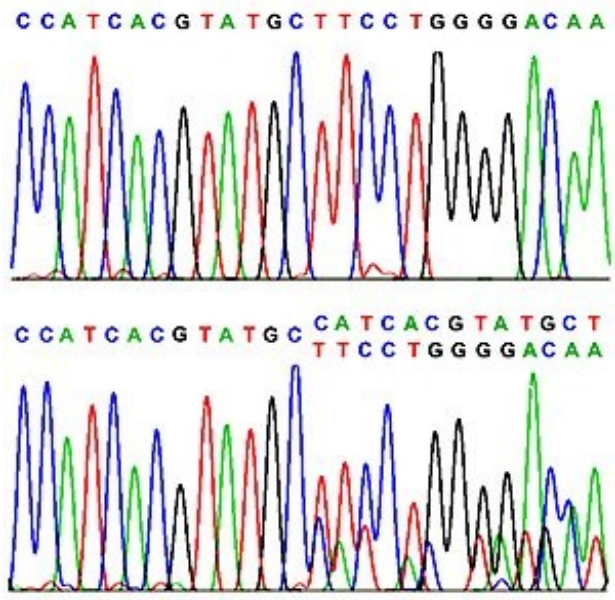
Website address:
https://www.gesundheitsindustrie-bw.de/en/article/news/uncovering-the-genetics-of-prostate-cancer

Uncovering the genetics of prostate cancer

The prostate genome project, which is part of the International Cancer Genome Consortium, is focused on the genetic and epigenetic causes of the development and progression of this highly variable cancer and finding markers that enable the reliable diagnosis of the disease. The German research groups involved in the project are coordinated by the German Cancer Research Center and concentrate on prostate cancer patients under 50 years of age, as these cases might be key to understanding the development of the disease.



Genome sequencing © Universität Heidelberg

The incidence rates of prostate cancer vary considerably by race and ethnicity. Chinese and Japanese men very rarely suffer from prostate cancer; in comparison, African American men in the USA have a prostate cancer incidence (number of disease cases per 100,000 people) over 100 times higher than Japanese and Chinese. Worldwide, prostate cancer has the highest incidence rate in the USA. In Greece, very few men contract prostate cancer, while the disease is more common in Germany (with an incidence of 126 per 100,000 in 2008) and other northern European countries. In Germany, prostate cancer is diagnosed in around 60,000 males per year, which makes it the most frequent malignant tumour and the second most frequent cancer-related cause of death in men in Germany.

Combined with findings obtained in twin and family studies, the broad range of variation in the world's different populations suggests that the genetic background may contribute to prostate cancer risk, which in turn might be subject to modulation by environmental factors such as diet, hormones, smoking and social influences. The National Cancer Institute in the USA concluded in 2012 that the malignant transformation of prostate epithelial cells and the progression of prostate cancer are most likely the result of a complex chain of events influenced by a person's genetics and environment. However, very little is in fact known about the specific causes of prostate cancer. The prostate cancer genome project, which is part of the International Cancer Genome Consortium (ICGC), is working on deciphering the genetic and epigenetic alterations that promote the development and growth of this cancer.

Enormous amounts of data

PD Dr. Holger Sültmann © DKFZ

Like many other tumours, prostate cancer is characterised by a huge number of genetic and epigenetic aberrations. It is rather difficult to identify the mutations that promote development and progression of prostate cancer. These mutations are known as "driver mutations". As the tumours of individual patients are fairly heterogenic, a huge number of tumour genomes needs to be analysed in order for a reliable diagnosis and prognosis of this tumour to be made. This has only been possible both technically and financially thanks to the latest next-generation sequencing technologies, which enable many small DNA aberrations to be identified. "We need to sequence 500 genomes of this tumour entity in order to be able to identify mutations that occur in at least three percent of this tumour entity," said PD Dr. Holger Sültmann from the Cancer Genome Research group at the German Cancer Research Center (DKFZ) and the National Center for Tumour Diseases (NCT). Sültmann is the spokesperson of the prostate cancer genome project.

The sequencing of a single genome leads to data of a magnitude of 400 gigabytes or more, which need to be stored. The enormous amount of data arising from the prostate cancer genome project (and other German projects that are part of the ICGC) are stored in one of the largest data storage centres in Europe, which is currently being established at the BioQuant centre at the University of Heidelberg under the leadership of Professor Dr. Roland Eils (Department of Theoretic Bioinformatics, DKFZ, and University of Heidelberg). It has a storage capacity of more than 5 petabytes (1 petabyte = 1 million gigabyte). Eils' department is also in charge of managing and analysing the data using bioinformatic methods.

