

The Sept9 DNA Methylation Biomarker

Through its marker discovery and validation process Epigenomics identified SEPT9 as a particularly robust methylation marker for detection of CRC. The SEPT9 gene, also called MSF, is a member of the Septin family of genes, which has been implicated in a variety of cellular processes including cytokinesis, membrane transport and fusion, exocytosis, and apoptosis. Disruption of Sept9 function results in incomplete cell division (19). SEPT9 and other proteins have been shown to be fusion partners of the proto-oncogene MLL suggesting a role in tumorigenesis (20). Sept9 has also been shown to be in a region frequently deleted in breast and ovarian cancers by loss of heterozygosity (LOH) studies, a finding that further implicates the gene as a possible tumor suppressor (21). Burrows et al. (2003) reported an in depth study of expression of the multiple isoforms of the Septin 9 gene in ovarian cancer and showed an altered expression pattern of various transcripts in tumor tissue (22). The V4a transcript of SEPT9 could be reactivated in several cell lines treated with 5-azacytidine including one colorectal cancer line. The authors speculate that the gene is likely a type II cancer gene where changes in RNA transcript processing control regulation of different protein products, and the levels of these altered protein isoforms may provide answers to the gene's role in tumorigenesis. It is clear that the gene and its isoforms have an important role in neoplastic events.

Although no data have yet been published to demonstrate the functional impact of methylation in certain regions of the SEPT9 gene, one may hypothesize that alteration of alternative splicing may be the consequence of methylation events in this gene. Whereas somatic genetic or epigenetic modifications of SEPT9 appear to play a role in tumorigenesis, the gene has also been implicated in Mendelian disease. Germline mutations in SEPT9 have been associated with 'Hereditary neuralgic amyotrophy', a autosomal dominant disorder resulting in recurrent episodes of painful neuropathy affecting the brachial plexus with weakness and atrophy of arm muscles (23).