Genetic prostate cancer variants as biomarkers of disease progression

Rendicontazione

Informazioni relative al progetto

PROMARK

ID dell'accordo di sovvenzione: 202059

Sito web del progetto

Progetto chiuso

Data di avvio
1 Gennaio 2008

Data di completamento
31 Dicembre 2012

Finanziato da
Specific Programme "Cooperation": Health

Costo totale
€ 4 045 219,00

Contributo UE
€ 2 709 577,00

Coordinato da
ISLENSK ERFDAGREINING EHF
Iceland

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Final Report Summary - PROMARK (Genetic prostate cancer variants as biomarkers of disease progression)

Executive Summary:

The greatest unmet clinical needs in prostate cancer is the development of predictive methods or markers that can help distinguish between early stage tumours that will remain confined to the prostate and those which will progress to an invasive, aggressive form of the disease. Biomarkers that help predict course of disease are urgently needed. The first major objective of PROMARK is to test if inherited genetic variants can serve as biomarkers for disease prognosis or treatment selection. The second major objective is to perform genomic and functional analysis of predictive variants in order to shed light on the patho-physiology of disease progression. The specific aims and main results of PROMARK are:

1. Establishment of comprehensive collections of biological specimens and clinical data for prostate cancer biomarker research in four European populations. Main results: Samples and clinical information from close to 5 500 prostate cancer cases and over 7 000 controls from different parts of Europe were collected. The first biospecimen repository for prostate cancer in Romania was established.
2. Testing of the utility of genetic prostate cancer risk variants as biomarkers of disease severity, progression and outcomes. Main results: Genetic studies of the samples collected in specific aim one led to the discovery of six sequence variants that affect the risk of prostate cancer. Only one of the variants showed a stronger association to the aggressive form of the disease. In addition, 6 sequence variants that associate with levels of prostate-specific antigen (PSA) in blood were identified. A risk model that included both the prostate cancer risk variants and PSA variants was shown to outperform risk models that include only the cancer risk variants.
3. Elucidation of the biological mechanisms that cause increased prostate cancer risk. Main results: Functional studies of the role of the transcription factor hepatocyte nuclear factor type 1ß (HNF-1ß) in normal and malignant prostate cells were performed but variants at the HNF-1ß gene locus have been shown to associate with prostate cancer risk. Expression analysis showed that HNF1ß levels decrease with increasing Gleason grade and higher levels of HNF-1ß are associated with improved prognosis. Overexpression of HNF-1ß in prostate cancer (PC3) cells shows that HNF-1ß has a measurable effect on the expression of a large number of genes, pathway analyses indicate that the largest effect is on genes that play a role in cell death and survival, movement and proliferation. Overexpression of HNF-1ß in PC3 cells reduces proliferation, adhesion, migration and colony formation in soft agar. Immortalised prostate epithelial cell cultures were produced from 10 prostate cancer cases. Overexpression of HNF-1ß in these cells had a pronounced effect on the morphology of the cells and decreased motility, affected the expression of cadherin and caused rearrangement of paxillin and integrins. Methylation studies showed that the HNF-1ß promoter is differentially methylated in paired tumour and benign patient samples with higher level of methylation in tumour cells. Moreover, promoter methylation is correlated with genotype at some single nucleotide polymorphisms (SNPs) in tumour tissue and cell lines.

Project outcome: Work conducted within PROMARK has resulted in eight peer-reviewed scientific publications and two invited written communications. Patent applications have been filed for all prostate

cancer and prostate specific antigen (PSA) sequence variants discovered in the project. The samples and data collected in the project provide a valuable resource for future studies on prostate cancer. The first genetic risk models that incorporate prostate cancer risk variants, as well as variants that affect PSA levels, have been produced and will be updated as more knowledge becomes available. Functional studies suggest that HNF1ß has tumour-suppressor properties in prostate tissue.

Project Context and Objectives:

Summary description of project context and objectives

Prostate cancer has become the most frequent incident form of cancer in males in Europe, with 345 900 new cases estimated per year (20.3 % of all incident cases). Prostate cancer is ranked third as a cause of cancer related mortality in males in the year 2006, with 87 400 deaths estimated (9.2 %). Within the European Union, prostate cancer is the most common form of cancer in males (301 500 incident cases, 24.1 % of all incident cases) and is the third most common cause of cancer related mortality (67 800, 10.4 %). Thus, prostate cancer is a public health problem of considerable importance for Europe, and because of Europe's ageing population, it can be predicted that these numbers will increase further even if age-specific rates remain constant.

Early diagnosis and treatment are key factors in determining the survival of certain sets of prostate cancer patients. Hence, a major effort has been put into trying to identify biomarkers that could be used for screening for the disease. The test most frequently used to screen for prostate cancer, the PSA blood test, is effective at detecting early stage prostate cancer. However, although the PSA test is useful as a diagnostic tool in many cases, it lacks both sensitivity and specificity. This is mainly due to the fact that PSA is not a specific marker of prostate cancer since its serum levels increases in prostatic hyperplasia and is affected by many factors such as age, medication, urologic manipulations and inflammation. Thus, the application of the test results in a high rate of 'over-diagnosis' of up to 50 %. Consequently, prostate cancer incidence has risen rapidly in those European countries where opportunistic PSA screening is commonplace and, due to lack of prognostic tests, has led to excessive treatment of localised lesions that might never progress to symptomatic cancer. This over-treatment carries heavy costs, both financial and personal as side-effects of treatment can be considerable, including impaired urinary continence and sexual dysfunction. Biomarkers that help determine which early stage tumours will remain confined to the prostate and those which will progress to an invasive, aggressive form of the disease are urgently needed.

Overall objective of PROMARK

The main objective of PROMARK is to attempt to translate recent breakthrough findings in prostate cancer genetics into biomarkers of clinical utility. Two members of our consortium, deCODE and RUNMC, were funded by the Sixth Framework Programme (FP6) to identify genetic variants that affect the risk of prostate cancer, using genome-wide association studies (see http://www.polygene.eu). Hence, we were the first to identify and report four common genetic variants that increase the risk of developing the disease. At least one of our variants showed a stronger association with more the aggressive form of the disease (Gleason score more than six), opening the possibility that genetic variants could be used as biomarkers to predict disease severity and outcome. To further explore this possibility, we compared the genotypes of

prostate cancer patients with aggressive disease (Stage T3 or T4, Gleason score less than six and/or metastatic disease) to those of patients with less aggressive disease (stage less than T2b, Gleason less than six in order to identify candidate markers of disease progression. In PROMARK, we proposed to examine if these markers have a predictive value for prostate cancer prognosis and could serve as biomarkers of disease progression.

