Familial clustering of prostate cancer has been known for a long time and the heritable component of this malignancy is expected to be stronger than for any other common cancer. Nevertheless, dissection of the responsible germline risk factors has proven difficult as various genes seem to be involved, each one hidden in a condition termed “complex inheritance.” The identification of high-risk genes remains especially challenging and is currently being approached by improved genome-wide research strategies.

The “Familial Prostate Cancer Project” established by the Institute of Human Genetics and the Department of Urology at Ulm University has its main study focus on sequencing whole exomes of prostate cancer patients. From the large prostate cancer study cohort available at Ulm, affected men are selected based on their family history and the most severe clinical manifestation of the disease. This project, as well as our efforts in genome-wide association studies, is integrated in large collaborative activities such as the International Consortium for Prostate Cancer Genetics (ICPCG) and the PRACTICAL consortium. Within the last two years, the networks have determined a series of 70 common variants associated with prostate cancer risk, and moreover, that the first tumor-specific high risk gene HOXB13 is responsible for 3% of familial clustering.

In the presence of genetic heterogeneity, sample splitting for the generation of more homogeneous study samples is a promising strategy to facilitate disease gene identification. For this purpose, the research group has introduced the previously identified oncogene fusion TMPRSS2-ERG as a surrogate marker for a homogeneous pathomechanism to define a potentially distinct entity of prostate cancer. The occurrence of the chromosomal rearrangement TMPRSS2-ERG further links tumorigenesis to cellular DNA-repair capacity, a mechanism that is presumably involved in the susceptibility of this tumor. In his PhD study, Manuel Lüdeke has discovered and investigated DNA repair genes which appeared to harbor rare germline variants substantially associated with fusion positive prostate cancer. Intriguingly, not only rare variants (as candidates for higher risk mutations) but also common risk polymorphisms seem associated with TMPRSS2-ERG fusion status, strengthening the hypothesis of an etiologically distinct tumor subtype. A series of known prostate cancer risk variants have been investigated for correlations with TMPRSS2-ERG status and...
TMPRSS2-ERG fusion positive prostate cancer.

The dual color FISH break apart assay uses a green probe downstream of the ERG gene and a red probe mapping upstream, towards the 3 Mb distant TMPRSS2 gene at chromosome 21. Colocalization of the signals indicate an intact chromosome 21. Absence or separation of a red signal indicates deletion of the intergenic region, suggesting the fusion of TMPRSS2 to ERG.

In three research groups (Ulm, FHCRC Seattle and University of Tampere) cases were split by TMPRSS2-ERG fusion status and separately compared to control groups of the referring study sites. Corresponding odds ratios appeared higher for the fusion positive subgroups (OR ≈ 1.5, red panel), while the SNP obviously does not have any effect in fusion negative cases (OR ≈ 1, green panel). Since unselected samples represent always a 50:50 mixture of fusion positive and negative cases, the effect size of rs10993994 known from literature lies intermediate (OR = 1.25, grey panel). Light bars denote 95% confidence intervals for the given odds ratios. The variant is also associated with DNA-repair capacity (data not shown).

Example of a common prostate cancer risk variant, rs10993994 at 10q11, which is specifically associated with the TMPRSS2-ERG fusion.

Selected Publications:


