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Inherited risk of prostate cancer

"Population study identifies common sequence variants that increase risk of prostate cancer"

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Summary

The strongest risk factor for prostate cancer, excluding age, is family history, highlighting the importance of heredity in the risk of prostate cancer. Extensive studies of prostate cancer families have led to the identification of mutations in three genes that segregate with the disease but the prevalence of these mutations is too low to be of clinical relevance.

The great majority of the remaining genetic risk of prostate cancer is likely due to the combined effects of many low-to-moderate risk variants which, until recently, remained elusive. Breakthrough genotyping technologies have revolutionized the search for these moderate risk variants. Here we review the results of a genome-wide association study of prostate cancer conducted by the Polygene consortium, coordinated by deCODE Genetics (www.polygene.eu), which has led to the identification of 4 common sequence variants that each confer a moderately increased risk of prostate cancer. These variants are all common and thus account for a substantial proportion of the population attributable risk (PAR) of prostate cancer.

Introduction

Epidemiological studies suggest that the genetic component of the risk of prostate cancer is greater than in any other cancer. Despite strong evidence for genetic factors, highly penetrant susceptibility genes for prostate cancer have proven difficult to find. This contrasts with other common cancers such as breast cancer, colon cancer and melanomas, where a small percentage of cases can be attributed to the inheritance of highly-penetrant mutations.

Analysis of data from large twin studies has suggested that the majority of genetic prostate cancer risk may be attributable to recessive and/or multiple interacting genetic variants (1). Each such variant might be expected to confer a small increase in risk but if the variant is common, it might contribute significantly to the population attributable risk (PAR). If this polygenic model is correct, linkage studies of families with multiple cases of prostate cancer would not suffice because they lack power to detect low-penetrance risk variants. In order to identify such variants, the association approach (i.e. the comparison of allelic frequencies of genetic variants between cases and controls) has proven to be effective. However, this study design requires a large number of cases and controls to be genotyped for hundreds of thousands of genetic markers, an undertaking that, until recently, remained prohibitively expensive.

Lately, advances in genotyping technologies have revolutionized genetic association studies of common diseases. Whole-genome scans using a large number of genetic markers in case-control study populations have led to an onslaught of landmark publications describing common genetic risk variants that affect complex diseases. Notably, genome-wide association studies on prostate cancer have led to the identification of several such variants, providing a new perspective on this complex disease.

"Whole-genome scans using a large number of genetic markers in case-control study populations have led to an onslaught of landmark publications describing common genetic risk variants that affect complex diseases."

Prostate cancer risk variants on Chr8q24

Using a combination of linkage and association studies in the Icelandic population, we initially discovered a common sequence variant on chromosome 8q24 that is associated with a moderate increase in prostate cancer risk (2). This variant is represented by a risk-allele of a microsatellite marker (allele -8 of marker DG8S737), with an odds ratio (OR) of 1.79. A further refinement of the locus showed that allele A of the single-nucleotide polymorphism (SNP) rs1447295 also showed a significant association with prostate cancer (OR=1.72).

We replicated these results in three additional cohorts, two of European origin and one African American cohort, demonstrating that the risk variants may confer considerable PAR in both Europe and the U.S., which are the regions of the world that have the highest incidence of prostate cancer. Combining the results from all the populations gave an OR of 1.62 for allele -8 of DG8S737 and 1.51 for allele A of rs1447295. We have subsequently replicated the associations of DG8S737 and rs1447295 to prostate cancer in Spanish and Dutch case-control samples (3) and several independent groups have also reported similar results as well as several additional variants in this region. Hereafter, we refer to the genomic region containing DG8S737 and rs1447295 as region 1.