In order to assess if inherited factors affect the course of disease, the genetic variants need to be tested in large cohorts of prostate cancer cases with accurately documented clinical follow-up. Such resources are costly and take a long time to build. Therefore, we formed a consortium of established investigators which had already initiated collections of samples and data from prostate cancer cases and controls. In addition, a new cohort for prostate cancer was to be established in Romania, the first in the country. This collection was expected to enable us to examine the effect genetic risk variants have in a population of low PSA screening and with different environmental factors from the Northern-European populations already involved in the study. The study was planned to eventually include samples and standardised clinical data from over 8 000 prostate cancer cases from different geographical locations within Europe. This collection was expected to greatly increase our power to pinpoint possible association between genetic variants and various parameters of disease severity and outcome.

If genetic findings are to be translated into clinical utility, it is vital to understand the functional aspects of how sequence variation leads to different phenotypes of disease. In PROMARK, we planned to perform functional studies on genetic variants that show association with disease severity and/or prognosis. We believe that by unravelling the cellular mechanisms that play a role in disease progression we may be able to identify additional predictive biomarkers and possibly new targets for treatment. The two variants we chose to study within the scope of this project have very different properties and therefore present good models for such studies. The risk variant we first identified on 8q24 shows the strongest association to disease severity. The variant is located in a region notably devoid of any known genes; however, we had detected several transcripts in this region and were in the process of characterising which sequences are being transcribed, using microarray studies. The second variant on 17q12, on the other hand, is located in a known protein-coding gene, the transcription factor HNF-1ß, setting the stage for direct functional studies of the effect of genetic variation on function. For both variants, we planned to create cell models from carriers and non-carriers and examine their function using a variety of functional and molecular assays, including over-expression and knock-down of transcripts, transcription factor binding studies and assessment of chromosomal instability. Subsequently, we planned to use these models to perform analogous studies on any new predictive biomarker(s) we might uncover in the course of the project.

The specific aims of PROMARK were as follows:

Establishment of comprehensive collections of biological specimens and clinical data for prostate cancer biomarker research in four European populations.

In order to identify associations between inherited genetic variation and clinical sub-forms of prostate cancer, a large collection of patient samples along with detailed and accurate diagnostic and clinical information is needed. We will focus on four European populations, each with its own distinct epidemiology and clinical relevance.

1. Cases and controls from the ProtecT clinical trial: We will ally with the ProtecT clinical trial in which 3 000 men with early stage prostate cancer will be randomised to three different treatments and followed for 10 to 15 years (see http://www.epi.bris.ac.uk/protect/). Thus, we will be able to access samples and extensive clinical data from 3 000 cases with localised disease, along with approximately 500 cases with advanced or metastatic disease that will be identified in the course of the initial screening effort. Samples from 3 000 men with high PSA but no cancer and 3 000 men with low PSA are available and a set of 1 000 samples will be selected from those to use as controls. This resource provides an invaluable opportunity to test the association of genetic risk markers with the progression of the disease. A further 1 000 additional non-screen detected 'clinically incident' cases from the West Anglia Cancer network will also be collected over the period of the study.
2. Prostate cancer families and sporadic cases from the Dutch population. We will recruit members of 153 registered and confirmed hereditary prostate cancer families from the Dutch population in order to assess the contribution of genetic variants in familial cases (estimated 400 cases). Second, extensive clinical data will be obtained for a group of 1 100 incident prostate cancer patients from the Netherlands that were recruited for the FP6 Polygene. These cases were used in the identification of the four risk variants. Third, approximately 200 sporadic patients who were diagnosed with prostate cancer in the Netherlands before the age of 50 will be invited to participate in the project.
3. Hospital-based prostate cancer cases and controls from the Romanian population. Prostate cancer screening is uncommon in Romania. Hence, the incidence of the disease is lower than in western Europe and most cases are diagnosed with a clinically significant disease. We will initiate a collection of samples and data from at least 1 000 Romanian prostate cancer cases and 1 000 controls in order to start dissecting the epidemiology and genetics of the disease in this population. Such a collection will be the first of its kind in the country.
4. Cases and controls from the Icelandic population. We will continue to recruit all incident prostate cancer cases in the Icelandic population, complemented with clinical data and genealogy information. In three years, our current collection of about 1 600 cases can be expected to have been expanded to about 2 000 cases. Our collection includes both sporadic and familial cases.

The outcome of this part of the project is a collection of samples and clinical information from over 8 000 prostate cancer cases from different parts of Europe. We will have established the first biospecimen repository for prostate cancer in Romania and greatly added to three existing sample collections. This resource will be used to assess the utility of inherited genetic variants as biomarkers of disease progression and outcomes. Importantly, we will have created a valuable resource for future studies on prostate cancer.

Testing of the utility of genetic prostate cancer risk variants as biomarkers of disease severity, progression and outcomes.

The four risk variants we have discovered are estimated to play a role in as much as 45 % of all new prostate cancers (population attributable risk, or PAR). The first of these variants was discovered using positional cloning but the other three were uncovered through analysis of data from a genome-wide association study. We will continue to mine the abundant genome-wide data for additional variants which will be included in the study as they become unveiled. At the same time, we will try to refine the genetic

signals in order to find the optimal marker(s) that defines the risk in each case.

In addition to variants that predispose to the disease, we have combined results from our genome-wide scan with publicly available data to search for variants that show different frequencies in prostate cancer cases with aggressive disease (Gleason score more than six, stage T3 or T4, and/or metastatic disease) versus cases with an early stage disease (Gleason less than six , stage T1a-T2b). The purpose of this analysis is to try to identify genetic variants that are directly associated with a more aggressive disease and less favourable outcome. Approximately 3 000 of these variants will be selected for replication in this study. Furthermore, we will select 20 previously reported variants in candidate genes in order to test their association to disease phenotype.

We will genotype all prostate cancer cases and controls defined in specific aim 1 for these variants and analyse the results in the context of clinical parameters. In total, we will be able to analyse over 8 000 prostate cancer cases from four different regions in Europe and a large number of controls. Almost 50 % of all cases from Iceland, the Netherlands, and Romania, are expected to have non-localised prostate cancer (N=2350). Combined with the 500 patients from the United Kingdom (UK), this large number of patients with aggressive disease guarantees statistical power to test associations of markers with disease aggressiveness. Major emphasis will be put on testing if the risk variants associate with any of the following:

1. stage and grade of disease
2. age at diagnosis
3. Recurrence
4. survival (disease-free and overall)
5. family history of the disease.

