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Genomic profiles and CRTC1-MAML2 fusion distinguish different subtypes of mucoepidermoid carcinoma

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Mucoepidermoid carcinoma is the most common salivary gland malignancy, and includes a spectrum of lesions ranging from non-aggressive low-grade tumors to aggressive high-grade tumors. To further characterize this heterogeneous group of tumors we have performed a comprehensive analysis of copy number alterations and CRTC1-MAML2 fusion status in a series of 28 mucoepidermoid carcinomas. The CRTC1-MAML2 fusion was detected by RT-PCR or fluorescence *in situ* hybridization in 18 of 28 mucoepidermoid carcinomas (64%). All 15 low-grade tumors were fusion-positive whereas only 3 of 13 high-grade tumors were fusion-positive. High-resolution array-based comparative genomic hybridization revealed that fusion-positive tumors had significantly fewer copy number alterations/tumor compared with fusion-negative tumors (1.5 vs. 9.5; P=0.002). Twelve of 18 fusion-positive tumors had normal genomic profiles whereas only 1 out of 10 fusion-negative tumors lacked copy number alterations. The profiles of fusion-positive and fusion-negative tumors were very similar to those of low- and high-grade tumors. Thus, low-grade mucoepidermoid carcinomas had significantly fewer copy number alterations/tumor compared with high-grade mucoepidermoid carcinomas (0.7 vs. 8.6; P<0.0001). The most frequent copy number alterations detected were losses of 18q12.2-qter (including the tumor suppressor genes DCC, SMAD4, and GALR1), 9p21.3 (including the tumor suppressor genes CDKN2A/B), 6q22.1-q23.1, and 8pter-p12.1, and gains of 8q24.3 (including the oncogene MAFA), 11q12.3-q13.2, 3q26.1-q28, 19p13.2-p13.11, and 8q11.1-q12.2 (including the oncogenes LYN, MOS, and PLAG1). On the basis of these results we propose that mucoepidermoid carcinoma may be subdivided in (i) low-grade, fusion-positive mucoepidermoid carcinomas with no or few genomic imbalances and favorable prognosis, (ii) high-grade, fusion-positive mucoepidermoid carcinomas with multiple genomic imbalances and unfavorable prognosis, and (iii) a heterogeneous group of high-grade, fusion-negative adenocarcinomas with multiple genomic imbalances and unfavorable outcome. Taken together, our studies indicate that molecular genetic analysis can be a useful adjunct to histologic scoring of mucoepidermoid carcinoma and may lead to development of new clinical guidelines for management of these patients.

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