Interestingly, while both DG8S737 and rs1447295 were associated with cancer in populations of European descent, only DG8S737 was associated with prostate cancer in African Americans. In this population, allele -8 of DG8S737 is present in 41% of cases and 30% of controls or at a frequency twice as high as in the European populations. This large difference may be partly responsible for the higher incidence of prostate cancer observed in African Americans than in Europeans. The frequency of the variants in region 1 was greater in affected individuals with high (7–10) compared with low (2–6) Gleason scores in all four case control groups, suggesting that the variant may be associated with an aggressive form of the disease.

After we reported the initial 8q24 findings, we conducted a genome-wide association study on 1,453 prostate cancer patients and 3,064 controls from Iceland using 317,000 genetic markers, followed by replication studies in three populations of European descent, as well as African Americans. The strongest signal detected in this genome-wide scan was the rs1447295 variant we had reported earlier. Subsequently, we identified a second novel genetic variant in the 8q24 region that was defined by a 14 SNP haplotype (HapC) and had an OR of 2.08 (4). However, the frequency of HapC was considerably lower than that of the rs1447295 variant, or 3% in Icelandic controls compared to 10.4% for rs1447295. By examining the HapMap data and later by further genotyping in the Icelandic study group, allele A of the SNP rs16901979 was shown to be strongly correlated with HapC as well as associated with prostate cancer (OR = 1.80). Both the results for HapC and the correlated SNP were replicated in case-control samples of European descent from the Netherlands, Spain and the US. The combined OR for allele A of rs16901979 in the three populations was about 1.8. The SNP was significantly associated with prostate cancer in African Americans with an OR of 1.34 and similarly to the variants in region 1, the frequency was found to be considerably higher (~10-times) than that of the European population. Again, our findings have been independently verified in other studies (5).

Contrary to the first region, no evidence was found for a stronger association between HapC and disease in individuals with a higher Gleason score. However, for each copy of allele A of rs16901979, carriers were diagnosed with prostate cancer 1.4 years younger than the non-carriers; HapC gave very similar results. Based on this observation and the fact that familial cancer cases tend to have younger age at diagnosis, it is not surprising that the frequency of allele A of rs16901979 is greater in individuals who have at least one first- or second-degree relative with prostate cancer compared with cases that have no closely related relative diagnosed with prostate cancer (OR of 1.6) (unpublished results).

The two genomic regions on 8q24 demonstrating association with prostate cancer are in a gene-poor area characterized by a high recombination rate of ~2 cM/Mb, compared to the genome-wide average of 1.2 cM/Mb. The only reported "known gene" in the interval defined by these two regions (spanning ~550kb) is a retrotransposed gene named AF268618 (POU5FLC20) (www.genome.ucsc.edu, May 2004 Assembly). Two known genes, FAM84B/NSE2 and c-MYC are located on either side of this interval but we observed no association between variants of these genes and prostate cancer. Thus the functional relevance of the genetic variants remains to be elucidated. A number of explanations can be proposed, e.g. the function may be conferred by long-range regulatory elements that affect c-MYC, the region may harbour regulatory transcripts or viral and transposon integration sites, or may be particularly sensitive to chromosome breakage. In this regard it is important to note that chromosome 8q24 is the most commonly gained or amplified genomic region in prostate tumours, as well as in a number of other cancers.

deCODE genetics uses a population approach to unravel the genetic causes of common diseases. The company's prostate cancer program has identified 4 sequence variants that impact the risk of developing prostate cancer.

Prostate cancer risk variants on Chr17q

Based on our experience with chromosome 8q24, we anticipated that results from family-based linkage studies could be used to guide the evaluation of results of a genome-wide association study. Using this approach, we identified two common variants in two distinct regions on the long arm of chromosome 17 that confer risk of prostate cancer (4). One locus is on 17q12, encompassing the 5' end of the TCF2 (HNF1β) gene (represented by rs7501939 and rs4430796) while the second locus is in a gene poor area on 17q24.3 (represented by rs1859962). Both risk variants are present in high frequency as about 24% of the populations are homozygous for the variant at 17q12 and 21% are homozygous for the variant at 17q24.3. In the homozygous state, both variants confer an OR between 1.4 and 1.5. The two loci are separated by approximately 33 Mb and no correlation was observed between them. Based on the combined results from the four study populations, the two variants on 17q have an estimated PAR of 20% each, and a joint PAR of about 36%. The large PAR is a consequence of the high frequencies of these variants. However, as their relative risks are not high, the sibling risk ratio accounted for by them is only approximately 1.009 each, and 1.018 jointly. Therefore, they can only explain a small fraction of the familial clustering of the disease.