We will analyse the data using multivariable logistic regression and proportional hazards regression analyses in order to quantify the independent effect of the genetic variants and clinical parameters, and to identify possible gene-gene interaction and interactions between genetic and clinical factors. Using these regression techniques, we will set up and test different predictive models for disease aggressiveness and outcome with the aim to improve on existing predictive devices.

The expected outcome of this part of the project is a new deoxyribonucleic acid (DNA) based prognostic test that predicts clinical outcomes for localised prostate cancer more accurately than existing methods. We will also have created scientific documentation of the association of genetic risk variants to clinical parameters and disease outcomes. The diagnostic test will most likely use DNA derived from a buccal swab or a small blood sample.

Elucidation of the biological mechanisms that cause increased prostate cancer risk

We will apply state-of-the-art molecular and cellular approaches to characterise the functional aspects of variants associated with different clinical forms of the disease, using exclusively cells and tissues from prostate cancer patients and individuals with benign prostate hyperplasia. Currently, one variant on 8q24 has been identified that reproducibly is associated with high Gleason score but the other variants remain to

be tested in this respect. We will focus our functional studies on two variants, the 8q24 variant and the variant in the HNF-1ß transcription factor. As a first step, we will create primary cultures of non-neoplastic human prostate epithelial cells from 20 individuals. The cells will be genotyped to identify carriers of the variants and immortalised to provide relevant cell line models for functional studies. To elucidate the function of the Chr8q24 variant, we will over-express and down-regulate selected transcripts, identified previously by remote analysis computation for gene expression (RACE) and through an ongoing microarray project, using lenti-viral vectors and stable small hairpin ribonucleic acid (shRNA), respectively. A comparison of global gene expression and pathway alterations in cells over and under-expressing the candidate genes will be performed to identify the relevant pathways involved. For HNF-1ß we will seek to identify binding sites for the different HNF-1ß variants in prostate cell-lines. By pairing this with expression array profiling we hope to uncover pathways regulated by HNF-1ß and potentially predictive of disease or recurrence.

The expected outcome of this part of the project is new knowledge on cellular pathways that are involved in carcinogenesis of the prostate. This information may lead to the identification of additional biomarker candidates and point the way to therapeutic targets.

Project Results:

Main scientific and technical (S&T) results/foregrounds

The PROMARK project has been generally successful in achieving its deliverables and milestones. To date, the project has resulted in eight peer reviewed publications in high-impact journals and several patent applications. In addition, thousands of blood samples and clinical data from prostate cancer cases and controls have been collected that will provide extremely valuable resource for future studies on prostate cancer.

The description of the project results are broken up by work packages (WPs) and tasks.

WP1: Extension of ProtecT database for biomarker research (lead: UCAM DONC)

Objectives:

1. to define and extract a collection of blood samples and a set of clinical data from the UK ProtecT clinical trial to use for biomarker studies in PROMARK
2. to obtain genotypes for candidate biomarkers for all cases and controls
3. to assess if candidate genetic biomarkers are associated with clinical variables or course of disease in the UK study material.

Task 1: Definition of study materials, isolation of DNA and genotyping

The ProtecT trial completed recruitment and blood samples are available on 3 000 men with prostate cancer and about 80 000 controls. The following materials were sent to deCODE for genotyping.

Samples and data from prostate cancer cases:

1. DNA samples from 384 early-stage prostate cancer cases from the ProtecT trial
2. DNA samples from 162 advanced stage prostate cancer cases, identified during ProtecT trial recruitment
3. Clinical data for prostate cancer cases includes information on ethnicity, age and date at diagnosis, clinical and pathological stage, serum PSA, Gleason score, node status, presence or absence of metastases, number of biopsies, number and description of positive biopsies.

Samples and data from controls:

1. DNA samples from 454 males with PSA < 3 ng/ml
2. DNA samples from 994 males with 3 < PSA < 10 ng/ml and a negative biopsy
3. Blood samples from 488 controls with low PSA (PSA < 3)
4. Blood samples from 1 000 controls with PSA between 3 and 10 ng/ml and a negative biopsy
5. DNA samples from 1 512 controls randomly selected from the total set of controls in the ProtecT trial
6. All groups include data on ethnicity and age and date of PSA measurement .

Deviation from project plan: The first pooled clinical results of ProtecT are expected in 2013 and it is not possible to analyse the clinical data until after that point. Therefore, although it was estimated that the ProtecT trial would contribute 3 000 early stage prostate cancer cases for genotyping, there was no imminent urgency to collect all these samples as the clinical outcome data were lagging. However, because the other participants either fulfilled or exceeded their sample recruitment, this did not hamper progress of the project.

Notably, the ProtecT trial contributed an extremely valuable set of samples with known PSA measurements which were included in our study on the genetics of PSA (see WP4, task 3).

Task 2: Genotyping of the top 50 markers emerging from the joint analysis of the Icelandic, Dutch and Romanian samples in the UK population

The samples in task 1 were genotyped for close to 40 candidate prostate cancer risk variants suggested from the analysis of the Icelandic data. Furthermore, the samples were genotyped for close to 20 markers that associate with PSA levels and therefore could be important in helping improve the sensitivity and specificity of the PSA screening test. The genotype data was sent to the UCAM partner.

Task 3: Analysis of UK data

The results of genotyping in the UK sample set were included in the combined analysis reported in the PROMARK publications.

WP2: Collection of Dutch familial prostate cancer cases and clinical data (lead: RUNMC)

Objectives:

1. to collect germline DNA and clinical information from patients in Dutch hereditary prostate cancer (HPC) families and germline DNA from unaffected men in HPC families
2. to collect germline DNA of deceased Dutch sporadic patients, and sporadic Dutch patients who are diagnosed under the age of 50
3. to examine the contribution of genetic prostate cancer risk variants to the disease in the different patient population
4. to determine if genetic risk variants are associated with disease progression in the different Dutch study populations.

Task 1: Recruitment of HPC families and task 2: Collection of archived tissues from deceased cases in the HPC families.

