DNA methylation signatures identify biologically distinct thyroid cancer subtypes

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Objective: The purpose of this study was to determine the global patterns of aberrant DNA methylation in thyroid cancer. Research Design and Methods: We have used DNA methylation arrays to determine, for the first time, the genome-wide promoter methylation status of papillary, follicular, medullary, and anaplastic thyroid tumors. Results: We identified 262 and 352 hypermethylated and 13 and 21 hypomethylated genes in differentiated papillary and follicular tumors, respectively. Interestingly, the other tumor types analyzed displayed more hypomethylated genes (280 in anaplastic and 393 in medullary tumors) than aberrantly hypermethylated genes (86 in anaplastic and 131 in medullary tumors). Among the genes indentified, we show that 4 potential tumor suppressor genes (ADAMTS8, HOXB4, ZIC1, and KISS1R) and 4 potential oncogenes (INSL4, DPPA2, TCL1B, and NOTCH4) are frequently regulated by aberrant methylation in primary thyroid tumors. In addition, we show that aberrant promoter hypomethylation- associated overexpression of MAP17 might promote tumor growth in thyroid cancer. Conclusions: Thyroid cancer subtypes present differential promoter methylation signatures, and nondifferentiated subtypes are characterized by aberrant promoter hypomethylation rather than hypermethylation. Additional studies are needed to determine the potential clinical interest of the tumor subtype-specific DNA methylation signatures described herein and the role of aberrant promoter hypomethylation in nondifferentiated thyroid tumors.