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14. ABSTRACT

We have created an informative set of high risk lethal prostate cancer pedigrees and recurrent prostate cancer cases. Linkage analysis has identified significant evidence for linkage several chromosomes; these findings will be followed with sequence analysis. We have begun sequence analysis and identified a set of candidate genes in a set of 6 pairs of lethal prostate cancer cases sequenced. We have begun GWAS analysis on our set of deeply phenotypes recurrent cases and have identified some significant findings. Manuscript preparation is underway.

Identification of genes predisposing to recurrent/lethal prostate cancer from this study will validate this powerful approach, which can be extended to other high risk prostate cancer pedigrees, and will identify genes and pathways that can be further examined to expand our knowledge of prostate cancer genetics.

15. SUBJECT TERMS
Recurrent/lethal prostate cancer, linkage analysis, association analysis, sequence analysis, bioinformatics analysis, genotype, prostate cancer genetics, chromosome 11

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Introduction (from original)
Decades of investigation into the genetic causes of prostate cancer (prca) and prostate cancer aggressiveness has yet to clearly identify genes or variants which explain much more than a small amount of risk for prostate cancer among a small population of men. Even less progress has been made in understanding why 30% of all patients with localized prostate cancer eventually develop recurrent, and subsequently fatal, prostate cancer, or in understanding the factors that are associated with the range of treatment response (survival time) after diagnosis and treatment for recurrent prostate cancer.

The purpose of this research was to perform a genetic study of the distinct subset of recurrent prostate cancer cases: those who will, in all likelihood, go on to die from their prostate cancer and stratify and study these cases by their response to castration (chemical or physical) treatment, the standard of care for patients with recurrent prostate cancer. Using a unique and powerful statewide, population-based resource, we sought to identify and sample over 800 recurrent cases of prostate cancer, perform genome wide genotyping on informative cases in high-risk pedigrees, and apply complementary genetic analyses to identify genes and variants predisposing to recurrent prostate cancer and variable response to treatment.

Key Words

Recurrent/lethal prostate cancer
genotype
association analysis
linkage analysis
sequence analysis
bioinformatics analysis
prostate cancer genetics
chromosome 11

Overall Project Summary – by Task

Task 1. Recruitment and sampling of new and returning recurrent prostate cancer patients at Huntsman Cancer Institute (HCI)

We have recruited and sampled 174 recurrent prostate cancer cases attending Dr. Agarwal's clinic at the Huntsman Cancer Institute. A DNA sample and prostate cancer questionnaire has been collected and stored for each. The prostate cancer characteristics phenotype form is in the Appendix.

We have also identified a total of 60 high-risk prostate cancer kindreds with an excess of lethal prostate cancer and have identified an additional 384 DNA samples for these prostate cancer cases in pedigrees that we have also genotyped.

sub task 1a. Assignment of phenotype for treatment response for recruited cases

Dr. Agarwal's fellow has computerized phenotypes (see the Appendix) for each case recruited in clinic. Some cases are being redrawn due to DNA problems (n=13). All other cases are genotyped and GWAS is completed for treatment response for Lupron and abiraterone. Three abstracts have been accepted for poster presentation at GUASCO (see Appendix) and 2 more are now being submitted to ASCO.

Task 2. Identification of most informative samples for genotyping

We identified 60 high-risk informative lethal prostate cancer pedigrees with at least 3 samples available for genotyping. We have just finished genotyping the last of 384 (96 x 4) prostate cancer cases in these high-risk informative recurrent prostate cancer pedigrees. These represent prostate cancer cases who died with prostate cancer contributing to their death who are members of high-risk prostate cancer pedigrees with at least 3 lethal prostate cancer cases already sampled. We have just selected an additional lethal prostate cancer cases for genotyping and the samples are being prepared for genotyping (n=96) this month.

Task 3. Genotype 200 samples each year

We have genotyped 384 samples (4 plates x 96 samples/plate) samples for genome wide genotyping for this year from the high-risk lethal/recurrent prostate cancer cases and pedigrees. This includes the 174 samples collected in Dr. Agarwal's clinic. We performed genome wide genotyping at the University of Utah Genotyping Core Facility using the Illumina 720,000 SNP Omni Express set of markers. An additional 96 samples are just being prepared for genotyping.

Task 4. Import and quality control of genotype data

We have acquired genotype data for the 384 samples. All data has undergone standard quality control and was imported into our family study database and linked to phenotype data.

Task 5. Association analysis of all genotyped samples

subtask 5.1 Selection of genotypically matched controls

Using existing software we have analyzed available iControl public data from Illumina for all Caucasians and selected an appropriate genotypically matched set of controls for Utah prostate cancer cases (see Methods in Teerlink et al., 2011).

subtask 5.2 Association Analysis

We have performed GWAS of the entire set of recurrent/lethal prostate cancer cases and of subsets of Dr. Agarwal's patients. We use existing public software that allows correction for relatedness of cases (GEMMA). We test for association of lethal prostate

cancer, recurrent prostate cancer, and treatment related and survival characteristics identified in the subset of recurrent prostate cancer cases seen in clinic.

subtask 5.3 Validation

We will collaborate with the International Consortium for Prostate Cancer Genetics (ICPCG) and other consortia who are also performing association analysis for aggressive prostate cancer to perform a validation of our findings after analysis in year 2. The ICPCG and PRACTICAL and ICOGS consortia have provided us with their list of candidate SNPS, for which we will perform validation testing in the Utah set of samples and phenotypes. We now have the ICPCG CIDR genotype data.

For the treatment-related phenotypes for Dr. Agarwal's patients we have tested published candidate genes/SNPs.

Task 6. Linkage analysis of all genotyped samples from informative pedigrees

subtask 6.1 Selection of markers for linkage

A set of markers with no linkage disequilibrium was selected for linkage analysis. From the intersection of SNP markers from the five Illumina genotyping platforms that we have used (550K, 610K, 1M,Omni_express (720k), and Omni_1M) we identified over 300,000 SNPs. We selected a set of 25,436 of these SNP genome wide markers with good chromosomal representation and low/no LD to be used for linkage analysis (Cannon-Albright et al., 2012).

subtask 6.2 Linkage analysis

We have performed genome-wide linkage analysis for 60+ genotyped high risk lethal prostate cancer pedigrees.

Multiple pedigrees provided significant evidence for linkage (LOD > 3.30) including 1 pedigree previously reported. This pedigree has 4 lethal prostate cancer cases and 10 additional prostate cancer cases genotyped. The segregating chromosome 11 haplotype providing linkage evidence is shown in Figure 2. We have identified 3 additional lethal prca cases to genotype in this pedigree. We have obtained whole exome sequence data for a pair of hypothesized carriers in this pedigree and analysis is underway but no variants have been identified.