"It is therefore unlikely that any single variant will be of clinical value alone. However, the combined effect of these and other prostate cancer risk factors may provide a sufficiently high predictive value to become clinically important."

The TCF2 gene on 17q12 has been reported to be mutated in individuals diagnosed with renal cysts, pancreatic atrophy, genital tract abnormalities, and maturity-onset diabetes of the young, type 5 (MODY5) (6, 7). Interestingly, several epidemiological studies have demonstrated an inverse relationship between type 2 diabetes (T2D) and the risk of prostate cancer (8). When the effect of the two SNPs in TCF2 were studied in an Icelandic T2D case-control group as well as in seven additional T2D case-control groups of African-, Asian- and European descent, both SNPs showed a protective effect against the disease (i.e. OR < 1.0). The discovery of variants in TCF2 that confer risk of prostate cancer but protect against T2D explains at least partly the inverse relationship previously described between the two diseases. A more detailed study of the function of TCF2 may possibly lead to the identification of mutual pathway(s) that could provide better diagnostic and/or therapeutic options for both diseases.

Concluding remarks

Four common sequence variants have been identified that have a significant impact on prostate cancer susceptibility. Three of them are common (>5% freq.) and they all confer low to moderate relative risk of 1.2 - 2. It is therefore unlikely that any single variant will be of clinical value alone. However, the combined effect of these and other prostate cancer risk factors may provide a sufficiently high predictive value to become clinically important.

Intriguingly, three of the four variants are located in regions with no annotated genes while the fourth one is in TCF2, a gene not previously implicated in prostate cancer. The fact that the majority of the variants discovered so far are not close to known genes is striking but evidence is mounting that prostate cancer does not present a unique case in this respect. Several high-density genome wide SNP association analyses have been done for some of the most frequently diagnosed cancers such as prostate, breast and colon cancer. Results from these studies

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Programme

Thursday, 18 October 2007

16.00 – 20.00 Registration

Friday, 19 October 2007

07.00 – 09.00 Registration

09.00 – 09.10 Introduction
T. Esen, Istanbul
H. Van Poppel, Leuven

09.10 – 09.35 State-of-the-art lecture on renal cell cancer
New options in the management of renal cell cancer
C. Sternberg, Rome

09.35 – 11.05 Update on prostate cancer
Does every prostate cancer need treatment?
Z. Kirkali, Izmir
Surgery, radiotherapy or minimally invasive curative therapy
R. Khauli, Beirut
Management of locally advanced disease
H. Van Poppel, Leuven
Biochemical progression after curative therapy: definition and management
H. Özen, Ankara

11.05 – 11.25 Coffee break

11.05 – 13.05 Poster sessions
(2 parallel sessions)
11.05 – 11.25 Mounting, viewing of posters
11.25 – 13.05 Presentation and discussion

13.05 – 14.05 Lunch

13.05 – 14.05 Advisory board meeting

14.05 – 14.35 Pro-contra debate
Laparoscopic/Robot vs open radical prostatectomy
Lap/Robot: S. Deger, Berlin
Open: H. Van Poppel, Leuven

14.35 – 15.00 State-of-the-art lecture on renal cell cancer
Watchful waiting or minimally invasive ablative therapy
M. Marberger, Vienna

15.00 – 15.30 Coffee break

15.00 – 17.00 Poster sessions
(2 parallel sessions)
15.00 – 15.30 Mounting, viewing of posters
15.30 – 17.00 Presentation and discussion

