The Impact of Multiple Type 2 Diabetes Susceptibility Genetic Variants in Prostate Cancer Outcomes

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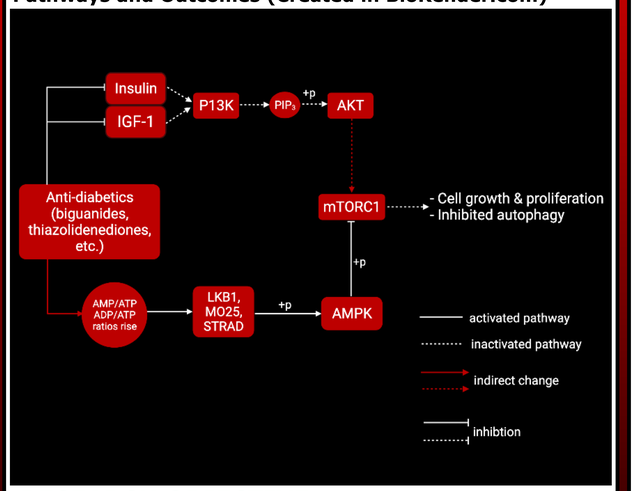
INTRODUCTION

- Aside from non-melanoma, PCa is the most common cancer and leading cause of cancer-related death in men.
  - In 2021, 246,530 men will receive a prostate cancer (PCa) and 34,130 will die from the disease.
- Several studies have found an inverse relationship between the association between prostate cancer and a history of diabetes mellitus. Specifically, as years diagnosed with diabetes increase, prostate cancer incidence and severity decrease.
- This protective relationship may be attributed to shared signaling pathways such as AMPK or P13K/AKT, insulin receptor sensitivity and level changes, and antidiabetic treatment strategies.
- The various antidiabetic treatment drugs have shown positive effects in their use in various cancer patients. A biguanide, Metformin, has been found to:
  - Upregulate let-7 miRNA
  - Inhibit pro-inflammatory cytokines
  - Lower insulin levels
  - Downregulate P13K/AKT pathway involved in cell growth, proliferation, differentiation, and motility
  - Activate AMPK pathway
    - Initiated by the inhibition of the electron transport chain in cancerous cells
    - Downstream effects lead to inhibition of mTORC1
- Many of these pathways play a role in cancerous cell growth and proliferation.

Figure 1. Metformin-induced Insulin, P13K, and AMPK Pathways and Outcomes (Created in BioRender.com)



RESEARCH OBJECTIVE

With an overall goal of enhanced detection of disease and improved treatment strategies in mind, we evaluated whether the inheritance of multiple diabetes-related gene variants alter prostate cancer risk and disease progression.

HYPOTHESIS

We hypothesize individuals who inherit two or more diabetes-related gene variants may lead to a decrease in the risk of developing prostate cancer and disease severity.

RESEARCH GAP

The joint-modifying effects of diabetes-related gene variants on prostate cancer outcomes remains understudied.

STUDY DESIGN

- Cancer Genetic Markers of Susceptibility (CGEMS)
  - Genome-wide Association Study (GWAS) dataset
  - Analysis of genomic data within the CGEMS dataset containing population data on prostate cancer participants of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial
  - 1320 European-American participants
    - 879 cases (391 aggressive, 488 nonaggressive) and 441 controls
- Quality Control Analysis
  - HWE p-value >0.05, genotype call rate ≥95%

METHODS

Assess differences in the genotype frequency comparing cases and controls using Chi-square and Fisher's Exact Test

- PLINK & Statistical Analysis Software (SAS) 9.4
  - Genome association analysis toolset
    - http://zzz.bwh.harvard.edu/plink/
  - Analyzed > 106,030 SNPxSNP interactions
  - All p-values were adjusted for confounders and multiple hypothesis testing using the false-discovery rate (FDR)
- Statistical Epistasis Network Analysis
  - Main and interaction effects were assessed by calculating information gain (IG) scores using statistical epistasis network analysis, powered by ViSEN. Emphasis was placed on the joint IG scores that exceeded the IG scores of either individual marker.