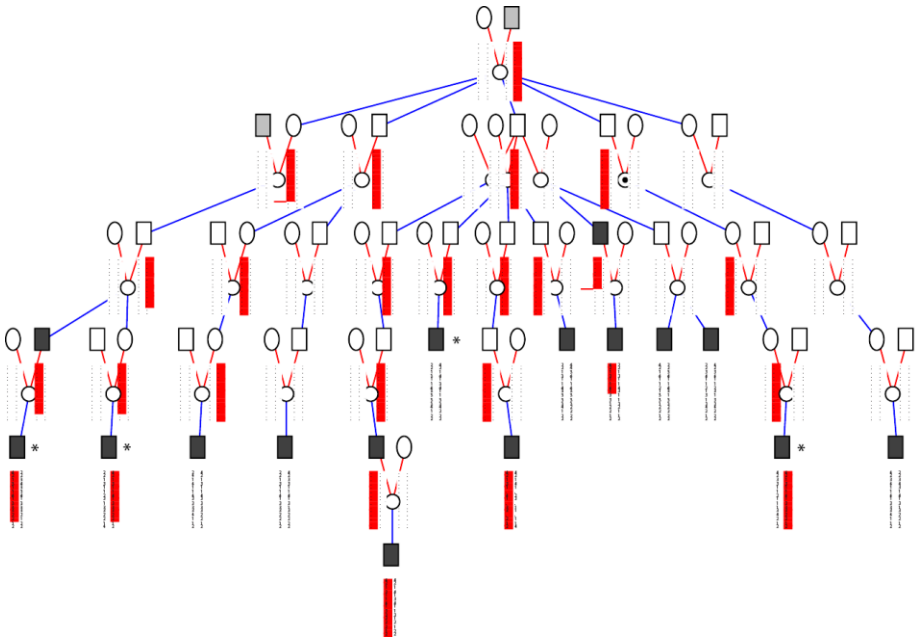

Figure 2. Prostate cancer pedigree with significant evidence for linkage to chromosome 11 (LOD = +3.56). Lethal prostate cancer cases are marked with *. Affected males are fully shaded. The red (dark) haplotype on chromosome 11 that segregates with prostate cancer is shown.

Additional linkage evidence in high-risk lethal prca pedigrees includes the following pedigrees with LOD > 3.0. The table shows the pedigree, the LOD score, the chromosome band, mode of inheritance, and whether any other pedigrees had LOD > 1.0 at the same location:

Kindred	LOD	chromosome band	mode of inheritance	other pedigrees
3600	3.18	4q12	dom	yes
3610	3.04	8p23.1	dom	
9938	3.26	20p12.2	dom	
9956	3.28	4q24	dom	no

Thirty four other pedigrees had LOD scores > 2.0 and < 3.0; these will also be evaluated for candidate genes and supporting evidence for other pedigrees.

Analysis of the lethal prostate phenotype has been performed in this set of genotyped high risk pedigrees and a linkage paper is in preparation.

Sequence Analysis

The pedigrees with significant evidence for linkage above now require sequence analysis in the regions of interest to identify the responsible predisposition genes.

Bioinformatic Analysis of Sequence Variation for 12 lethal prostate cancer cases.
We received an internal grant from the Utah Genome Project to sequence 6 pairs of lethal prostate cancer cases in high risk pedigrees. Sequence reads were aligned to the human genome. Aligned reads were then analyzed to determine the location of genetic variants exist in each sample. Variants were then prioritized for their potential impact on the disease. Raw sequence data was generated at Huntsman Cancer Institute on the Illumina hi-seq2 high-throughput sequence analyzer with the Illumina TruSeq target library. Individual sequence reads coming from the sequence instrument were mapped back to the human reference genome (hg 19) and Novoaligner software which uses uses pairing information from paired end reads to more accurately assign reads with multiple matches to the genome. We used The Broad Institutes's Genome Analysis Tool Kit (GATK) for variant calling of single nucleotide variants (SNVs) and small insertions or delestions (indels). We followed the Broad Institute's best practice guidelines concerning re-aligment and recalibration of aligned reads in order to produce the most reliable set of called variants. GATK software also provides a rich set of quantitative variant annotations, which it uses to estimate the probability that the called variants are true positives, thus providing an optimally derived set of SNVs and short indels. We used the Annovar software package to further annotate called variants.

After a reliable set of possible variants across all samples was derived from the above process, we used a set of filtering rules to derive a set of potential candidates for lethal prostate cancer susceptibility. Our filtering strategy was as follows: we eliminated variants with read depth less than 10 reads; that are not shared by both members of a sequenced pair; that have a high observed frequency (> 1%) in 1000 Genomes project or the NHLBI Whole Exome project. We then prioritized variants according to their predicted post translational impact. Tier 1 variants are those classified as frameshift mutations (insertions or deletions) and non-sense mutations (stop-gain SNVs or stoploss SNVs). Tier 2 variants include missense mutations that were characterized as damaging (score > 0.99) by the MutationTaster software package (Schwarz 2010). MutationTaster incorporates information from several other variant scoring freely available software packages to determine the expected potency of the mutation. All other variants passing the filtering scheme will be assigned to Tier 3, and will be considered the lowest priority variants for further investigation.

As a further refinement to our variant filtration scheme, we used evidence that a variant was inherited from a common ancestor, derived from shared genomics segment (SGS) analysis. SGS analysis, developed by the PI, essentially counts the number of contiguous SNPs that could be shared between a set (in this case a pair) of related cases of interest (Thomas et al., 2008). Long runs of SNPs indicate regions likely to be inherited from a common ancestor (identical-by-descent, or IBD). The distribution of identical-by-state (IBS) sharing also emerges from this analysis. Hence, IBD regions of the genome can be distinguished from IBS regions via SGS analysis. Simulation techniques can be employed to assess significance of findings. When sequenced cases are from the same high-risk pedigree, we can reduce our search for variants to those regions that appear IBD among cases. In this analysis, variants between a related pair (all were approximately cousins) of sequenced lethal prostate cases that occurred in a genetic segment denoted as likely to be IBD were given highest priority. Evidence for IBD sharing is consistent with our assumption that the variants we are attempting to identify convey predisposition and should occur in multiple affected people in the pedigree. We used high-density SNP genotype data to conduct SGS analysis in the 12 lethal prostate cancer cases.

A brief summary of the Tier 1 mutations identified in the 12 sequenced lethal prostate cases that meet all of these criteria appear in Table 1. We did not see any frameshift mutations that were shared by both pedigree members in any pedigree, but we did detect 4 stop-gain mutations that met this criteria. Only the variant in GPATCH 2 appears in a genomic region identified as IBD and is our candidate of highest interest at this point of our analysis.

Table 1. Stop-gain mutations passing the variant filtering scheme post bioinformatics analysis.

Pedigree	Band	bp position (b37)	dbSNP name	MAF in 1K Genomes	SGS segment length	Gene
3	1q41	217,604,657	NA	NA	2805	GPATCH2
5	1p36	17,034,125	rs141324796	0	26	ESPNP
6	2q34	209,302,328	rs617423329	A=0.0082	110	PTH2R
6	10q21	61,122,268	rs3078330	0	27	FAM13C

We have been invited by the Utah Heritage 1K Project to have the 12 lethal prostate cancer cases undergo whole genome sequencing and some bioinformatics analysis will be provided.

Finally in a collaboration with International Consortium for Prostate Cancer Genetics (ICPCG), we have also had exomic sequencing performed on 124 prostate cancer cases in high risk pedigrees. Twenty two of these cases are also "lethal" prostate cancer cases whose cause of death was prostate cancer. We recently received summary files from the ICPCG, and have performed bioinformatics analysis of these data for lethal prostate cancer cases in search of prostate cancer predisposition genes or variants. We have provided a set of candidate variants from our data to the ICPCG Sequencing Core at Mayo.

subtask 6.3 Validation

Most prostate cancer linkage studies do not use the recurrent/lethal phenotype that we use, so these findings may be difficult to validate. We will continue to review all prostate cancer linkage reports and contact appropriate groups to attempt to validate our regions of interest in high-risk prostate cancer pedigrees.

