

Hypermethylation at the *NDRG4* CpG island is associated with the risk of gastric cancer

Ying Jieer (Zhejiang Cancer Hospital, China) , Li Cong (Zhejiang Cancer Hospital, China) , Xu Qi (Zhejiang Cancer Hospital, China)

BACKGROUND: N-Myc downstream regulated gene 4 (NDRG4) is a candidate tumor suppressor gene whose hypermethylation was reported to contribute to the risk and poor prognosis of colorectal cancer, meningioma, and glioblastoma. Here we tested whether NDRG4 methylation was associated with the risk and the prognosis of gastric cancer.

METHODS: A fragment (hg19: chr16:58535416-58535478) on the CpG island of NDRG4 was selected in the current methylation assay, which measured a total of five CpG sites among 110 pairs of gastric cancer and its adjacent tissues using the bisulfite pyrosequencing technology. Pearson χ^2 test, Fisher's exact test or Cox proportional hazard models were applied to assess the association of NDRG4 methylation with clinicopathological phenotypes and survival outcomes.

RESULTS: Our data showed that NDRG4 average methylation level was significantly increased in tumors compared with their matched adjacent tissues ($19.87 \pm 11.88\%$ versus $13.80 \pm 4.38\%$, $P < 0.001$). There were 40 (36.36%) of 110 tumors with over 19.87% average methylation of NDRG4, which was significantly associated with age ($P < 0.001$) and tumor differentiation ($P = 0.004$). Meanwhile, multivariate linear regression showed that there was an age-dependent mode of changed methylation level ($r = -0.349$, adjusted $P = 0.001$). Further data mining in the Cancer Genome Atlas (TCGA) dataset showed a significantly reverse correlation between NDRG4 methylation and gene expression ($P < 0.001$), suggesting a pivotal role of NDRG4 methylation in the regulation of gene function.

CONCLUSIONS: In conclusion, NDRG4 hypermethylation was significantly associated with the risk of gastric cancer. Age-dependent mode of changed methylation level might be a relevant marker for gastric cancer prognosis.