

Genetic imbalance in immune system linked to biliary tract cancer

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Patients with biliary tract cancer have altered genetic architecture in some immune system receptors. This has been shown by researchers at Karolinska Institutet in Sweden in a new study published in the journal *Gastroenterology*. It is hoped that the discovery will lead to new effective

immunotherapy for these difficult to treat tumour types.

Biliary tract cancers, including cholangiocarcinoma and gallbladder [cancer](#), are rare but lethal tumours with limited treatment options.

One of the main functions of our [immune system](#) is to target and eliminate [cancer cells](#). When a tumour arises it was for long thought that it had won the "battle" against the immune system. However, in recent years we have learnt that it is possible to reinvigorate and redirect an exhausted immune system in patients with cancer with excellent clinical outcomes using for instance checkpoint blockade. This reactivation is based on specific targeting of certain immune system receptors.

Researchers at Karolinska Institutet have now investigated the [genetic architecture](#) of two large genetic clusters encoding immune system receptors, the so called KIR-HLA system.

"We found that the genetic architecture of the KIR-HLA system is in imbalance in patients with [biliary tract cancer](#). These results provide a theoretical framework for future targeted immunotherapy design focused on these receptors," says Niklas Björkström, physician and researcher at Karolinska Institutet's Department of Medicine, Huddinge.

The KIR-HLA system controls the function of so called natural killer (NK) cells.

"One of the most important functions of NK cells is to eliminate cancer, and many previous researchers have found links between the KIR-HLA system and risk for cancer," says Niklas Björkström. "Based on this, there are now treatments in clinical trials aimed at altering the function of NK cells by targeting receptors on the cell surface."

The two families of genes that make up the KIR-HLA system are among

the most complex gene families in the human genome, which have made it difficult to map their genetic composition.

To study the full complexity of the genetic architecture of the KIR-HLA system, researchers from Karolinska Institutet performed sequencing of these gene families and developed a number of new tools to analyse, depict, and interpret the studied gene families. These tools were subsequently used on a prospective cohort of 148 patients with biliary tract cancer and compared with two geographically matched and six non-geographically matched control populations.

"Our analysis revealed multiple layer of imbalance in the KIR-HLA system and an increased frequency of rare combinations of KIRs in patients with biliary tract cancer," says Martin Cornillet, postdoc at Karolinska Institutet's Department of Medicine, Huddinge, who led the project. "As compared to geographically matched populations, the patients appeared to have different associations between the activating and inhibitory KIR genes. We also managed to show that NK [cells](#) expressing KIRs infiltrate the actual tumours of these [patients](#)."

More information: Martin Cornillet et al. Imbalance of Genes Encoding Natural Killer Immunoglobulin-like Receptors and Human Leukocyte Antigen in Patients With Biliary Cancer, *Gastroenterology* (2019). [DOI: 10.1053/j.gastro.2019.06.023](https://doi.org/10.1053/j.gastro.2019.06.023)

Provided by Karolinska Institutet

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