Two groups of collaborators in the ICPCG have told us that they are similarly focused on the subset of lethal prostate cancer cases and are moving forward with genotyping and sequencing; one of these groups has a significant GWAS hint at our chromosome 11p region in lethal prca cases.

Task 7. Publication of linkage and association manuscripts

See Publications, Abstracts and Presentations

Key Research Accomplishments

- Creation of a set of 60+ high risk prostate cancer pedigrees with DNA samples representing an excess of the most clinically significant subset of prostate cases: those with recurrent/lethal disease
- Identification of significant linkage in multiple regions
- We have sampled 174 newly recurrent prostate cancer cases and collected detailed cancer characteristics data; GWAS has resulted in multiple accepted abstracts at GUASCO 2015.

Conclusion

We have published analysis of the UPDB showing that there is strong evidence that the subset of lethal prostate cancer cases cluster more in pedigrees than all prostate cancer cases. These results form the basis of our hypothesis that analysis of these homogeneous pedigrees will result in predisposition gene identification (Nelson et al., 2013).

Publications, Abstracts and Presentations

Nelson Q, Agarwal N, Stephenson R, **Cannon-Albright LA**. (2013). A population-based analysis of clustering identifies a strong genetic contribution to lethal prostate cancer. *Front Genet, 4*, 152.

We submitted 4 abstracts regarding lethal prostate cancer to GUASCO 2015.

Other publications using the data from this project:

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Inventions, Patents and Licenses

None

Reportable Outcomes

The 3 years of this grant resulted in an informative set of DNA, high risk pedigrees, and phenotype data for a set of pedigrees representing an excess of a highly significant clinic subset of prostate cancer cases: those who will go on to die of the disease.

We have already identified significant evidence for linkage and have found collaborators and begun sequence analysis of the regions of interest. Additional funding is required to complete that task.

We have accomplished GWAS analysis for treatment outcomes with Dr. Agarwal's recurrent patients and have multiple significant findings that will be presented at GUASCO and submitted to ASCO 2015.

Identification of genes predisposing to recurrent/lethal prostate cancer from this study will validate this powerful approach, which can be extended to other high-risk prostate cancer pedigrees, and will identify genes and pathways that can be further examined to expand our knowledge of prostate cancer genetics.

Other Achievements

None

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Appendix

Data Collection for prostate characteristics phenotype.

DOD project ID number/ MRN:
Age:
Race:

- Caucasian =1
- African American =2
- Hispanic =3
- Asian/Pacific Islander=4
- Southeast Asian=5
- Other=6

Family history of Prostate Cancer:

- No=1
- First degree relative =2
- Other =3

BMI:

- <18.5 (underweight)=1
- 18.5-25 (healthy weight)=2
- 25-30(overweight)=3
- 30-34.99 (obese class 1)=4
- 35-39.99 (obese class 2)=5
- >40 (obese class 3)=6 * WHO classification of BMI

Number of comorbidities:

- None=1
- One=2
- Two=3
- Three or more= 4

History of Smoking:

- Yes= 1
- No= 2

Current Smoking: **2**

- Yes=1
- No=2

Smoking in pack years:

- 1-10=1
- 11-20=2
- 21-30=3
- 31=40=4
- 41-50=5
- >51=6

PSA before diagnosis of Prostate Cancer:

PSA doubling time before diagnosis of Prostate Cancer:

Primary Gleason (needle) Grade:

- 5=5
- 4=4
- 3=3
- 2= 2
- 1=1

Secondary Gleason Grade (needle) :

- 5=5
- 4=4
- 3=3
- 2=2
- 1=1

Tertiary Gleason Grade (needle):

- 5=5
- 4=4
- 3=3
- 2=2
- 1=1

Clinical Stage:

- T0=1
- T1a=2
- T1b=3
- T1c=4
- T2=5
- T2a=6
- T2b=7
- T2c=8
- T3=9
- T3a=10
- T3b=11
- T4=12
- TX=13

Number of cores:

Actual number of cores involved:

LVI:

- Absent=1
- Present = 2

Prostate MRI prior to treatment:

- Yes=1
- No=**2**

MRI positive ECE:

- Positive=1
- Negative =2

Pathological Stage (surgical):

- pT2= 1
- pT2a=2
- pT2b=3
- pT2c=4
- pT3=5
- pT3a=6
- pT3b=7
- pT4=8

Pathological Gleason score (surgical):

- 5=5
- 4=4
- 3=3
- 2=2
- 1=1

Pathological tertiary Gleason score (surgical):

- 5=5
- 4=4
- 3=3
- 2=2
- 1=1

Seminal Vesicle Involvement:

- SVI Type I=1
- SVI Type II=2
- SVI Type III=3 * from *Anatomic considerations in prostate carcinoma*, Department of Urology, Baylor School of Medicine, 1989

Lymph node involvement:

- NX=1
- NO=2
- N1=3

Number of Lymph Nodes involved:

Metastatic disease present at diagnosis:

- Present=1
- Absent=2

PSA doubling time before starting ADT:

- <3 months= 1
- 3-6 months = 2
- 6-9 months = 3
- 9-12 months= 4
- >12 months= 5

Time of initiation of androgen deprivation therapy (castration) after definitive therapy:

- 0-6 months=1
- 6-12 month=2
- 12-24 months =3
- 24 months = 4

PSA after 7 months of castration:

- <. 02= 1
- 0.02-4=2
- 4-10=3
- 10=4

PSA after 1 year of castration:

Best PSA response to castration:

- 90%= 1
- >50%=2
- >30 %=3
- No response = 4

Best imaging response to castration:

- Stable= 1
- Partial= 2
- Complete = 3
- No response=4

Time to PSA progression on castration (25% increase from nadir):

- 0-3 months=1
- 3-6 months=2
- 6-12 months=3
- 12-18 months=4
- 18-24 months=5
- > 24 month=6

Time to imaging or clinical progression on castration:

- 0-3 months=1
- 3-6 months=2
- 6-9 months =3
- 9-12months =4
- 12-18 months=5
- 18-24 months=6
- > 24 month=7

Line of treatment after onset of castration refractory disease:

- First line=1
- Second line=2
- Third line= 3
- Fourth line=4
- Fifth line=5
- Sixth line=6

Best PSA response to:

- 90%= 1
- >50%=2
- >30 %=3
- No response = 4

Best imaging response to:

- Stable= 1
- Partial= 2
- Complete = 3
- No response =4

Time to PSA progression on drug:

- 0-3 months=1
- 3-6 months=2
- 6-12 months=3
- 12-18 months=4
- 18-24 months=5
- >24 months=6

Time to imaging or clinical progression on:

- 0-3 months=1
- 3-6 months=2
- 6-9 months =3
- 9-12months =4
- 12-18 months=5
- 18-24 months=6
- > 24 month=7

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- First line=1
- Second line=2
- Third line= 3
- Fourth line=4
- Fifth line=5
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- > 90%= 1
- >50%=2
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Best imaging response to:

- Stable= 1
- Partial= 2
- Complete = 3
- No response= 4

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- 0-3 months=1
- 3-6 months=2
- 6-12 months=3
- 12-18 months=4
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- > 24 months=6

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- 3-6 months=2
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- 18-24 months=6
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- Second line=2
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- 0-3 months=1
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- > 24 months=6

Time to imaging or clinical progression on:

- 0-3 months=1
- 3-6 months=2
- 6-9 months =3
- 9-12months =4
- 12-18 months=5
- 18-24 months=6
- > 24 months=7

Concomitant bisphosphonates:

- Yes=1
- No=2

Concomitant RANKL inhibitor:

- Yes =1
- No=2

Pathologic fractures:

- Yes=1
- No=2

Bone Density:

- Normal=1
- Osteopenia=2
- Osteoporosis=3

Overall Survival:

- # of months

Appendix.

