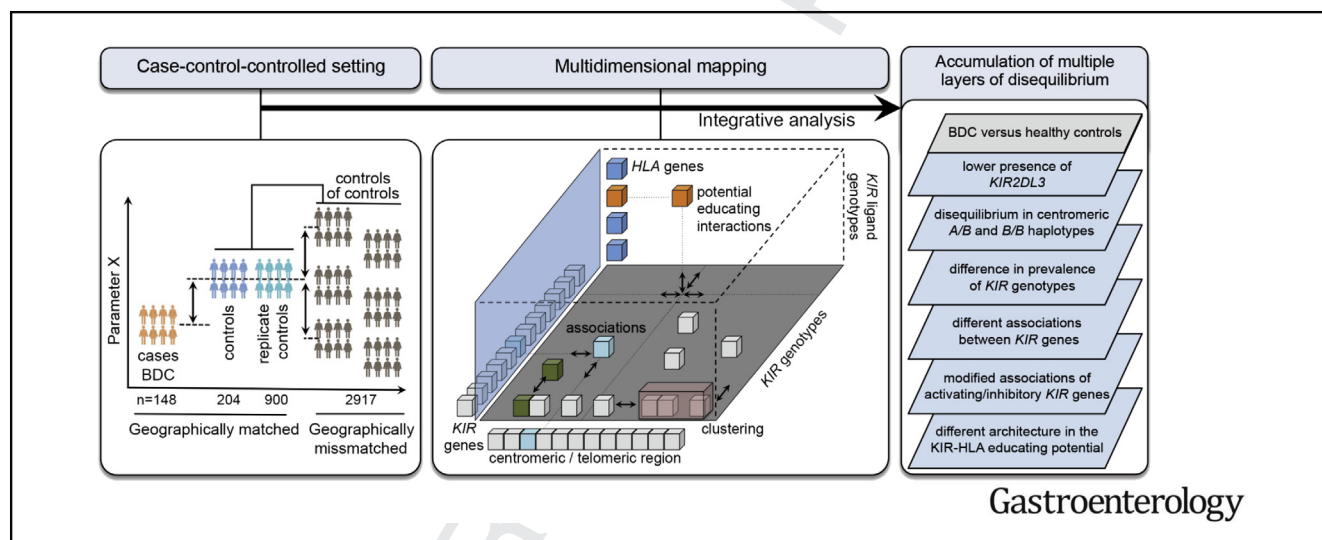


Imbalance of Genes Encoding Natural Killer Immunoglobulin-Like Receptors and Human Leukocyte Antigen in Patients With Biliary Cancer

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BACKGROUND & AIMS: Bile duct tumors are rare and have poor prognoses. Natural killer (NK) cells are frequent in human liver and infiltrate these tumors but do not control their progression. Responses of NK cells are regulated by NK immunoglobulin-like receptors (KIRs), which interact with HLA class I ligands. We aimed to characterize the features of the KIR gene loci and their ligands in patients with bile duct cancer (BDC). **METHODS:** We performed combined multidimensional characterization of genes that encode KIRs and their ligands in blood samples from patients with BDC from Sweden, followed for up to 8 years after diagnosis (n = 148), in 2 geographically matched cohorts of healthy individuals from Northern Europe (n = 204 and n = 900), and in healthy individuals from 6 geographically unrelated populations (n = 2917). We used real-time polymerase chain reaction, RNA sequencing, immunohistochemistry, and flow cytometry to evaluate NK-cell presence, as well as KIR and KIR-ligand expression in bile duct tumors and control tissues. **RESULTS:** Patients with bile duct tumors had multiple

alterations at the KIR gene loci. KIR loci are grouped into genotypes that encode more inhibitory (group A) and more activating (group B) receptors, which can be subdivided into centromeric and telomeric fragments. Patients with BDC had a lower prevalence of *KIR2DL3*, which was linked to disequilibrium in centromeric A/B and B/B genotypes, compared with control individuals. The associations between KIRs and KIR ligands differed between patients with BDC and control individuals; patients had an altered balance between activating and inhibitory KIRs. KIR-positive NK cells infiltrated biliary tumors that expressed matched KIR ligands. **CONCLUSIONS:** In a multidimensional analysis of DNA from blood samples of patients with BDC in Europe, we found patients to have multiple alterations at the KIR and HLA gene loci compared with control individuals. These alterations might affect NK-cell tumor surveillance. NK cells from bile duct tumors expressed KIRs and were found in tumors that expressed cognate ligands. This should be considered in development of immune-based therapies for BDC.