In total, 191 families with a total of 663 verified prostate cancer cases (registered at the Netherlands Foundation for the Detection of Hereditary Tumours - NFDHT) were contacted. Collection of germline DNA was successfully completed for 316 HPC cases from 154 families. In addition to this, germline DNA together with information on prostate cancer testing was collected for 31 family members at risk. For 12 deceased cases, germline DNA was obtained from paraffin-embedded tissue from the radical prostatectomy specimen. Extensive clinical information was successfully collected for 318 of the prostate cancer cases by trained registration staff of the different Dutch Comprehensive Cancer Centres. For eight other cases, no information could be found, but limited clinical information was already available at the NFDHT. For the remaining two cases, sufficient clinical information could not be retrieved.

Task 3: Collection of clinical data and archived samples from sporadic cases

For the collection of germline DNA of deceased and non-responsive Dutch sporadic patients (patients who could not be contacted for the FP6 POLYGENE project), paraffin blocks from radical prostatectomies were selected and collected at the four pathology laboratories in the region of the Comprehensive Cancer Centre East (Radboud University Nijmegen Medical Centre, Canisius Wilhelmina Hospital Nijmegen, Rijnstate Hospital Arnhem, Meander MC Amersfoort). The paraffin blocks were selected based on the pathology report, aiming for the tissue with the lowest percentage of tumour tissue. From these paraffin blocks, thick slices were cut, DNA was isolated and sent to deCODE. Clinical information was successfully collected for 150 sporadic cases, generating (including the collected germline DNA and clinical DNA from the EU-FP6 Polygene project) an analysable group of a total of 955 sporadic cases.

Task 4: Collection of samples from cases diagnosed at an early age

The objective to collect germline DNA from all early-onset cases in the Netherlands (age at diagnosis less than 50) was abandoned. The major reason for this is that the total number of prostate cancer cases diagnosed at this early age is very small and it is unlikely that meaningful results would have been gained from genetic analysis of these samples. Instead, more resources were spent on collecting samples from the other case groups.

Task 5: Analysis of data for the Dutch population

Collection of data on disease progression was executed by the registrars of the Comprehensive Cancer Centre the Netherlands, location Nijmegen, for all Polygene patients throughout 2012 and 2013 and by the registrars of the NFDHT for the HPC patients and men at risk. In preparation of the analysis of the association between genotype and clinical parameters, such as a particular course of disease or disease outcomes, 37 sequence variants were genotyped in HPC patients, sporadic patients and controls. The genotype data were sent to RUN-MC and the results of the analysis are being prepared for publication. The results of genotyping in the Dutch sample set were included in the combined analysis reported in the PROMARK publications.

WP3: Establishment of a cohort with biospecimens and clinical data for prostate cancer research in Romania (lead: ISP)

Objectives:

1. to establish a biobank and database containing samples and clinical data from 1 000 prostate cancer cases and 1 000 controls in the Romanian population
2. to map the genetic prostate cancer variants in the Romanian population
3. to assess the potential association between genetic risk variants and disease progression and outcome.

Task 1: Protocol preparation and ethical approval

Ethical issues were carefully reviewed to ensure that all current legislation relating to data protection, genetic analysis of humans and DNA storage were complied with. All the information needed by study staff was included in the 'Protocol for standard procedures'. The project protocol was submitted to The Romanian Ethical Board which evaluated the protocol favourably and granted ethical approval.

ISP trained the project personnel from the two recruiting centres (Hospital 'Theodor Burghele' and Hospital 'St. Mary' both from Bucharest): in total 12 physicians and two nurses. The use of the questionnaires and forms and the data coding were explained in details. Subjects (cases and controls) registers were created in order to avoid duplicates in recruitment. Special attention was given to the biological samples collection and storage.

The specialised staff from ISP was trained to apply the standard procedures for samples transportation from the recruiting centres to the laboratories and shipment from ISP to deCODE.

Task 2: Enrolment of cases and controls, collection of clinical and lifestyle data

UMP-CD started the recruitment of cases on 1 July 2008. The procedure involved identifying all prostate cancer cases with pathological confirmation referred to the Hospital 'Theodor Burghele'. All the urologists or physicians were informed about the study and were encouraged to approach their patients and to explain to them the aims of the project. All the subjects accepting the participation received detailed information on the study procedures and after signing the informed consent were interviewed by the trained nurses or doctors. In case of refusal, a minimum data set was recorded (date, reason of refusal).

After the interview, a venous whole-blood sample, two 9 ml plastic ethylenediaminetetraacetic acid (EDTA) tubes, was extracted from each subject. The samples were frozen at -20°C on the spot. One tube for each subject remained in the ISP biobank. The second tube was prepared at ISP for shipment to deCODE following special rules as indicated by deCODE. In addition, tumour material is available for 98% of the cases through biopsies or radical prostatectomy (RP).

The goal of collecting 1 000 cases and 1 000 controls has been reached in effect, the total number of samples in the INSP biobank now amounts to 990 cases and 1 034 controls. Detailed clinical and lifestyle data has been collected and preliminary analysis done on survival. Notably, although PSA screening has become more prevalent recently in Romania, 80 % of cases diagnosed are grouped as high-risk (Gleeson more than seven, stage C-D). About 18 % of cases have family history of cancer versus 9% of controls.

Task 3: Analysis of association between genotype and disease, dissemination of results

The case controls samples from the Romanian study population have been genotyped for 37 published PSA and/or PrCa SNPs at deCODE. The results were included in the consortium papers. Also, the Romanian data is being analysed in the context of clinical parameters and will be presented as a stand-alone study in a manuscript in 2013.

WP4: Association of genetic variants with clinical parameters (lead: deCODE)

Objectives:

1. to complete a collection of samples and clinical data from 2 000 prostate cancer patients from the Icelandic population
2. to refine the genetic signals of the prostate cancer variants as much as possible
3. to test for association between the genetic risk variants and clinical parameters, focusing on measures of disease severity, prognosis and survival, gene-gene interactions
4. to develop a predictive method for prostate cancer prognosis that improves upon existing methods.

Task 1: Recruitment of all incident prostate cancer cases in Iceland during the study period

The recruitment of Icelandic prostate cancer cases proceeded as planned and to date, 2 626 cases have donated DNA and signed an informed consent form, exceeding the planned number of 2 000. Collection of clinical data is completed for all cases diagnosed before 2008. Collection of diagnostic and initial treatment data is completed for the newly recruited cases which will be followed-up on a yearly basis in the future.

Task 2: Standardisation of clinical assessments such as staging, grading, PSA testing, radiological assessments, etc. in the study material from the various countries.

The Clinical Board of PROMARK finalised a protocol for the acquisition of clinical data that aims to standardise the process between recruitment centres. The protocol was evaluated and approved by all partners and subsequently used for data collection.