Abstracts accepted for posters at GUASCO 2015

1.

Risk for Death from Prostate Cancer Predicted from Complete Family History of Lethal Prostate Cancer (LPC).

Frederick S. Albright, Neeraj Agarwal, William Thomas Lowrance, Robert A Stephenson, Anitha Alex, Lisa A Cannon-Albright; University of Utah Department of Pharmacotherapy, Salt Lake City, UT; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, Salt Lake City, UT; University of Utah Division of Genetic Epidemiology, Salt Lake City, UT

Abstract Text:

Background: There are few published reports of relative risk (RR) for LPC based on family history of prostate cancer (PC) lethality. This study provides LPC RR using complete LPC family history data obtained from a statewide Cancer Registry linked to a genealogy database. **Methods:** The Utah Population Data Base (UPDB), which includes a statewide SEER cancer registry, includes 1,192,768 individuals with at least 12 of their 14 immediate ancestors. All males (probands) with specific LPC constellations were identified in the UPDB, and the observed number of LPC cases among these probands was compared to the expected number of LPC cases using internal cohort-specific rates from Utah death certificates including all deceased males with no 1st, 2nd, or 3rd degree relatives with LPC. LPC Family history was estimated for 1st degree to 3rddegree relatives for: number of LPC relatives affected, paternal versus maternal family history, and age at first PC diagnosis. **Results:** 3,921 individuals in UPDB were diagnosed with histologically confirmed PC, and had a Utah death certificate indicating PC as a cause of death and were designated LPC. The RR for LPC was significantly elevated with each additional first-degree relative (FDR) with LPC; even in the absence of FDR family history of LPC, significantly increased risk for LPC was observed in the presence of at least 1 LPC affected second degree relative (SDR). In the absence of positive FDR and SDR family history for LPC, there was still increased risk for LPC for males with 2 or more third degree relatives with LPC. Early age PC diagnosis in the LPC relative did not appear to affect LPC RR. Higher risks of LPC were associated with the maternal compared to the paternal lineages. **Conclusions:** Examination of lethal prostate cancer family history (in FDRs through TDRs) may be useful in identifying the cohort of men with prostate cancer most at risk for death from prostate cancer. Focused screening and treatment of this cohort holds potential to decrease the rates of under treatment of lethal disease while avoiding over diagnosis and overtreatment in inconsequential disease.

2.

Germ line predictors of response to androgen deprivation therapy in men with advanced prostate cancer.

Neeraj Agarwal, Jim M. Farnham, Tyler Howard Buckley, Shiven B. Patel, Anitha Alex, Craig Teerlink, Frederick S. Albright, Robert A Stephenson, Lisa A Cannon-Albright; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; University of Utah Division of Genetic Epidemiology, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Hunstman Cancer Institute, Salt Lake City, UT; University of Utah, Division of Genetic Epidemiology, Salt lake City, UT; University of Utah Department of Pharmacotherapy, Salt Lake City, UT; Division of Urology, Department of Surgery, School of Medicine, University of Utah, salt lake city, UT

Abstract Text:

Background: Germline variations in genes involved in sex steroid biosynthesis and metabolic pathways may predict time to response to androgen deprivation therapy (ADT) in advanced prostate cancer, serve as prognostic and predictive biomarkers, and guide towards more individualized upfront therapy.

Methods: 47 polymorphisms in 22 genes involved in the steroid hormone metabolic pathway were investigated using tagging SNPs for association with time to onset of castration resistance in Caucasian men diagnosed with advanced prostate cancer undergoing ADT. Linear regression was employed using Gleason score as a covariate and assessing each SNP under one of three genetic models: 1) an additive model in which the number of minor alleles contributes increasing risk (or protection), 2) a dominant model in which the presence of 1 or 2 minor alleles have the same effect, and 3) a recessive model in which the presence of 2 minor alleles are necessary.

Results: Polymorphisms in 3 genes (CYP1A1, HSD17B3, and HSD17B12) were significantly associated with time to prostate cancer recurrence after medical castration while controlling for Gleason Score. Table 1 summarizes the genes found to be significantly associated with time to recurrence and the modes of inheritance considered. (Only SNPs found to be nominally significant ($p < .05$) either with or without controlling for Gleason score in at least one model are shown.)

Gene	Chr	Position (B36 bp)	Variant	Regression Coefficient P values without Gleason correction	with Gleason correction	
				Additive model		Dominant
			gleason score	.024		
CYP1A1	7	99203018	rs4646421*	.018	.042	.134
HSD17B3	9	98052097	rs407179*	.005	.031	.039
HSD17B3	9	98055915	rs2026001*	.033	.213	.249
HSD17B12	11	43684152	rs7934642*	.032	.051	.192
HSD17B2	16	80672649	rs9889094*	.044	.070	.070
SULT2A1	19	53095295	rs182421**	.048	.123	.242

* Confers increased time to failure. ** Confers decreased time to failure.

Conclusions: In this preliminary report of the ongoing work, germ line variations in multiple genes in the sex steroid hormone metabolic pathway predicted time to response to ADT, and warrant further validation to define their role as prognostic and predictive markers in this setting.

3.

2015 GUASCO Prostate lethal linkage abstract

LA Cannon-Albright, CC Teerlink, A Alex , R Stephenson, N Agarwal

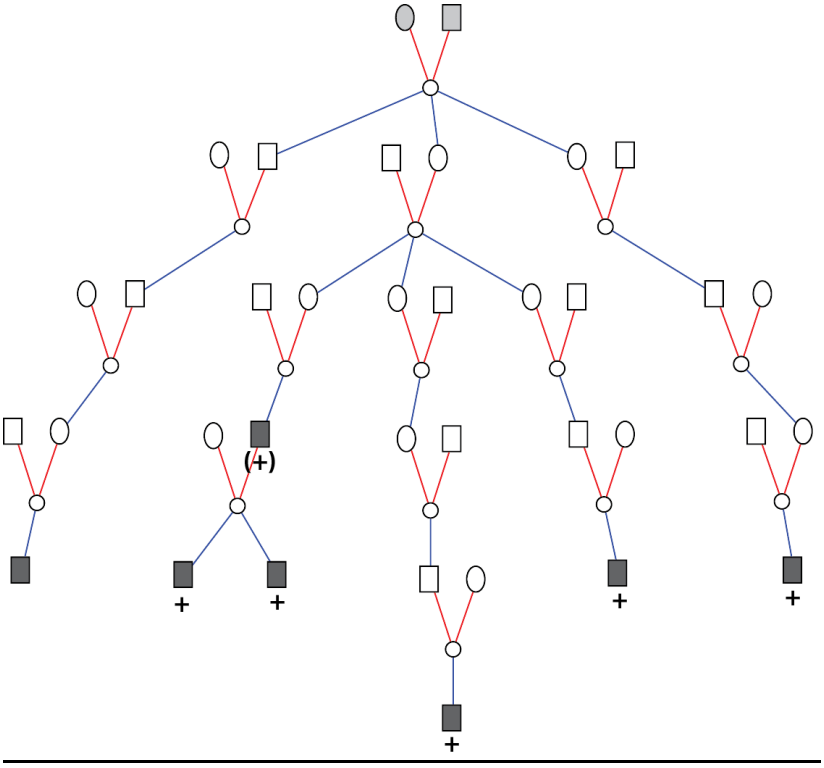
A genomewide linkage study of lethal prostate cancer predisposition gene in a set of high-risk pedigrees

Background: Using the unique Utah genealogical resource linking 12 generations of genealogy data to a statewide cancer registry from 1966 and statewide death certificates from 1904 we have identified a set of high-risk prostate cancer pedigrees with multiple cases having died from prostate cancer.