17.00 – 18.00 Panel discussion
Update on management of BPH
Chair: T. Esen, Istanbul
Panel: D. Kantzavelos, Neos Voutzas
D. Yachia, Herzliya

Saturday, 20 October 2007

08.00 – 09.30 Update on bladder cancer
Staging/grading revisited
L. Turkeri, Istanbul
T_1G_3: The treatment decision
R. Khauli, Beirut
Cystectomy 2007
H. Abol-Enein, Mansoura

09.30 – 10.00 Coffee break

09.30 – 11.30 Poster sessions
(2 parallel sessions)
09.30 – 10.00 Mounting, viewing of posters
10.00 – 11.30 Presentation and discussion

11.30 – 12.30 State-of-the-art lectures
Severe OAT syndrome/Azospermia: Varicocelectomy vs TESE/ICSI
A. Kadioglu, Istanbul
Update on indwelling urethral and ureteral stents
D. Yachia, Herzliya
Management of female stress incontinence
B. Cetinel, Istanbul

12.30 – 13.30 Panel discussion
Modern stone therapy
Chair: M. Marberger, Vienna
Panel: T. Esen, Istanbul
A. Chamssuddin, Damascus

13.30 Awards and closing remarks
T. Esen, Istanbul
M. Marberger, Vienna

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European Association of Urology

Clinical challenge

Prof.Dr.Med. Oliver Hakenberg
Section editor
Rostock (DE)

The recently introduced Clinical challenge section presents interesting or difficult clinical problems which in a subsequent issue of EUT will be discussed by experts from different European countries as to how they would manage the problem.

Case study 1 - Advanced testis cancer (EUT June 2007)

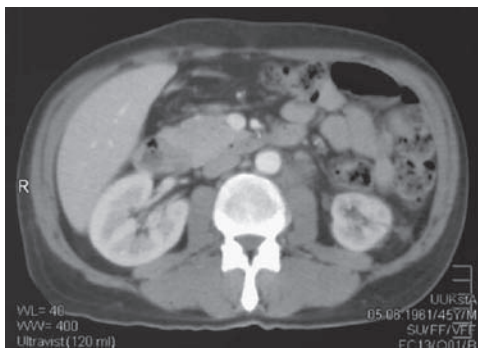
A **46-year-old man** was referred by a urologist from a small hospital with the diagnosis of **advanced testicular cancer.**

The patient had a huge left-sided scrotal solid mass of 15 cm in diameter. CT scan showed retroperitoneal lymph node enlargement (see figure, 12x6x7 cm), smaller left-sided pelvic masses, a small hydronephrotic left kidney but no pulmonary or mediastinal masses. The patient admitted to having noticed an enlarging painless scrotal swelling for up to 12 months, recently intermittent scrotal pain, constant back and epigastral pain as well as a weight loss of about 30 kg over the last 6 months. There was no dyspnea. The patient was a self-employed truck driver living with a girl-friend and two children from a previous marriage.

Serum creatinin was 88 µmol/L, hemoglobin 8,2 mmol/L, C-reactive protein 233 mg/L, α-fetoprotein (AFP) 1,6 IU/mL (normal < 8.3), ß-human chorionic gonadotropin (HCG) 145 mIU/mL (< 5), serum lactate dehydrogenase (LDH) 369 U/L (<250) and human placental alkaline phospatase (PLAP) > 1000 mU/L (< 100).

A percutaneous nephrostomy was inserted into the left kidney which drained clear urine. Inductive chemotherapy consisting of etoposide, bleomycine and cisplatinum (PEB) was commenced. One week later, left sided radical orchiectomy was performed and a 14x10x10 cm testicle removed with infiltration of the spermatic cord up to the internal inguinal ring which was pathologically staged as pT3R0 and classified as a largely necrotic anaplastic seminoma. Immunohistochemistry showed positive PLAP, c-KIT and MIB1 reactions and negativity for AFP, CD30 and ß-HCG.