Task 3: Genotyping of the risk variants in 8 000 prostate cancer cases and 5 000 controls from all four study populations. Correlation of genotypes with clinical parameters.

deCODE's whole-genome genotype data served as the discovery dataset for sequence variants that associate with risk of prostate cancer and with disease severity. This dataset was continually mined throughout the duration of the project and promising candidate variants were followed up in the case control sample sets from the UK, Netherlands and Romania. To summarise, this effort resulted in the discovery of six sequence variants that confer risk of prostate cancer and that were reported in three separate publications in Nature genetics.

We also performed a study on the genetic variation of PSA measurements, using data from thousands of males that have undergone PSA testing for screening purposes and have been genotyped for 300 000 markers at deCODE. The hypothesis was that if a PSA measurement can be adjusted for natural genetic variation, it may be possible to improve its specificity as diagnostic marker for early stage prostate cancer. Several candidate variants were identified and subsequently verified in sample sets from the other PROMARK partners. The results of this study were published in a high-profile paper in Science Translational Medicine.

Task 4: Refinement of genetic signals in order to find the markers that correlate best with the underlying risk using case control groups from the Icelandic and Dutch populations

Refinement of genetic signals was done for all variants discovered by imputation in the following manner. deCODE has whole-genome sequenced about 2 000 individuals in the Icelandic population. All variants (SNPs and INDELS) identified are subsequently imputed into the prostate cancer study population to test if any of them shows a stronger association to prostate cancer or PSA levels than the genotyped marker. If such markers were identified, they were used for subsequent replications.

Task 5: Development of a predictive method for prostate cancer prognosis

In the five years since PROMARK was started, it has become increasingly clear that inherited variants that predict disease progression or severity are hard to find. Only a few variants have been discovered (through PROMARK or by others) that show a moderately stronger association to aggressive disease and it has not been possible to build a model based on these variants that improves upon current diagnosic methods. However, we were able to provide a different approach to improving diagnosis and management of prostate cancer.

Measuring serum levels of the PSA is the most common screening method for prostate cancer. However, PSA levels are affected by a number of factors apart from neoplasia. Notably, around 40 % of the variability of PSA levels in the general population is accounted for by inherited factors, suggesting that it may be possible to improve both sensitivity and specificity by adjusting test results for genetic effects. To search for sequence variants that associate with PSA levels, we performed a genome-wide association study and follow-up analysis using PSA information from 15 757 Icelandic and 454 British men not diagnosed with prostate cancer. Overall, we detected a genome-wide significant association between PSA levels and single-nucleotide polymorphisms (SNPs) at six loci: 5p15.33 10q11, 10q26, 12q24, 17q12, and

19q13.33 each with Pcombined less than 3 × 10-10. Among 3834 men who underwent a biopsy of the prostate, the 10q26, 12q24, and 19q13.33 alleles that associate with high PSA levels are associated with higher probability of a negative biopsy (odds ratio between 1.15 and 1.27). Assessment of association between the six loci and prostate cancer risk in 5325 cases and 41,417 controls from Iceland, the Netherlands, Spain, Romania, and the United States showed that the SNPs at 10q26 and 12q24 were exclusively associated with PSA levels, whereas the other four loci also were associated with prostate cancer risk (Gudmundsson et al. Correction of PSA values with sequence variants associating with PSA levels. Science Translational Medicine 15;2(62):62ra92 (2010)).

Based on this work, we proposed that a personalised PSA cutoff value, based on genotype, should be used when deciding to perform a prostate biopsy. Furthermore, in combination with information about age, ethnicity, and family history of the disease, estimates of the effect of genetic variation on prostate cancer risk and PSA levels could lay a foundation for the development of individual prostate cancer screening strategies that would have the ultimate goal of reducing cost and improving quality of life.

In summary, although we were not able to produce a predictive test for early stage prostate cancer, the work performed in PROMARK has the potential to develop into improvements in prostate cancer prevention and management.

WP5: Functional studies on genetic prostate cancer risk variants (lead: UCL)

Objectives:

1. to develop the resources needed to study the influence of the genetic variants on the behaviour of prostate cells
2. to investigate the function of transcripts from the first candidate locus associated with disease severity (HapA on Chr8q24)
3. to perform functional assays on HNF-1ß in prostate cells.

Task 1: Development of 20 primary cultures of non-neoplastic human prostate epithelial cells

After some delay in starting this task due to the implementation of the new European Regulations on clinical trials and new UK legislation on the use of human tissue (Human Tissue Act), a standard protocol which generates prostate epithelial cells grown on collagen and mitomycin-treated 3T3 feeder layers was set up. A total of 10 normal cell lines were produced.

Deviation from the workplan: In the project proposal, we estimated that we would produce 20 primary cell cultures of defined genotype to use for the functional studies. However, because the establishment and immortalisation of these cell lines is very time consuming, it was agreed by the partners that it would be in the best interest of the project to stop at 10 cell lines and focus the effort on the functional analysis of these cells.

Task 2: Immortalisation of selected cultures to provide relevant cell line models

The 10 cell lines produced in task 1 were immortalised using human telomerase reverse transcriptase (hTERT) and the large T antigen and frozen stocks generated. The cell lines were sent for short tandem repeat (STR) profiling and tested for Mycoplasma after which they were shipped to deCODE where they were genotyped using the OmniExpress chip from Illumin (close to 700 000 SNPs).

Task 3: Overexpression of HapA transcripts and HNF-1ß

An expression vector for human myc-tagged HNF-1ß was obtained from Gerhart Ryffel (Essen, Germany). A matched pair of normal and cancer cell lines (1532N and 1532C) from the same patient, as well as the prostate cancer cell line PC3, were was stably transfected. Clones selected in G418 were selected, grown up and shown to express HNF-1ß by Western blotting.

Deviation from the workplan: We originally planned to over-express and down-regulate transcripts from two validated prostate cancer risk loci (tasks 3 to 5). The risk locus on 8q24 (HapA) does not contain known genes prompting us to search for transcripts, using expression microarrays. However, our results, as well as those of others, have not led to the identification of good candidate transcripts to test in expression assays. Furthermore, two reports that dissected the region with regard to risk variants for colorectal cancer suggest that looping of the DNA may be the causative mechanism by which risk of the disease is increased (Pomerantz MM, et al. and Tuupanen S, et al. both in Nature Genetics 2009). In light of these results, we abandoned work on HapA transcripts and focused our efforts on the transcription factor HNF-1ß.