Methods: Clusters of prostate cancer cases descended from a common ancestor, among whose descendants is observed a statistical excess of prostate cancer (high-risk prostate cancer pedigrees) were recruited and sampled. Pedigrees with 4 or more cases dying from prostate cancer (as evidenced by inclusion as a cause of death on a Utah death certificate) were genotyped with high-density SNPs across the genome. Linkage analysis was performed to identify regions hypothesized to contain a prostate cancer predisposition gene.

Results: A single extended Utah high-risk prostate cancer pedigree including 6 sampled and distantly related prostate cancer cases who went on to die as a result of their cancer showed significant evidence for linkage at chromosome arm 4q24 (LOD score = +3.28), with 5 of the 6 cases having inherited the same region of chromosome 4 from a common ancestor (see Figure)

Conclusions: The inability of association studies to identify prostate cancer predisposition genes has returned focus to linkage studies of highly informative high-risk pedigrees, which provide power for identifying and localizing regions of interest for predisposition genes. A focus on only those cases are members of high-risk prostate cancer pedigrees, who also went on to die as a result of their prostate cancer, has resulted in the identification of evidence for a prostate cancer predisposition gene on chromosome arm 4q24, confirming a previous GWAS reporting association with prostate-cancer-specific-survival (Pomerantz MM et al., 2011) in this region harboring *TET2* (a tumor suppressor gene involved in pathogenesis of acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms), and *PP2A* (implicated in androgen receptor regulation in prostate cancer cell lines).



frontiers in GENETICS

ORIGINAL RESEARCH ARTICLE
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A population-based analysis of clustering identifies a strong genetic contribution to lethal prostate cancer

Quentin Nelson[1], Neeraj Agarwal[1,2], Robert Stephenson[2,3,4] and Lisa A. Cannon-Albright[1,2,3]*

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Background: Prostate cancer is a common and often deadly cancer. Decades of study have yet to identify genes that explain much familial prostate cancer. Traditional linkage analysis of pedigrees has yielded results that are rarely validated. We hypothesize that there are rare segregating variants responsible for high-risk prostate cancer pedigrees, but recognize that within-pedigree heterogeneity is responsible for significant noise that overwhelms signal. Here we introduce a method to identify homogeneous subsets of prostate cancer, based on cancer characteristics, which show the best evidence for an inherited contribution.

Methods: We have modified an existing method, the Genealogical Index of Familiality (GIF) used to show evidence for significant familial clustering. The modification allows a test for excess familial clustering of a subset of prostate cancer cases when compared to all prostate cancer cases.

Results: Consideration of the familial clustering of eight clinical subsets of prostate cancer cases compared to the expected familial clustering of all prostate cancer cases identified three subsets of prostate cancer cases with evidence for familial clustering significantly in excess of expected. These subsets include prostate cancer cases diagnosed before age 50 years, prostate cancer cases with body mass index (BMI) greater than or equal to 30, and prostate cancer cases for whom prostate cancer contributed to death.

Conclusions: This analysis identified several subsets of prostate cancer cases that cluster significantly more than expected when compared to all prostate cancer familial clustering. A focus on high-risk prostate cancer cases or pedigrees with these characteristics will reduce noise and could allow identification of the rare predisposition genes or variants responsible.

Keywords: familiality, prostate cancer, lethal, UPDB

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men and is the second leading cause of cancer deaths among men (ACS, 2013). While there is significant evidence of a genetic contribution (Cannon et al., 1982; Carter et al., 1993; Stanford and Ostrander, 2001; Langeberg et al., 2007), decades of investigation into the genetic causes of familial prostate cancer has yet to clearly identify genes or variants which explain much more than a small number of pedigrees with an excess of prostate cancer. Traditional linkage analysis of thousands of high-risk prostate cancer pedigrees has elucidated little in the identification of predisposition genes responsible for prostate cancer pedigrees. This may reflect the heterogeneous nature of prostate cancer, and this could confound identification of informative homogeneous pedigrees segregating rare predisposition variants.

We hypothesize that there exist rare prostate cancer predisposition variants that are responsible for our observation of high risk prostate cancer pedigrees including homogeneous prostate cancer cases (defined by clinical characteristics). We present a methodology to compare subsets of prostate cancer cases and identify those that show more familial clustering than expected for all prostate cancer cases.

Using a population-based resource in Utah that combines genealogy and cancer data, we identified 3 subsets of prostate cancer cases that cluster in pedigrees more than expected: prostate cancer which is diagnosed before age 50 years, lethal prostate cancer (leading to metastasis and death from prostate cancer), and prostate cancer in men with BMI $\geq$ 30. We propose that analysis of the high-risk prostate cancer cases or pedigrees with an excess of prostate cancer cases with these characteristics could lead to identification of the rare predisposition variants responsible.

DATA AND METHODS

The Utah Population Data Base (UPDB) integrates three key electronic datasets: a Genealogy of the Utah pioneers constructed in the 1970s and kept current (Skolnick, 1980), death certificates for Utah, and a statewide cancer registry. The original Utah genealogy had approximately 1.6 million individual records for

186,000 three-generation families. Since the genealogy was created in the 1970s, state vital records have been used to create genealogy triplets (mother, father, and child) to extend the genealogy to present day. The UPDB has become a person-oriented database with information on 7 million Utahns, some 2.5 million of whom have at least three generations of genealogy. The Utah Cancer Registry (UCR) was created in 1966 to collect data on all cancer diagnosed in Utah. It became a SEER (Surveillance, Epidemiology, and End-Results) Registry of the National Cancer Institute in 1973. The UCR individual records are linked to the Utah genealogy annually; approximately 2/3 of UCR cases link to a record in the UPDB. Cause of death from Utah state death certificates from 1904 to present have been coded to ICD Revisions 6–10, and record linked to the UPDB. Utah Drivers License records from 1970 have been linked to the UPDB and include height and weight measurements for calculation of body mass index (BMI). The combination of genealogy, death certificates, drivers license data, and cancer registry data facilitates the identification of all Utah prostate cancer cases and the genetic relationships between them.

To perform the genetic analyses presented here we restrict ourselves to those individuals in the UPDB with ancestral genealogy data. We identified all individuals in the UPDB who were born before 1972 (when the original Utah genealogy was constructed) and whose parents, four grandparents, and six (of eight total) great grandparents are present in the UPDB genealogy data. This identifies 1.2 million individuals with ancestral genealogy data who are used for all analyses.

