

Molecular Profiling of Clear Cell Myoepithelial Carcinoma of Salivary Glands With EWSR1 Rearrangement Identifies Frequent PLAG1 Gene Fusions But No EWSR1 Fusion Transcripts

[Alena Skálová^{1,2}](#), [Abbas Agaimy³](#), [Tomas Vanecek⁴](#), [Martina Baněčková^{1,2}](#), [Jan Laco⁵](#), [Nikola Ptáková⁴](#), [Petr Šteiner⁴](#), [Hanna Majewska⁶](#), [Wojciech Biernat⁷](#), [Luigi Corcione⁸](#), [Václav Eis⁹](#), [Olena Koshyk¹⁰](#), [Jan Vondrák Jr¹¹](#), [Michal Michal¹](#), [Ilmo Leivo^{12,13}](#)

The American Journal of Surgical Pathology

45(1):p 1-13, January 2021. | DOI: 10.1097/PAS.0000000000001591

PMID: 33027073

Abstract

Myoepithelial carcinoma of salivary glands is an underrecognized and challenging entity with a broad morphologic spectrum, including an EWSR1-rearranged clear cell variant. Myoepithelial carcinoma is generally aggressive with largely unknown genetic features. A retrospective review of Salivary Gland Tumor Registry in Pilsen searching for the key words "clear cell myoepithelial carcinoma," "hyalinizing clear cell," and "clear cell malignant myoepithelioma" yielded 94 clear cell myoepithelial carcinomas (CCMCs) for molecular analysis of EWSR1 rearrangement using fluorescence in situ hybridization (FISH). Tumors positive for EWSR1 gene rearrangement were tested by next-generation sequencing (NGS) using fusion-detecting panels. NGS results were confirmed by reverse-transcription polymerase chain reaction or by FISH. Twenty-six tumors originally diagnosed as CCMC (26/94, 27.6%) revealed split signals for EWSR1 by FISH. Six of these tumors (6/26, 23%) displayed amplification of the EWSR1 locus. Fifteen cases were analyzable by NGS, whereas 9 were not, and tissue was not available in 2 cases. None of the CCMCs with EWSR1 rearrangements detected by FISH had an EWSR1 fusion transcript. Fusion transcripts were detected in 6 cases (6/15, 40%), including LIFR-PLAG1 and CTNNB1-PLAG1, in 2 cases each, and CHCHD7-PLAG1 and EWSR1-ATF1 fusions were identified in 1 case each. Seven cases, including those with PLAG1 fusion, were positive for PLAG1 rearrangement by FISH, with notable exception of CHCHD7-PLAG1, which is an inversion not detectable by FISH. One single case with EWSR1-ATF1 fusion in NGS showed ATF1 gene rearrangement by FISH and was reclassified as clear cell carcinoma (CCC). In addition, another 4 cases revealed ATF1 rearrangement by FISH and were reclassified as CCC as well. Moreover, 12/68 (17%) CCMCs with intact EWSR1 gene were selected randomly and analyzed by NGS. PLAG1 fusions were found in 5 cases (5/12, 41.6%) with LIFR (2 cases), FGFR1 (2 cases), and CTNNB1 (1 case) as partner genes. Overall, PLAG1 gene rearrangements were detected in 10/38 (26%) tested cases. None of the tumors had SMARCB1 loss by immunohistochemistry as a possible explanation for the EWSR1 abnormalities in FISH. Novel findings in our NGS study suggest that EWSR1-FISH positive CCMC is a gene fusion-driven disease with frequent oncogenic

PLAG1 fusions, including LIFR-PLAG1 and CTNNB1-PLAG1 in most cases. Productive EWSR1 fusions are found only in a minority of EWSR1-ATF1-rearranged cases, which were in part reclassifiable as CCCs. Detectable EWSR1-FISH abnormality in CCMCs without gene fusion perhaps represents a passenger mutation with minor or no oncologic effect.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.