Three full courses of PEB were given which were well tolerated, nausea could be controlled pharmacologically and two episodes of asymptomatic neutropenia passed uneventfully. Secondary wound healing occurred but resolved with local treatment. A repeat CT scan showed marked regression of the retroperitoneal masses (9x3x3 cm) and the nephrostomy was removed. At the beginning of the 3rd course of chemotherapy AFP had been 3,39 IU/mL (normal < 8.3), ß-HCG 1,16 mIU/mL (< 5), LDH 102 U/L (<250) and PLAP <0.1 mU/L (< 100). At the completion of the third course, AFP had increased to 16.7 IU/mL (normal < 8.3), ß-HCG <0.1 mIU/mL (< 5), LDH 545 U/L (<250) and human placental AP was 57 mU/L (< 100).



CT scan before the beginning of systemic treatment.

Discussion points
1. What is going on?
2. Are our guidelines helpful in this situation?
3. What further treatment would you advise?
4. What is the patient's prognosis?

Case provided by Oliver Hakenberg, Dept. of Urology, Rostock University, Germany
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Comments on Case study 1

Prof.Dr. P. Albers
Kassel (DE)

The initial presentation suggested a stage IIC seminoma of the left testis (IGCCCG classification "good prognosis"). However, the prechemotherapy CT scan of the abdomen showed that the suspicious large mass in the abdomen is mainly at the right side, precaval, extending into the mesentery. Since the bowel and vena cava contrast is not optimal on this CT slice, the extension of the mass is hard to evaluate (12x6x7 cm in the text).

The metastases at the typical landing zone (left paraaortal) are comparatively small (about 3 cm in transverse diameter of the given CT slice). This left retroperitoneal mass correlates perfectly with the serum levels of HCG and LDH which are only moderately elevated. PLAP is not of additional use. It remains unclear why the left kidney is hydronephrotic with only moderate metastases at the left retroperitoneum (perhaps due to the pelvic metastases that are not shown).

The clinical response to the adequately applied 3 cycles of BEP (according to "good prognosis" IGCCCG) is insufficient regarding the large right-sided precaval mass. In seminoma we expect a major response to chemotherapy and usually a shrinkage of >90% of the initial metastatic volume. This was true for the left side since the nephrostomy tube could be removed and this was reflected in the markers which normalized. The right sided mass, however, did not respond adequately to 3 cycles BEP with a reduction of only 30-40% of volume (pictures not shown). In summary, the localisation of the larger volume metastatic disease and the response to chemotherapy did not fit to a typically left-sided metastatic seminoma. In addition, the weight loss with 30 kg over 6 ms is not really typical for a stage IIC metastatic seminoma patient at the age of 46 years.

After 3 cycles of BEP, AFP and LDH start to rise (2x N) with HCG remaining normal. The normalisation of HCG in a HCG-expressing metastatic seminoma usually is a good clinical sign of adequate treatment response of the seminoma cells. No information is given on the size of the residual right-sided mass at this time.

The clinical suspicion is that this mass has a different histology, perhaps even non-germ cell origin. I would therefore try to get a histology, preferably by open surgery, for two reasons: CT guided biopsy is not representative and at this special location not easy to perform. False-positive AFP elevations (e.d. due to altered liver function or infections) are possible but in this case unlikely since LDH is elevated as well.

Further treatment is strongly dependent on the histology of the residual mass. Without histology I would not start salvage chemotherapy because a non-germ cell tumor is not excluded. The prognosis is dependent on the histology of the residual mass and the possible treatment options.

Case history continued by Oliver Hakenberg, Rostock (DE)

Given the insufficient response in conjunction with a rising AFP and LDH we assumed that the histological assessment of the largely necrotic primary testicular tumour had not been representative and that we were dealing with a metastatic non-seminoma. A fourth cycle of BEP chemotherapy was undertaken. However, towards the end of this fourth cycle the patient presented with marked jaundice and ascites.