We have extended a well-published analysis method, the Genealogical Index of Familiality (GIF), to enable comparison of the relatedness of a subset of prostate cancer cases to the relatedness of *all* prostate cancer cases. Those subsets with evidence for significantly more relatedness than all prostate cancer cases are hypothesized to represent homogeneous genetic subsets that will be most informative for gene identification studies.

GENEALOGICAL INDEX OF FAMILIALITY (GIF) METHOD

For decades the GIF statistic has been used to quantify familial clustering of cancer and other phenotypes in the UPDB. This well-established statistical method has yielded strong evidence of heritability for several cancer phenotypes (Cannon et al., 1982; Cannon-Albright et al., 1994; Larson et al., 2006; Albright et al., 2012). The GIF was developed to test the hypothesis of excess relatedness of individuals with a common phenotype. Excess relatedness is measured by comparing the average relatedness between all pairs of cases of interest to the expected relatedness of matched controls from the Utah population. Since record linkage of any subset of UPDB records may indicate better or different quality data, for individuals with a death certificate, we select controls from all UPDB individuals who have a Utah death certificate. Since the UCR is statewide, we select controls for cancer cases from the entire UPDB resource.

The relatedness of a pair of individuals in a set is measured using the Malécot coefficient of kinship. The Malécot coefficient of kinship mathematically expresses Mendelian inheritance pattern probabilities that randomly selected homologous chromosomes are identical due to inheritance from a common ancestor. For example, the Malécot coefficient for siblings is 1/4, avunculars is 1/8, and first cousins 1/16. The GIF analysis tests excess relatedness by comparing all pairwise relationships within a set of cases to the expected relatedness measured in all pairwise relationships in 1000 sets of matched controls randomly selected from the UPDB. Controls were matched on characteristics that might be associated with record linking and disease rates, including five-year birth year cohort, sex, and birth state (Utah or not).

The overall GIF analysis tests for significant excess relatedness (over what is expected in the UPDB population) among a group of individuals. It can be performed on all prostate cancer cases, and on subsets of cases based on cancer characteristics. It cannot, however, determine which, if any, of these subsets exhibits the best evidence for a genetic predisposition, and which therefore might be the best set of high-risk pedigrees in which to search for genes.

NEW SUBSETGif TEST

Here we consider a modified GIF test and test the relatedness of multiple subsets of prostate cancer cases to identify those which exhibit excess relatedness above the observed relatedness among *all Utah prostate cancer cases*. This modified GIF test is referred to as the SubsetGif. Evidence for significant excess relatedness for a subset of prostate cancer cases above the expected for *all prostate cancer cases* could indicate the presence of a common genetic cause shared by the homogeneous subset. The identification and subsequent study of pedigrees including cases of such a homogeneous subset might facilitate the identification of rare predisposition genes.

CONTRIBUTION TO THE GIF BY GENETIC DISTANCE

It is possible to view the distribution of the contribution to the GIF statistic by the pairwise genetic distance of the different relationships observed in cases (and controls). The genetic distance represents the number of paths between a pair of individuals. Genetic distance 1 represents parent/offspring pairs, genetic distance 2 represents siblings or grandparent/grandchild, genetic distance 3 represents avunculars, and so forth.

RESULTS

In the UPDB resource, 18,291 prostate cancer cases were identified who also had ancestral genealogical records. The available prostate cancer subsets and their corresponding sample sizes are outlined in **Table 1**.

Table 1 | Subsets of prostate cancer and sample size.

Set of prostate cancer cases	*n*
All prostate cancers	18,291
Age at diagnosis <50 years	213
Metastatic disease at diagnosis	912
With at least 1 primary cancer of other site	2922
Gleason score >7 at diagnosis	4784
Short survival (0–9 months)	1180
Long survival (240 + months)	806
High BMI (≥30)	2459
Prostate cancer cause of death (lethal prostate cancer)	3982

ANALYSIS OF EXCESS RELATEDNESS

Previous studies have strongly supported evidence for a genetic contribution to predisposition to prostate cancer in the Utah population, as well as other populations (Cannon et al., 1982; Cannon-Albright et al., 1994, 2005). When all prostate cancer cases with genealogy data in the UPDB are analyzed there is evidence of excess relatedness (represented by both close and distant genetic relationships) over expected relatedness in matched Utah population controls. **Table 2** shows the traditional GIF test for excess relatedness compared to matched Utah population controls for all prostate cancer cases, and for each subset. The mean relatedness for cases and controls is shown. All prostate cancer cases and subsets, except prostate cases who survived less than 10 months after diagnosis, show strong evidence for excess clustering compared to Utah population controls. These results suggest a genetic contribution to prostate cancer predisposition, and suggest that study of almost all subsets of prostate cancer could be fruitful, but the results do not allow identification of which, if any, of the subsets are significantly more related than expected when compared to all prostate cancer cases, and thus show the best evidence for a genetic contribution.

In order to consider the hypothesis that a subset of prostate cancer cases represents a more homogeneous subset of highly related cases, we propose use of the SubsetGif analysis. The average pairwise relatedness of each subset of cases is compared to the average pairwise relatedness of 1000 sets of matched "controls"; these controls are selected from the set of 18,291 Utah prostate cancer cases. The results for this SubsetGif test are shown in **Table 3**. The average pairwise relatedness of the cases does not change for any subset (as expected), but the mean control GIF statistic is higher than in **Table 2** for each subset because the "controls" here are randomly selected prostate cancer cases, who are more closely related than random members of the Utah population.

Table 3 results show that the average pairwise relatedness of three different subsets of prostate cancer cases is significantly higher than expected among prostate cancer cases, supporting the hypothesis that these subsets of cases cluster more than all prostate cancer cases and represent sets on which to focus for predisposition gene identification. The three subsets include prostate cancer cases diagnosed before age 50 years, prostate cancer cases with BMI $\geq$ 30, and prostate cancer cases whose cause of death is prostate cancer (lethal prostate cancer).

It is difficult to determine whether these three subsets represent independent groups of interest or whether there is overlap between the groups because not all cases have BMI and death certificate data. There were 222 prostate cancer cases with BMI $\geq$ 30 among the 3982 cases with prostate cancer as a cause of death (6% total and 17% of the 1300 lethal cases with BMI data), and 58 prostate cancer cases with BMI $\geq$ 30 of the 213 cases who were

Table 2 | GIF analysis of prostate cancer relatedness compared to expected relatedness in the UPDB population.

Group	*n*	Case GIF	Mean control GIF	Empirical significance
All prostate cancers	18,291	5.54	4.74	<0.001
Age at diagnosis <50 years	213	11.72	4.54	<0.001
Metastatic disease at diagnosis	912	5.94	4.89	<0.001
With at least 1 primary cancer of other site	2922	5.58	4.74	<0.001
Gleason score >7 at diagnosis	4784	5.41	4.69	<0.001
Short survival (0–9 months)	1180	5.19	4.92	0.138
Long survival (240 + months)	806	5.64	4.75	0.005
BMI $\geq$ 30	2459	5.81	4.71	<0.001
Prostate cancer cause of death* (lethal)	3982	5.98	4.93	<0.001

Because the subset of lethal prostate cancer cases differs from all prostate cancer cases with respect to the identification of a linked death certificate record, and because the fact of record linking may suggest different data quality, we performed the GIF analysis for the subset of cases with prostate cancer contributing to death in **Tables 2, **3** using only the 10,421 prostate cancer cases with a linked Utah death certificate as controls; this is the standard for analysis of sets of individuals selected from Utah death certificate data (Cannon-Albright, 2008).*

Table 3 | Subset prostate cancer relatedness compared to expected prostate cancer case relatedness in the UPDB.

