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# *A minority of cases of acinic cell carcinoma of the salivary glands are driven by an NR4A2 rearrangement: the diagnostic utility of the assessment of NR4A2 and NR4A3 alterations in salivary gland tumors*

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### Abstract

Acinic cell carcinoma (AciCC) is a common salivary gland malignancy, typically composed of neoplastic acinic cells with zymogen granules. The vast majority of cases are driven by a t(4;9)(q13;q31) leading to enhancer hijacking and upregulation of the *NR4A3* gene. However, a minority of cases do not display *NR4A3* overexpression on immunohistochemical examination and are negative for the rearrangement involving the *NR4A3* gene when tested by FISH. Such cases overexpress *NR4A2*, and the protein product is detectable by immunohistochemistry. In this study, we aimed to assess the utility of NR4A2 and NR4A3 immunohistochemistry in the differential diagnosis of salivary gland tumors. Eighty-five cases of classic low-grade ACiCC, as well as 36 cases with high-grade transformation (HGT) and 7 high-grade AciCC cases were included in the analysis. NR4A3 was at least focally positive in 105/128 (82%) cases. Out of the 23 cases that were immunohistochemically negative for NR4A3, 6 displayed nuclear immunopositivity with the NR4A2 antibody.
The *NR4A3* rearrangement was confirmed by FISH in 38/52 (73%) cases. In addition, this is the first report of an *NR4A2* rearrangement being detected by FISH in 2 AciCC cases that were negative for the *NR4A3* rearrangement. Our analysis confirms that the majority of AciCC, including high-grade cases and cases with HGT, are immunopositive for NR4A3, and suggests that NR4A3 immunohistochemistry is a powerful tool in the differential diagnosis of salivary gland tumors. However, its utility is limited in sub-optimally fixed samples which often display weaker and focal positivity. Our study also indicates that in a minority of cases, AciCC might be negative for NR4A3 immunostaining, because the pathogenic genetic event in these cases is instead a rearrangement involving the *NR4A2* gene.