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## **Reprimo as a Potential Biomarker for Early Detection of Sporadic Diffuse-Type Gastric Carcinoma in Serum**

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Sporadic diffuse-type gastric carcinoma (SDGC) including mucinous/signet ring cell histology, is the most aggressive form of gastric cancer and does not have well defined precursor lesions. To search for biomarkers for early detection of SDGC, we studied the aberrant hypermethylation profile by mutagenically separated (MS)-PCR using the candidate gene approach of 24 genes covering all cellular pathways in 31 cases of SDGC. We performed hierarchical clustering analysis to identify subgroups and evaluated the most relevant genes in an independent group of 84 SDGC cases, including 47 cases in which non-tumor mucosa was available. Furthermore, the presence of methylated DNA in serum was explored in pretherapeutic serum of 10 patients with confirmed SDGC and 22 age-matched non-cancer controls.

Twelve genes were hypermethylated in at least 50% of the tested cases, 21 genes showed promoter methylation in at least one of the tested cases, whereas no promoter methylation was evident for the remaining 2 (9.1%) genes. Unsupervised hierarchical cluster analysis for all 24 genes clustered the cases in two branches that appeared to differ in mucinous/signet ring cell histologic classification ( $P = .03$  by Fisher's exact test). Ten genes (p73, SEMA3b, SHP1, APC, ER, Reprimo, CDH1p14, p16, FHIT, BRCA1) were screened in the independent group of 84 SDGC cases from which clinicopathologic, clinical outcome and precursor lesions were available. The most frequently methylated genes in tumors were also frequently methylated in non-tumor adjacent mucosa. The only exception was p73 which was significantly more methylated in tumor vs non-tumor adjacent mucosa ( $P = .01$ ). Two of these genes (APC and Reprimo) were additionally examined in pretherapeutic serum of 10 patients with confirmed SDGC and 22 age-matched non-cancer controls. Preferential methylation of Reprimo, but not APC, was found in the serum of 9 out of 10 SDGC patients, while it was not seen in serum of 22 normal subjects ( $P < .001$ ).

These results suggest that the detection of Reprimo DNA methylation in the serum may be useful for early detection of SDGC. Further cooperative studies will be necessary for clinical validation of these data.