Prostate cancer subsets	*n*	Case GIF	Mean control GIF	Empirical significance
Age at diagnosis <50 years	213	11.72	7.51	0.024
Metastatic disease at diagnosis	912	5.94	5.95	0.506
With at least 1 primary cancer of other site	2922	5.58	5.51	0.303
Gleason Score >7 at diagnosis	4784	5.41	5.39	0.417
Short Survival (0–9 months)	1180	5.19	6.08	1.000
Long Survival (240 + months)	806	5.64	5.56	0.400
BMI $\geq$ 30	2459	5.81	5.27	<0.001
Prostate cancer cause of death (lethal)	3982	5.98	5.76	0.030

Controls randomly selected from 18,291 prostate cancer cases.

diagnosed before age 50 years (27%). Overall, 11,536 prostate cancer cases had BMI data, and 21.3% were BMI $\geq$ 30. There were 26 prostate cancer cases diagnosed before age 50 years (0.7%) among the 3982 lethal prostate cancer cases, and overall the 213 prostate cancer cases diagnosed before age 50 years represented 1% of all cases.

In order to determine the overall distribution of excess relatedness we can view the contribution to the GIF statistic by the pairwise genetic distance for cases and for controls. **Figure 1** shows the GIF distribution for all 18,291 prostate cancer cases compared to the distribution for the 1000 sets of matched Utah population controls. The comparison shows that the relatedness for prostate cancer cases exceeds that expected in the Utah population, as observed in random matched Utah controls, for genetic distances up to 7 (e.g., second cousins once removed).

Figures 2–4 show the contribution to the GIF statistic for the three subsets of cases, with matched controls randomly selected from all Utah prostate cancer cases. **Figure 2** shows this distribution for prostate cancer cases with BMI $\geq$ 30; as seen in **Table 3** there is significant excess relatedness for prostate cases with BMI $\geq$ 30. This excess extends to a genetic distance of 5, equivalent to first cousins once removed, for example. **Figure 3** shows this distribution for prostate cancer cases diagnosed before age 50 years, which is also observed to show significant excess relatedness. The excess relatedness is irregular, but is clearly observed for genetic distance = 2 (siblings primarily), and distance = 8 (third cousins, for example). **Figure 4** shows the GIF distribution for lethal prostate cancer cases, also observed to show significant excess clustering when compared to all deceased prostate cancer cases. The excess extends to genetic distance = 4, equivalent to first cousins, for example.

Figures 5–7 show examples Utah high-risk prostate cancer pedigrees for each of the subset characteristics identified.

DISCUSSION

Analysis of a population-based Utah resource linking cancer characteristics data with genealogy data has previously shown evidence for a genetic contribution to prostate cancer predisposition (Cannon et al., 1982; Cannon-Albright et al., 1994, 2005; Albright et al., 2012; Teerlink et al., 2012). Here we have extended a well-published analysis method which tests for excess relatedness in a set of individuals to allow the identification of subsets of prostate cancer cases who show the strongest evidence for excess familial clustering. The subsets identified might be argued to represent the most informative sets of cases or pedigrees to be studied for rare predisposition gene identification.

Some of the subsets of prostate cancer cases that show significant evidence of clustering in excess of expected for prostate cancer were expected, some represent new subsets of interest for genetic studies. The subset of men diagnosed with prostate cancer before age 50 years is not surprising; there is much literature suggesting a strong genetic contribution to cancer of most sites that is diagnosed early (Goldgar et al., 1994; Brandt et al., 2008) and much analysis of this subset of prostate cancer cases and pedigrees has been performed (Gronberg et al., 1999; Xu et al., 2005). However, the other two groups of prostate cancer

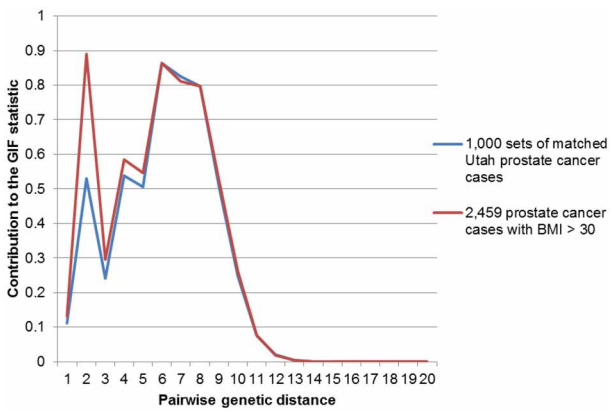

FIGURE 2 | Contribution to the GIF statistic by pairwise genetic distance for cases and controls for prostate cancer cases with a BMI of 30 or greater.

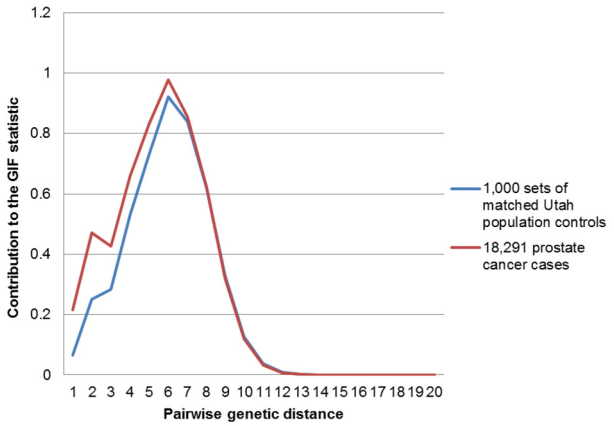

FIGURE 1 | Contribution to the GIF statistic by pairwise genetic distance for cases and controls for all prostate cancers vs. population.

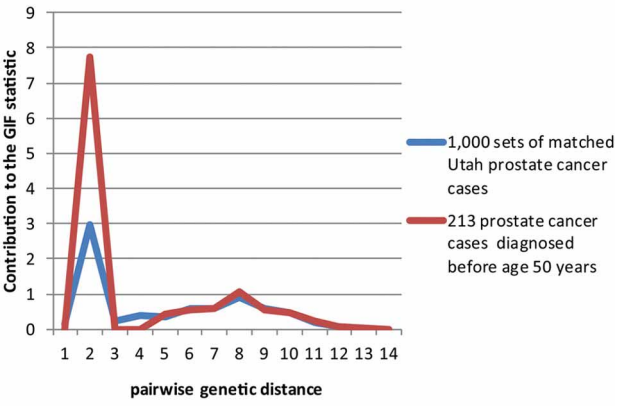

FIGURE 3 | Contribution to the GIF statistic by pairwise genetic distance for cases and controls for prostate cancer cases diagnosed before age 50.