Task 4: Down-regulation of HapA transcripts and HNF-1ß using stable shRNA

As a first step in assessing the effect of down-regulating the HNF-1ß transcript, we tested multiple prostate cell lines for expression of HNF-1ß. The paired normal and cancer cell lines 1542C and N were found to express HNF-1ß. Using 3 siRNAs from Ambion transiently reduced expression in the paired cell lines, as well as in the HNF-1ß over-expressing PC3 and DU145 cell lines. The best sequence gave an 80 % knock-down with an effective window of around 4-5 days, which was very useful for functional studies. The UCAM group also developed a lentiviral-based system to provide a stable downregulation of HNF-1ß in cell lines. The normal/cancer line pairs - 1542CP & 1542NP and 1532CP & 1532CP - were transduced with four distinct shRNAs targetting HNF-1ß using the lentiviral system, to produce stable knock-downs. Of these, the 1542CP/1542NP pair yielded a set of cell lines that have a consistent knock-down of HNF-1ß levels of more than 80 %, and have survived several passages.

Task 5: Comparison of global gene expression and pathway alterations in cells over and under-expressing the HapA transcripts and HNF-1ß using Illumina's Human-6 v2 BeadChips

Two cell line pairs, PC3/PC3+ HNF-1ß and HEK293/HEK293+ HNF-1ß were screened using Illumina H12 gene expression arrays. A total of 632 differentially expressed genes (DEGs) were identified. KEGG pathway analysis showed enrichment for pathways in cancer, focal adhesion and ECM-receptor interactions. We subsequently applied more stringent criteria to the dataset, in order to focus our attention on fewer, more likely targets. Further analysis was limited to the top fifty most significant genes based on corrected p-value, together with a fold-change of =3.5. Ingenuity pathway analysis of the final set of 32

genes suggested their involvement in specific cellular and molecular functions, namely cell-to-cell signalling and interactions, cellular development and movement, and cell function and maintenance. This information was used to inform the functional assays subsequently performed.

The most significant gene in this dataset was UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1; p=1.27-14 log fold-change 5.48) encoding an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble, excretable metabolites. In addition, only one gene was common to both the PC3+ HNF-1ß and HEK293+ HNF-1ß comparisons - GCNT3 (glucosaminyl (N-acetyl) transferase 3, mucin type).

Task 6: Identification of HNF-1ß -binding sites in prostate cells, using chromosome immunoprecipitation (ChIP) and hybridisation to high-density oligo arrays.

Chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) was performed in triplicate in PC3 HNF-1ß-overexpressing lines to identify transcriptionally active binding partners of HNF-1ß using the following antibodies: HNF-1ß (transcription factor target), RNA Pol II (identifies transcriptionally active genes) and H3K4Me3 (histone mark typical of promoters).

These data were analysed in several different ways:

1. Cell line gene expression data was tested for overlap with chromatin immunoprecipitation sequencing (ChIP-seq) data in order to identify likely directly regulated targets of HNF-1ß transcription factor.
2. Genes strongly co-expressed (0.5 = r2 = -0.5) with HNF-1ß were identified from our own clinical dataset, as well from several publically available datasets.
3. Benign and tumour samples expression profiles were stratified by HNF-1ß SNP genotype, in order to identify any possible correlation with clinical parameter that could allow predictions as to outcome or prognosis.

Task 7: Effect of over-expression and down-regulation of HapA transcripts assessed using functional assays, such as cell proliferation, mobility, invasiveness and sensitivity to chromosomal breakage.

Functional assays show that overexpression of HNF-1ß has no effect on viability or invasion but reduces proliferation, adhesion, migration and colony formation in soft agar. Overexpression had a pronounced effect on the morphology of the cells and decreased motility in Matrigel. Furthermore, overexpression of HNF-1ß affects the expression of cadherin and causes rearrangement of paxillin and integrins. The lentiviral-based system that stably down-regulated the HNF-1ß overexpressing cells, was found to reverse the changes seen in cell attachment and migration induced by overexpression of HNF-1ß. These findings confirm that the changes seen are due to HNF-1ß.

Finally, methylation studies show that the HNF-1ß promoter is differentially methylated in paired tumour & benign patient samples with higher level of methylation in tumour cells than in benign prostate tissue. Moreover, promoter methylation is correlated with genotype at some SNPs in tumour tissue and cell lines. The results suggest that silencing HNF1ß by methylation may explain the reduction in expression with increasing Gleason grade. In summary, HNF1ß has tumour-suppressor properties, which are lost with

increasing methylation and the progression to advanced disease.

The results of WP5 are currently being written into a manuscript for submission in the first quarter of 2013.

WP6: Management (lead: deCODE)

Objectives:

1. the overall coordination of the project by participant one.

In summary, the project management progressed without any problems according to the plan laid out in Annex 1. All deliverables were produced.

One administrative change occurred during the project: by Government Decision, the National Institute of Public Health (INSP) was established by merger of the Institutes of Public Health in Bucharest, Iasi, Cluj, Timisoara, Sibiu and Targu Mures. All the tasks and activities in the project assigned to ISP were subsequently carried out by INSP. The PI for the institute (Dr. Mates) remained unchanged.

Potential Impact:

Potential impact and main dissemination activities and exploitation of results

In the year 2006, over 3 million new cancer cases were registered in Europe and 1.7 million cancer-related deaths. Prostate cancer has become the most common form of cancer in males, with 301 500 new cases diagnosed per year and 87 400 deaths. The incidence of the disease is increasing steadily worldwide, affecting all age groups but is more pronounced in younger men. Based on the additional effect of increased life expectancy, epidemiologic estimates show that prostate cancer is becoming one of the leading health issues in the world.

Advanced prostate cancer carries a poor prognosis and inevitably results in death. Therefore, huge emphasis has been put on the development of screening methods that can detect the disease at an early stage when curative treatment can be applied. However, although multiple screening modalities have been invented, they all suffer from the same shortcomings; lack of sensitivity and specificity. Thus, on one hand, a large number of men with a positive screening test do not have disease that needs clinical attention and on the other hand, some men with negative screen test may have cancer that can lead to death if untreated. Because of the inefficiency of current prostate cancer screening protocols, organised screening for the disease has not been implemented in any country. However, large clinical trials are ongoing where the effect of PSA-based prostate cancer screening on mortality from the disease is being investigated. First results from these trials suggest that organised screening with the PSA test does reduce disease-specific mortality but at a large cost of overtreatment which includes the possible side-effects of impotence and urinary incontinence.

