Loss of Chromosome 18 in Neuroendocrine Tumors of the Small Intestine: The Enigma Remains.

Abstract:

Neuroendocrine tumors of the small intestine (SI-NETs) exhibit an increasing incidence and high mortality rate. Until now, no fundamental molecular event has been linked to the tumorigenesis and progression of these tumors. Only the loss of chromosome 18 (Chr18) has been shown in up to two thirds of SI-NETs, whereby the significance of this alteration is still not understood. We therefore performed the first comprehensive study to identify Chr18-related events at the genetic, epigenetic and gene/protein expression levels. We did expression analysis of all seven putative Chr18-related tumor suppressors by quantitative real-time PCR (qRT-PCR), Western blot and immunohistochemistry. Next-generation exome sequencing and SNP array analysis were performed with five SI-NETs with (partial) loss of Chr18. Finally, we analyzed all microRNAs (miRNAs) located on Chr18 by qRT-PCR, comparing Chr18+- and Chr18++ SI-NETs. Only DCC (deleted in colorectal cancer) revealed loss of/greatly reduced expression in 6/21 cases (29%). No relevant loss of SMAD2, SMAD4, elongin A3 and CABLES was detected. PMAIP1 and
maspin were absent at the protein level. Next-generation sequencing did not reveal relevant recurrent somatic mutations on Chr18 either in an exploratory cohort of five SI-NETs, or in a validation cohort (n = 30). SNP array analysis showed no additional losses. The quantitative analysis of all 27 Chr18-related miRNAs revealed no difference in expression between Chr18+/− and Chr18+/+ SI-NETs. DCC seems to be the only Chr18-related tumor suppressor affected by the monoallelic loss of Chr18 resulting in a loss of DCC protein expression in one third of SI-NETs. No additional genetic or epigenetic alterations were present on Chr18.