Early onset prostate cancer

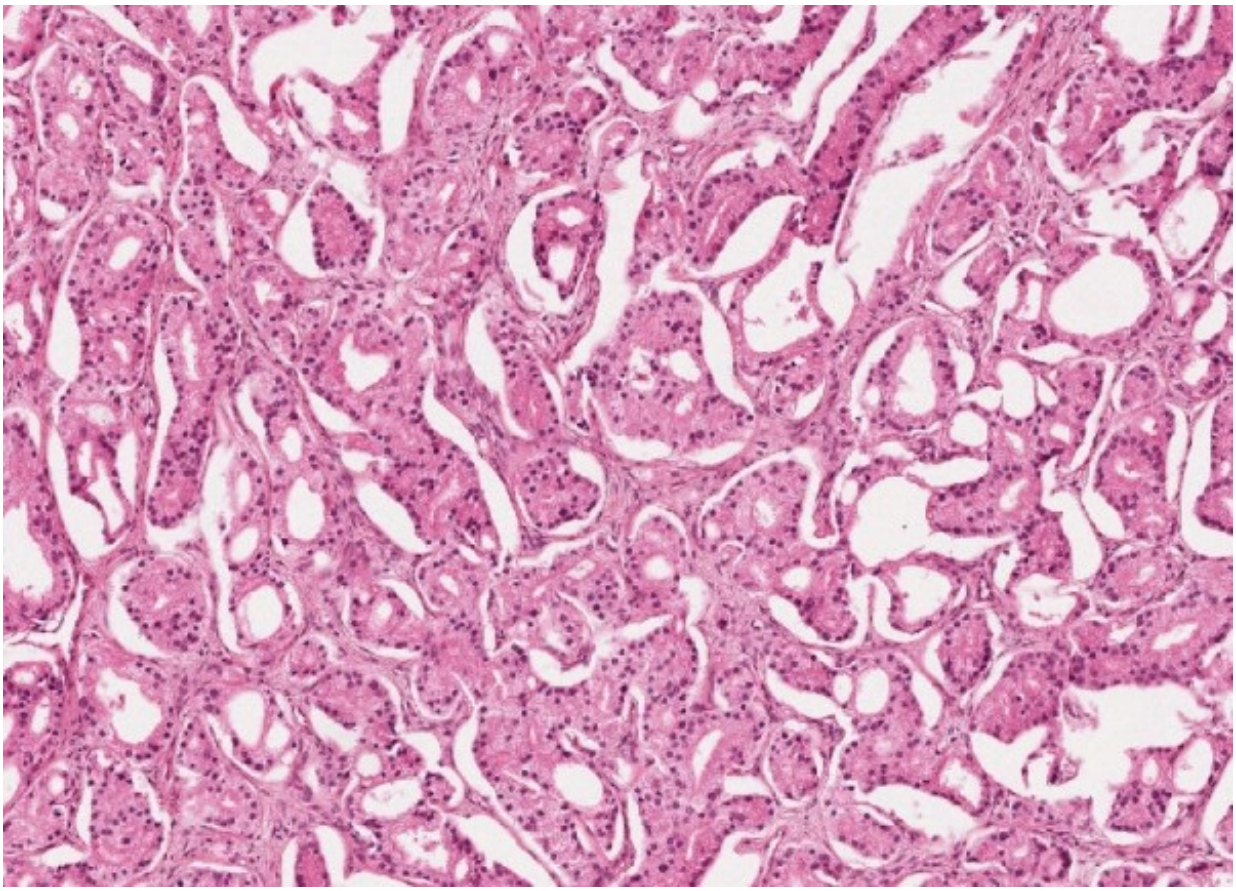
The probability of developing prostate cancer increases with age; prostate cancer is very infrequent in younger men (under 50 years of age). The project "The genomes of early onset prostate cancer", which began in November 2010, specifically deals with prostate cancer in younger men. It is assumed that these early onset prostate cancers may be key to understanding the biology of prostate cancer. The reasons for this are the following:

1. they are potentially characterised by fewer non-tumour associated aberrations (known as "passenger aberrations"), which might enable the easier identification of so-called driver mutations for prostate cancer development;

2. they might have accumulated molecular changes that could be instrumental in the early detection of "classical" prostate cancers, i.e. those occurring in people over 50;

3. they might display molecular changes that can be used as targets for the development of new treatment regimens for specific use in patients in the under 50 age group;

4. the comparison of datasets of young men with prostate cancer with "classical" prostate cancer datasets might provide information on the mechanisms of hereditary prostate cancer.