The reasons why some cancers are more aggressive than others remain poorly understood. The major objective of PROMARK was to test the hypothesis that inherited genetic variation not only affects the risk

of developing prostate cancer but may also associate with a particular course of disease. If any variant, or a combination of variants, were shown to have prognostic value, the plan was to combine them with current prognostic indicators such as stage, Gleason score and PSA value to develop a new prognostic test that predicts clinical outcomes for localised prostate cancer more accurately than existing methods. Ultimately, such a prognostic test was to be realised in product form soon after the invention through a DNA-based diagnostic kit.

The expected outcome of PROMARK was broadly divided into the following three categories:

Collection of samples and clinical information from over 8 000 prostate cancer cases from different populations in Europe, including the first biorepository for prostate cancer in Romania.

In order to assess if inherited factors affect the course of disease, these genetic variants need to be tested in large cohorts of prostate cancer cases with accurately documented clinical follow-up. Such resources are costly and take a long time to build. Therefore, the PROMARK consortium was formed by established investigators which had already initiated collections of samples and data from prostate cancer cases and controls. In addition, a new cohort for prostate cancer was established in Romania, the first in the country. In total, samples from close to 5 500 cases and 7 000 controls were collected. For the cases, clinical information was collected according to the protocol approved by PROMARK's clinical board. In addition, PSA values were available for a large fraction of controls in the UK and Romania and a smaller fraction in the Netherlands and Iceland. Although the total number of cases (5 464) falls short of the estimated 8 000 cases planned, this did not hamper the project.

Discovery of new genetic variants that associate with prostate cancer risk and/or clinical course of the disease. Prognostic test that predicts clinical outcome for localised prostate cancer more accurately than existing methods.

During the course of PROMARK, six new prostate cancer risk variants were discovered, validated and published in high-impact journals (three papers in Nature genetics). These findings, along with results on additional risk variants from other groups, help explain the contribution of genetic factors to prostate cancer and yield important information on disease aetiology. Furthermore, this knowledge provides the necessary foundation for the development of genetic risk models for the disease. However, as described in the previous section, almost all the common prostate cancer risk variants discovered to date by the PROMARK consortium or other research groups show similar associations with the different disease forms, i.e. indolent or aggressive. These variants have therefore not proven to be candidates for a predictive test.

In light of the failure to find risk variants that could distinguish between indolent and aggressive forms of prostate cancer, we decided to address another important problem in prostate cancer diagnosis, i.e. the lack of sensitivity and specificity of the commonly used PSA screening test. Measuring serum levels of the prostate-specific antigen (PSA) is the most common screening method for prostate cancer; however, PSA levels are affected by a number of factors apart from neoplasia. Notably, around 40 % of the variability of PSA levels in the general population is accounted for by inherited factors, suggesting that it may be possible to improve both sensitivity and specificity by adjusting test results for genetic effects. To search

for sequence variants that associate with PSA levels, we performed a genome-wide association study and follow-up analysis using PSA information from 15 757 Icelandic and 454 British men not diagnosed with prostate cancer. Overall, we detected a genome-wide significant association between PSA levels and SNPs at six loci. Importantly, three of these loci were found to be associated with higher probability of a negative biopsy. Assessment of association between the six loci and prostate cancer risk in 5 325 cases and 41 417 controls from Iceland, the Netherlands, Spain, Romania, and the United States showed that SNPs at two of the loci were exclusively associated with PSA levels, whereas the other four loci also were associated with prostate cancer risk. These results were published in a high-profile paper in Science Translational Medicine.

Based on this work, we proposed that a personalised PSA cutoff value, based on genotype, should be used when deciding to perform a prostate biopsy. Furthermore, in combination with information about age, ethnicity, and family history of the disease, estimates of the effect of genetic variation on prostate cancer risk and PSA levels could lay a foundation for the development of individual prostate cancer screening strategies that would have the ultimate goal of reducing cost and improving quality of life.

In summary, although we were not able to produce a predictive test for early stage prostate cancer, the work performed in PROMARK has the potential to develop into improvements in prostate cancer prevention and management.

New knowledge on cellular pathways that are involved in carcinogenesis of the prostate which might lead to the discovery of additional biomarkers or therapeutic targets.

If we are to be able to translate genetic findings into clinical utility, it is vital to understand the functional aspects of how genetic variation leads to different phenotypes of disease. In PROMARK, we aimed to perform functional studies on genetic variants that showed association with disease severity and/or prognosis, hoping that by unravelling the cellular mechanisms that play a role in disease progression we may be able to identify additional predictive biomarkers and possibly new targets for treatment. Originally, two prostate cancer risk loci were chosen for study, 8q24 and 17q12. However, as explained in the previous section, the 8q24 locus proved not to be amenable for functional studies and was abandoned. The second variant, on the other hand, harbors a known protein-coding gene, the HNF-1ß transcription factor, and a major effort was put into characterising the role of this gene in prostate cancer.

The large body of genomic and cellular work performed on HNF1ß within PROMARK sheds light on the importance of this gene in prostate cancer. The details of this work are presented in the previous section but in summary, we found that HNF1ß has tumour-suppressor properties, which are lost with increasing methylation and the progression to advanced disease. The results from the functional analysis of HNF1ß provide useful knowledge that may in the future have implications for improved diagnosis and treatment of prostate cancer.

Main dissemination activities:

To date, the following publications have originated from PROMARK and include a statement acknowledging the grant as a source of funding:

