

First Evidence of Expression of the New Human Kallikrein Gene Family Members (KLK4, KLK5, hK6) in Epithelial Ovarian Cancer: Genomic Organization, Molecular Characterization and Clinical Implications.

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Abstract: Kallikreins are a subgroup of serine proteases with diverse physiological functions. Growing evidence suggests that many kallikreins are involved in carcinogenesis. By using molecular cloning techniques, we and others identified three new human kallikrein genes named KLK4, KLK5 (for kallikrein 4 and 5 genes) and human kallikrein 6 (hK6). All new genes map to chromosome 19q13.4. By using linear sequence information, restriction analysis endsequencing, PCR and blotting techniques as well as bioinformatic approaches, we were able to construct the first detailed map of the human kallikrein gene family which currently includes 15 genes. We have examined the mRNA expression of KLK4 and KLK5 in 147 and 142 malignant ovarian tissues, respectively. We found a strong positive association between KLK4-KLK5 expression and tumor grade ($p=0.02$, $p=0.006$) and clinical stage ($p<0.001$, $p=0.027$). Univariate analysis revealed that patients with ovarian tumors positive for KLK4-KLK5 expression had an increased risk for relapse and death ($p<0.003/0.001$, $p=0.018/0.022$ respectively). In multivariate analysis both KLK4-KLK5 expression showed independent prognostic value in patients with grade I and II tumors. Using a sensitive and specific immunofluorometric assay and antibodies developed by us, we determined the amount of hK6 protein in extracts of 180 ovarian tumors. hK6 was also retained as an independent prognostic variable in several subgroups of patients (low tumor grade optimally debulked). These newly discovered genes have potential of being used as a diagnostic and/or prognostic marker for ovarian cancer.