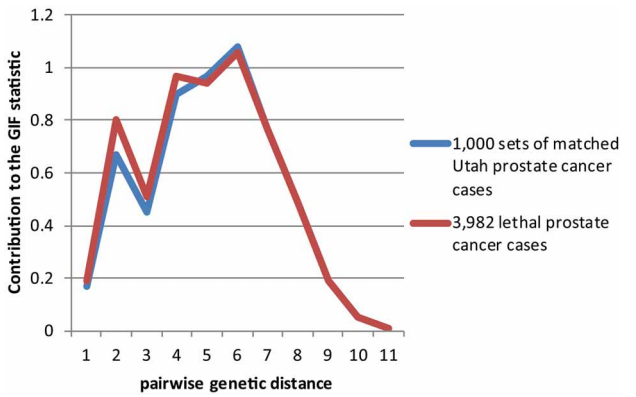

FIGURE 4 | Contribution to the GIF statistic by pairwise genetic distance for cases and controls for prostate cancer cases that have prostate cancer as a cause of death.

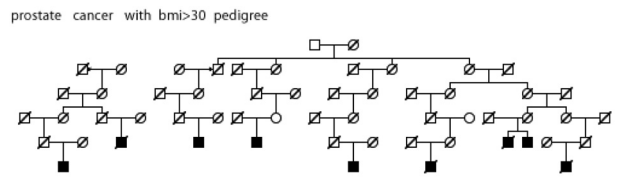

FIGURE 5 | High risk Utah prostate cancer pedigree (56 prostate cancer cases observed among descendants of the pedigree founder, 36 expected, $p = 0.001$); cases with BMI ≥ 30 are shown.

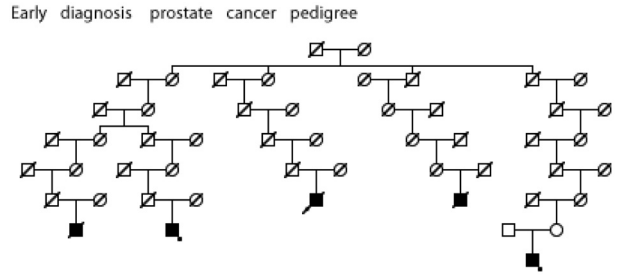

FIGURE 6 | High risk Utah prostate cancer pedigree (173 prostate cancers observed among descendants of the pedigree founder, 131 expected, $p = 0.0003$); cases diagnosed before age 50 years are shown. The two cases with an asterisk were also observed to have BMI ≥ 30 (data not available for all cases).

cases identified, high BMI (≥30) and lethal prostate cancer cases, have not been suggested previously as associated with a strong genetic contribution for prostate cancer. There was some overlap of prostate cancer cases between these sets; further investigation of specific high-risk pedigrees will determine whether they are independent.

Although epidemiologic studies have shown that systemic metabolic disorders including obesity might increase risk for prostate cancer, BMI in the context of high risk prostate cancer

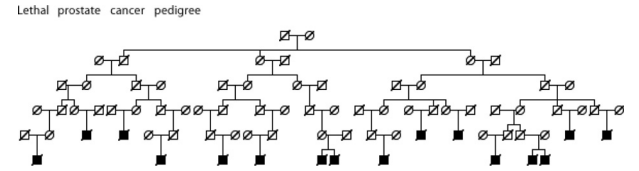

FIGURE 7 | High risk Utah prostate cancer pedigree (76 prostate cancer cases observed among descendants of the pedigree founder, 51.5 expected, $p = 0.0008$); cases known to have died from prostate cancer are shown.

pedigrees does not appear to have been studied. Since there is evidence for familial clustering of high BMI or obesity (independent of cancer status), it is possible that these results are due, at least in part, to a shared predisposition to obesity. Nevertheless, these results suggest this is an informative set of pedigrees to be studied for prostate cancer risk.

The familiality of *aggressive* prostate cancer has been noted, and subsets of aggressive prostate cancer cases have been studied, without any gene identifications (Paiss et al., 2003; Lange et al., 2006; Schaid et al., 2006; Christensen et al., 2007). Little progress has been made in understanding why 30% of all patients with localized prostate cancer eventually develop recurrent, and subsequently fatal, prostate cancer. Rather than subset aggressive prostate cancers, we specifically targeted the pathogenesis of lethal prostate cancer. This subtle definition difference focuses on the subtype of prostate cancer which is associated with the worst prognosis i.e., which kills, but our definition ignores age at onset and pathology grading data for the individual, both of which are more commonly used to classify prostate cancer cases for aggressive status, but which can be poor markers for survival. This subset of lethal prostate cancer cases, among all others, is the most clinically significant and that which could yield the most translational opportunities were genes to be identified.

The Utah population has proven valuable to the study of many common cancers, and to the isolation of multiple cancer predisposition genes. The University of Utah group has been studying high-risk cancer pedigrees since 1972, and has built a resource of thousands of extended high-risk pedigrees that includes over 35,000 DNA samples. The study of extended pedigrees allowed our research group to isolate *BRCA1* (Miki et al., 1994), to localize and isolate *BRCA2* (Wooster et al., 1994; Tavtigian et al., 1996), to localize and isolate *p16* (Cannon-Albright et al., 1992, 1994; Kamb et al., 1994), and to localize and isolate *HPC2/ELAC2* (Tavtigian et al., 2001). These findings of excess relatedness in the UPDB for three subsets of prostate cancer cases represent multiple Utah high-risk prostate cancer pedigrees for each of the subsets. Analysis of these high risk pedigrees will lead to identification of the predisposition genes responsible, which might otherwise not be identifiable in studies of all high-risk prostate cancer pedigrees combined.

We have identified significant evidence for three characteristics of prostate cancer that independently coaggregate in both close and distant relatives. We have identified multiple high-risk prostate cancer pedigrees that independently include multiple prostate cancer cases with the characteristics of interest.

Figures 5–7 show an example Utah high-risk prostate cancer pedigree for each of the three characteristics identified. We propose that linkage analysis or shared genomic segment (Thomas et al., 2008) analysis can identify chromosomal regions shared in the related cases and that sequence analysis of predisposition carriers in the targeted regions located will lead to identification of the responsible predisposition genes. Rather than studying all high-risk prostate cancer pedigrees, we instead will focus on those that exhibit multiple cases with those characteristics most likely to have a genetic contribution. These studies will examine fewer pedigrees than a typical prostate cancer pedigree study, but will focus on the homogeneous subsets most likely to represent rare segregating predisposition genes or variants.

These findings should be generalizable to the U.S.A. population. Utah was originally settled by ∼10,000 Mormons of British, Scandinavian, and German origin. They, and the more than 50,000 migrants from the same areas who arrived in the next generations, have typical Northern European gene frequencies (McLellan et al., 1984) and low to normal levels of inbreeding compared to the U.S. (Jorde, 1989). These characteristics make this population appropriate for inferences in populations of Northern European descent. The predisposition genes identified in Utah are represented similarly in other studies in terms of frequency, penetrance, and interactions with risk factors and modifier genes. Utah cancer rates are lower than U.S. rates, most likely due to lower rates of smoking and alcohol use.

Recent advances in mapping the genome, combined with the unique resources of Utah, provide a rare opportunity for a successful search for predisposition genes or variants for prostate cancer and the definition of their role at a population level. Recent evidence has shown the advisability and efficiency of rare predisposition gene identification by study of extended pedigrees (Ewing et al., 2012; Roberts et al., 2012). Here we identify characteristics of prostate cancer that can be used to more specifically focus gene identification efforts on appropriate pedigrees. The eventual identification of predisposition genes for prostate cancer, accompanied by a greater understanding of how these genes contribute to morbidity and mortality, will lead to the development of diagnostic tests and more personalized treatments for prostate cancer.

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