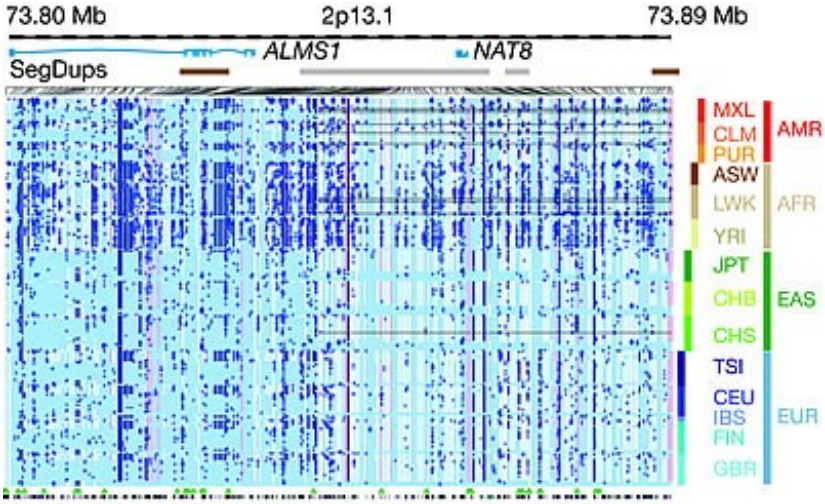
Prostate histology of a biopsy removed from a patient suspected of having prostate cancer. © Martini Hospital, University Medical Center Hamburg-Eppendorf

All tumour samples used in the study will be matched with non-tumorous prostate tissue of the same patients as reference. The collection of tissues, histopathological diagnostics and the isolation of DNA and RNA from the tissue samples, along with cryoconservation and biobanking will take place at the Martini Hospital at the University Medical Center Hamburg-Eppendorf, which

is the only German hospital with a special focus on prostate cancer. The researchers work closely with research groups in the USA and Canada who are also part of the ICGC and who deal with the sequencing of the genomes of prostate cancers of people in the over 50 age group.

Supported by the DKFZ, the genome sequencing activities related to the German prostate cancer genome project are carried out at the Max Planck Institute for Molecular Genetics. Cancer-related DNA rearrangements are analysed by a group of researchers led by Dr. Jan Korbel at the European Molecular Biology Laboratory using massively parallel "paired end-sequencing". The sequencing of RNA, including analyses of mRNA for the determination of the transcriptome as well as microRNAs, is carried out at the DKFZ and NCT by groups led by Dr. Holger Sültmann and Professor Dr. Christof von Kalle (Department of Translational Oncology). DNA methylation (methylome sequencing) patterns are analysed in the Division of Epigenomics and Cancer Risk Factors at the DKFZ under the supervision of Professor Dr. Christoph Plass. Over the last few years, the methylome has become of increasing importance for tumour research. For example, a histone demethylase enzyme has been identified that is assumed to play a crucial role as epigenetic regulator and hence in the development and progression of prostate cancer.

Future genetic diagnostics of prostate cancer



Genetic variations in a segment of human chromosome 2. © G. McVean, 1000 Genomes Consortium

The researchers hope that this comprehensive and time- and resource-consuming research approach will provide them with in-depth insights into the development and wide variability of prostate cancer, especially with regard to its aggressiveness and speed of growth. The diagnosis of prostate cancer is still unsatisfactory and there is an urgent demand for reliable markers. It is expected that the study will also lead to the identification of such markers, whether they are markers related to the over- and underexpression of genes or to complex gene expression patterns. The technological prerequisites for using such markers in the diagnosis of prostate cancer are increasingly available at big institutes and hospitals. Based on the results gained in the prostate cancer project, the researchers will establish methods for the genetic diagnosis of prostate cancer with which new, differentiated therapy decisions can be made and tailored to the requirements of patients with particular tumour characteristics. This is another important step on the path towards personalised medicine.

The project can also be expected to come up with an answer to the question related to the huge differences in the incidence and mortality of prostate cancer around the world. Initial results of the

"1000 Genomes Project", which also involves Jan Korbel from EMBL, were recently published. This project is the largest international genome sequencing project ever aimed at determining the genetic variations of human populations and finding genetic variants that occur in disease-associated regions with a frequency of one in under 50 people. It is thought that this is a high enough accuracy to be able to look for mutations relevant for prostate cancer. What is required to make this possible is knowing where to look for such mutations. The prostate cancer genome project is expected to be able to come up with the sought-after data.

Article

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