1. Rafnar T and Gudmundsson J. PROMARK: genetic prostate cancer variants as biomarkers. European Urology Today 20(5), 27 (2008)
2. Gudmundsson J, Sulem P, Gudbjartsson DF, Bondal T, Gylfason A, Agnarsson BA, Magnusdottir DN, Orlygsdottir G, Benediktsdottir KR, Jakobsdottir M, Stacey SN, Sigurdsson A, Wahlfors T, Tammela T, Breyer JP, McReynolds KM, Bradley KM, Saez B, Godino J, Navarrete S, Fuertes F, Murillo L, Polo E, Aben KK, van Oort IM, Suarez BK, Kan D, Zanon C, Frigge ML, Kristjansson K, Gulcher JR, Einarsson GV, Jonsson E, Catalona WJ, Mayordomo JI, Kiemeney LA, Smith JR, Schleutker J, Barkardottir RB, Kong A, Thorsteinsdottir U, Rafnar T, Stefansson K. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nature genetics 41, 1122-6 (2009)
3. Cremers RGHM, Karim-Kos HE, Houterman S, Verhoeven RHA, Schröder FH, van der Kwast TH, Kil PJM, Coebergh JWW, Kiemeney LALM; Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. Eur J Cancer 46, 2077-2087 (2010)
4. Gudmundsson J, Besenbacher S, Sulem P, Gudbjartsson DF, Olafsson I, Arinbjarnarson S, Agnarsson BA, Benediktsdottir KR, Isaksson HJ, Kostic JP, Gudjonsson SA, Stacey SN, Gylfason A, Sigurdsson A, Holm H, Bjornsdottir US, Eyjolfsson GI, Navarrete S, Fuertes F, Garcia-Prats MD, Polo E, Checherita IA, Jinga M, Badea P, Aben KK, Schalken JA, van Oort IM, Sweep FC, Helfand BT, Davis M, Donovan JL, Hamdy FC, Kristjansson K, Gulcher JR, Masson G, Kong A, Catalona WJ, Mayordomo JI, Geirsson G, Einarsson GV, Barkardottir RB, Jonsson E, Jinga V, Mates D, Kiemeney LA, Neal DE, Thorsteinsdottir U, Rafnar T, Stefansson K. Correction of PSA values with sequence variants associating with PSA levels. Science Tranlational Medicine 2(62), 62ra92 (2010)
5. Cremers RGHM, Aben KKH, Vermeulen SH, den Heijer M, van Oort IM, Kiemeney LALM; Androgenic alopecia is not useful as an indicator of men at high risk of prostate cancer. Eur J Cancer 46(18), 3294-9 (2010)
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7. Rafnar T, Sulem P and Gudmundsson J. The genetics of prostate cancer (editorial). Revista Romana de Urologie (The Journal of the Romanian Urology Association) Vol. 3(9), p.5-10 (2010)
8. Stacey SN, Sulem P, Jonasdottir A, Masson G, Gudmundsson J, Gudbjartsson DF, Magnusson OT, Gudjonsson SA, Sigurgeirsson B, Thorisdottir K, Ragnarsson R, Benediktsdottir KR, Nexø BA, Tjønneland A, Overvad K, Rudnai P, Gurzau E, Koppova K, Hemminki K, Corredera C, Fuentelsaz V, Grasa P, Navarrete S, Fuertes F, García-Prats MD, Sanambrosio E, Panadero A, De Juan A, Garcia A, Rivera F, Planelles D, Soriano V, Requena C, Aben KK, van Rossum MM, Cremers RGHM, van Oort IM, van Spronsen D-J, Schalken JA, Peters WHM, Helfand BT, Donovan JL, Hamdy FC, Badescu D, Codreanu O, Jinga M, Csiki IE, Constantinescu V, Badea P, Mates IN, Dinu DE, Constantin A, Mates D, Kristjansdottir S, Agnarsson BA, Jonsson E, Barkardottir RB, Einarsson GV, Sigurdsson F, Moller PH, Stefansson T, Valdimarsson T, Johannsson OT, Sigurdsson H, Jonsson T, Jonasson JG, Tryggvadottir L,Rice T, Hansen HM, Xiao Y, Lachance DH, O'Neill BP, Kosel ML, Decker PA, Thorleifsson G, Johannsdottir H, Helgadottir HT, Sigurdsson A, Steinthorsdottir V, Lindblom A, Swedish Low-risk Colorectal Cancer Study Group, Sandler RS, Keku TO, Banasik K, Jørgensen T, Witte DR, Hansen T, Pedersen O, Jinga V, Neal DE, Catalona WJ, Wrench M, Wiencke J, Jenkins RB, Nagore E, Vogel UB, Kiemeney LA, Kumar R, Mayordomo JI, Olafsson JH, Kong A, Thorsteinsdottir U, Rafnar T, Stefansson K. A Germline Variant in the TP53 Polyadenylation Signal Confers Cancer Susceptibility. Nature genetics 43, 1098-103 (2011)

9. Cremers, R., van Asperen, C., Paul Kil, Vasen, H., Wiersma, T., van Oort, I., Kiemeney, L. Urologists' and GPs' knowledge of hereditary prostate cancer is suboptimal for prostate cancer counselling: a nation-wide survey in the Netherlands. Fam Cancer 11(2), 195-200 (2012)
10. Gudmundsson J, Sulem P, Gudbjartsson DF, Masson G, Agnarsson BA, Benediktsdottir KR, Sigurdsson A, Magnusson OT, Gudjonsson SA, Magnusdottir DN, Johannsdottir H, Helgadottir HT, Stacey SN, Jonasdottir A, Olafsdottir SB, Thorleifsson G, Jonasson JG, Tryggvadottir L, Navarrete S, Fuertes F, Helfand BT, Hu Q, Csiki IE, Mates IN, Jinga V, Aben KK, van Oort IM, Vermeulen SH, Donovan JL, Hamdy FC, Ng CF, Chiu PK, Lau KM, Ng MC, Gulcher JR, Kong A, Catalona WJ, Mayordomo JI, Einarsson GV, Barkardottir RB, Jonsson E, Mates D, Neal DE, Kiemeney LA, Thorsteinsdottir U, Rafnar T, Stefansson K. A study based on whole-genome sequencing yields a rare variant at 8q24 associated with prostate cancer. Nature genetics 44, 1326-9 (2012).

Presentations and conferences:

The results from PROMARK have been presented at a number of meetings and seminars for scientists and health-care workers by the different consortium partners.

Intellectual protection rights (IPR) exploitation measures taken or intended:

Patent applications have been filed for all cancer risk variants and PSA variants identified through PROMARK. The following patent applications have been filed.

1. PCT/IS2010/050002 and EP 10772098.9: Three variants conferring risk of prostate cancer
2. PCT/IS2008/000021 and EP 08854482.0: Prostate cancer risk locus on 11q13
3. PCT/IS2012/000006: New risk variant on 8q24 cancer
4. PCT/IS2011/050012 and EP 11821224.0: Three variants that associate with levels of PSA
5. PCT/IS2012/050013: Variant that associates with increased risk of prostate cancer, glioma and basal cell carcinoma.

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A project website was also set up by ISP in Romania: http://www.promark-romania.ro

Documenti correlati

Final Report - PROMARK (Genetic prostate cancer variants as biomarkers of disease progression)

Ultimo aggiornamento: 14 Agosto 2013

Permalink: https://cordis.europa.eu/project/id/202059/reporting/it