with Uitzicht (UZ 2025-15)

Instructions

Please let us know if you would like to join this study by sending an e-mail to Jolique.vanIpenburg@radboudumc.nl with the subject "inclusion in uveal melanoma 8q study" so we can provide you with the needed information regarding the online database.

Prevalence and implications of TERT promoter mutation in uveal and conjunctival melanoma and in benign and premalignant conjunctival melanocytic lesions. Koopmans AE, Ober K, Dubbink HJ, Paridaens D, Naus NC, Belunek S, Krist B, Post E, Zwarthoff EC, de Klein A, Verdijk RM; Rotterdam Ocular Melanoma Study Group. *Invest Ophthalmol Vis Sci.* 2014 Aug 26;55(9):6024-30.

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2. Molecular Genetics of Conjunctival Melanoma and Prognostic Value of TERT Promoter Mutation Analysis. van Poppel NM, van Ipenburg JA, van den Bosch Q, Vaarwater J, Brands T, Eussen B, Magielsen F, Dubbink HJ, Paridaens D, Brosens E, Naus N, de Klein A, Kiliç E, Verdijk RM. *Int J Mol Sci.* 2021 May 28;22(11):5784.
3. Prognostic value of TERT promoter mutations in conjunctival melanomas in addition to clinicopathological features. van Ipenburg JA, Naus NC, Dubbink HJ, van Ginderdeuren R, Missotten GS, Paridaens D, Verdijk RM. *Br J Ophthalmol.* 2021 Oct;105(10):1454-1461.
4. Integrative Exome and Transcriptome Analysis of Conjunctival Melanoma and Its Potential Application for Personalized Therapy. Demirci H, Demirci FY, Ciftci S, Elnar VM, Wu YM, Ning Y, Chinnaiyan A, Robinson DR. *JAMA Ophthalmol.* 2019 Dec 1;137(12):1444-1448.
5. Mutational Landscape and Outcomes of Conjunctival Melanoma in 101 Patients. Lally SE, Milman T, Orloff M, Dalvin LA, Eberhart CG, Heaphy CM, Rodriguez FJ, Lin CC, Dockery PW, Shields JA, Shields CL. *Ophthalmology.* 2022 Jun;129(6):679-693.
6. ATRX Loss in the Development and Prognosis of Conjunctival Melanoma. van Ipenburg JA, van den Bosch QCC, Paridaens D, Dubbink HJ, Kiliç E, Naus N, Verdijk RM; Rotterdam Ocular Melanoma Study Group. *Int J Mol Sci.* 2023 Aug 20;24(16):12988.