OR24-5 Aberrant DNA Methylation in Regulatory Genomic Elements Are Associated with Invasive Behavior of Pituitary Macroadenomas: An Integrative Analysis of Epigenome-Wide Studies

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Abstract

A significant proportion of pituitary tumors (PT) invade adjacent structures. Few putative somatic mutations or copy number alterations have been associated with PT invasiveness. DNA methylation abnormalities in regulatory regions are known to impact gene expression and cancer behavior, but have not been fully explored in PT. Herein, we surveyed the genome-wide DNA methylation landscape of regulatory elements (promoter and enhancer) in the invasive behavior of PT. We performed a meta-analysis of genome-wide methylome profiling of invasive (Inv) and noninvasive (NInv) PT from 3 independent cohorts (32 InvPT; 35 NInvPT). Wilcoxon Rank-sum ($\Delta\beta$=0.2; non-adjusted p-value <0.001) and integrative analyses using bioinformatics tools were performed. We identified 34 differentially methylated probes (DMP) in InvPT that were overall hypomethylated in relation to NInvPT. The DMPs were mainly located in distal/open sea genomic regions (OpS), enriched for enhancer regions (47%). We retrieved 6 invPT-related DMP common among the three cohorts and 4 genes previously reported to be deregulated in association with promoter and gene body methylation alterations (*ITPKB*; *KRT12*; *DSC*2 and *LRRK1*). The DMPs-associated genes were involved in myeloid cell differentiation; regulation of membrane potential and signaling by receptor tyrosine kinases. In one cohort, we also identified a few DMP in enhancer regions possibly associated with motifs predicted to bind transcription factors associated with proliferation and inflammation. Our analyses showed the association of PT invasiveness and epigenetically regulated genes as well as revealed novel candidates genes known to be therapeutic target in other tumors. These results suggest the role of distinct methylation pattern in regulatory genomic elements in the pathogenesis of invasive pituitary macroadenomas.

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