All liver function tests were markedly elevated (ALAT/SGPT1685 U7L (normal < 50), ASAT/SGOT 1492 U/L (normal < 50), LDH 328 U/l, total bilirubine 383 µmol/l (normal < 22). Intrahepatic and extrahepatic cholestatsis were excluded by sonograohy and CT scan. Serologic investigations and repeated liver biopsy revealed an active hepatitis B together with an alcoholic liver degeneration with cirrhotic changes. The patient developed progressive hepatic failure despite supportive and substitution treatment in addition to a course of hepatic dialysis by MARS treatment which was uneffective.

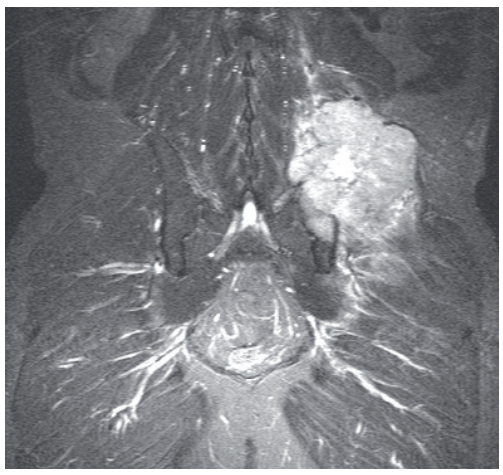
Two months after the presentation with jaundice the patient died of progressive hepatic and renal failure.

Case study 2 - Renal cell carcinoma

A **50-year old man** presented with a lumbar painful mass. The patient had first noticed mild lumbar left sided pain 5 months previously. Treatment by the general practitioner and orthopedic physician had first been based on the assumption of chronic back pain due to degenerative lumbar problems. Antiphlogistic medication had been effective for some time.

With time, however, pain increased and became constant and independent of movement or posture and the patient noticed a palpable left-sided lumbar 'hardness'. MR imaging showed a 12x10 cm lumbar mass arroding the dorsal iliac crest and invading the lateral and dorsal musculature (see figure).

The patient had undergone left-sided laparoscopic radical nephrectomy for a renal cell carcinoma staged as pT1cN0cM0G2 just under two years previously. In view of this fact and the new finding the patient was now referred to the Urology Department.



MRI image of the left-sided lumbar tumour (frontal view at the level of the spinal musculature)

On examination, the left sided lumbar tumour was clearly palpable, not mobile and not painful to touch and there were no local or systemic signs of inflammation. Sonographically guided percutaneous biopsy was performed with a true-cut needle. Histology confirmed malignant tissue in all cores compatible with the metastasis of a renal cell carcinoma.

Local pain is still mild to moderate and well controlled by analgesic first-line medication (diclofenac 50 mg b.i.d.). Apart from this problem, the patient is in good health, without any comorbidity. Extensive further staging by CT, MRI and bone scan did not show any other signs of metastatic disease.

Discussion points
1. What treatment options can be offered?
2. What is a good management strategy for this patient?
3. What is the patient's prognosis?

Case provided by Oliver Hakenberg, Dept. of Urology, Rostock University, Germany
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Readers are encouraged to provide interesting and challenging cases for discussion

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indicate that a sizeable fraction of variants that associate with disease status do not fall within protein-coding genes. Thus, in order to understand the causal link between non-gene risk variants and disease, focused genomic approaches have to be undertaken to characterize in detail the regions over and around the signals with regard to transcribed sequences, structural properties and genomic stability.

In summary, genome-wide association analysis done in a population based case-control samples demonstrate that low-to-moderate risk variants contribute significantly to the overall prostate cancer susceptibility. However, the variants discovered to date do not make a large contribution to the familial clustering of prostate cancer. Hence, additional susceptibility variants remain to be identified.

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