Assessing the pathological relevance of SPINK1 promoter variants.

The SPINK1 gene, encoding the human pancreatic secretory trypsin inhibitor, is one of the major genes involved in predisposition to chronic pancreatitis (CP). In this study we have assessed the potential functional impact of 11 SPINK1 promoter variants by means of both luciferase reporter gene assay and electrophoretic mobility shift assay (EMSA), using human pancreatic COLO-357 cells as an expression system. The 11 promoter variants were found to be separable into three distinct categories on the basis of the reporter gene assay results viz loss-of-function, gain-of-function and functionally neutral. These findings, which were validated by EMSA, concurred with data from previous deletion studies and DNase I footprinting assays. Further, binding sites for two transcription factors, HNF1 and PTF1, were newly identified within the SPINK1 promoter by virtue of their being affected by specific variants. Combining the functional data with epidemiological data (derived by resequencing the SPINK1 promoter region in French, German and Indian CP patients and controls), then allowed us to make meaningful inferences as to each variant's likely contribution to CP. We conclude that only the three promoter variants associated with a loss-of-function (ie, -53C>T, -142T>C and -147A>G) are likely to be disease-predisposing alterations.