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Department of Urology

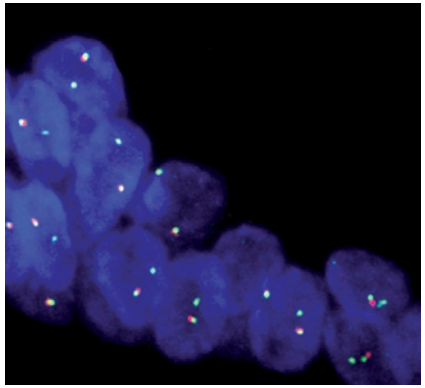
Molecular Genetics of Familial Prostate Cancer

Head: Mark Schrader

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*.

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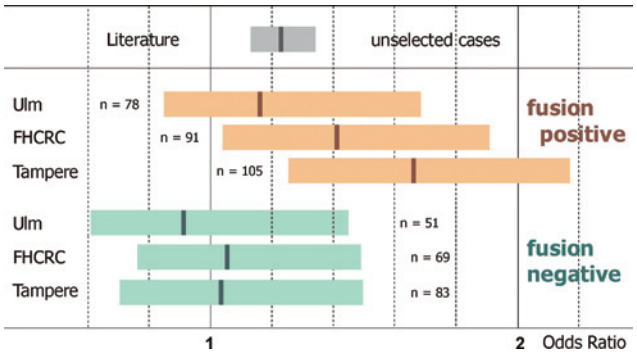
their influence on the individual DNA-repair capacity of carriers according to their genotypes (PhD work of Antje Rinckleb). Further experiments on candidate polymorphisms and genes are currently being processed by Andrea Nottelmann-Mariné in the Study Programme in Experimental Medicine.



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

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).

Selected Publications:

- *Hofer MD*, Kuefer R*, Maier C*, Herkommer K, Perner S, Demichelis F, Paiss T, Vogel W, Rubin MA, Hoegel J (2009): Genome-wide linkage analysis of TMPRSS2-ERG fusion in familial prostate cancer. Cancer Res 69, 640-646. *equal contribution*
- *Luedeke M, Linnert CM, Hofer MD, Surowy HM, Rinckleb AE, Hoegel J, Kuefer R, Rubin MA, Vogel W, Maier C (2009): Predisposition for TMPRSS2-ERG fusion in prostate cancer by variants in DNA repair genes. Cancer Epidemiol Biomarkers Prev 18, 3030-3035.*
- *Luedeke M*, Coinac I*, Linnert CM, Bogdanova N, Rinckleb AE, Schrader M, Vogel W, Hoegel J, Meyer A, Dork T, Maier C (2012): Prostate Cancer Risk Is not Altered by TP53AIP1 Germline Mutations in a German Case-Control Series. PLoS One 7, e34128. *equal contribution*
- *Rinckleb AE*, Surowy HM*, Luedeke M, Varga D, Schrader M, Hoegel J, Vogel W, Maier C (2012): The prostate cancer risk locus at 10q11 is associated with DNA repair capacity. DNA Repair (Amst) 11, 693-701. *equal contribution*
- *Xu J, et al. (2013): HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 132, 5-14.*
- *Eeles RA, et al. (2013) Identification of 23 novel prostate cancer susceptibility loci using a custom array (the iCOGS) in an international consortium, PRACTICAL. Nat Genet, in press.*