RESULTS

Table 1. Evaluation of Main Effects among Diabetes Susceptibility Gene Variants and Prediction of PCa Risk

Gene_dbSNP ID	Allele Change	FDR adj_dom	FDR adj_rec	FDR adj_geno
IGF1R_rs12908437	C/T	9.22E-19	4.7E-10	2E-20
IGF2BP3_rs13229367	C/T	3.74E-20	1.3E-18	4E-26
IGF2BP3_rs13242451	C/T	3.98E-40	1.9E-09	5.9E-39
IGF1R_rs1357112	G/A	5.53E-31	2.6E-16	5.5E-33
KCNQ1_rs17743926	A/G	1.07E-18	5.3E-08	5.2E-19
TCF7L2_rs2094405	T/C	3E-25	1E-07	5.6E-25
KCNQ1_rs231358	C/T	5.77E-21	8E-10	4.8E-22
KCNQ1_rs231362	G/A	3.74E-20	2.5E-09	8E-19
KCNQ1_rs231906	G/A	2.49E-16	1.9E-07	3.9E-17
IGF1R_rs4616271	C/T	4.8E-16	3.7E-08	1.3E-16
NFKB1_rs4648024	C/T	4.76E-21	2.4E-07	6.2E-21
IGF2BP3_rs6461708	A/C	8.34E-36	1.2E-09	3.2E-35
KCNQ1_rs6578273	A/G	5.12E-54	2.8E-25	3.2E-54
IGF1R_rs7168213	G/T	7.54E-19	3.6E-21	8E-27
THADA_rs7578597	C/T	2.72E-39	3.2E-09	3.5E-38
KCNQ1_rs760419	A/G	8.67E-42	6E-51	3.1E-55
KCNQ1_rs7929804	A/G	6.89E-51	2.7E-16	8.7E-50
AKT2_rs892119	T/C	2.11E-19	8.6E-11	2.9E-21
IGF1R_rs9672965	C/T	3.21E-20	1.6E-08	1E-20
IGF1R_rs9920651	C/T	3.88E-17	5.7E-11	1.4E-19

Table 2. Evaluation of Main Effects among Susceptibility Gene Variants and Prediction of Aggressive PCa

SNP	Allele Change	FDR adj_dom	FDR adj_rec	FDR adj_geno
SLC30A8_rs13266634	C/T	1.65E-59	3.51E-33	1.52544E-62
SLC22A1_rs1443844	A/G	8.55E-67	4.76E-41	4.3232E-72
IGF2BP3_rs17796841	C/T	1.99E-51	1.93E-30	3.1872E-56
HNF4A_rs1885088	A/G	9.56E-50	2.00E-16	1.48512E-48
PPARG_rs2120825	G/T	9.56E-50	4.64E-18	4.21527E-48
KCNQ1_rs231361	G/A	2.19E-45	2.29E-21	2.3296E-44
KCNQ1_rs231841	T/G	4.36E-41	2.29E-21	1.55548E-43
KCNQ1_rs231899	G/A	6.00E-45	3.20E-19	4.776E-46
SLC22A3_rs2457571	C/T	9.05E-55	2.88E-32	1.0192E-56
IGF1R_rs4616271	C/T	4.80E-39	3.01E-25	2.66933E-43
IGFBP1_rs4619	A/G	9.00E-40	1.49E-25	4.599E-44
KCNQ1_rs6578296	C/T	1.49E-124	2.51E-73	7.9968E-126
IGF1R_rs7168671	C/T	6.61E-35	3.32E-45	1.75093E-52
KCNQ1_rs736609	C/T	1.73E-40	5.88E-15	4.62E-40
PPARG_rs7626560	C/T	5.13E-105	3.96E-124	6.6192E-134
SLC22A3_rs7758229	G/T	5.60E-42	3.84E-27	2.10905E-46
KCNQ1_rs800336	A/G	4.60E-58	1.44E-14	1.8396E-55
HNF4A_rs8116574	A/C	6.21E-70	2.22E-32	1.6968E-70
AKT2_rs892119	T/C	2.40E-47	7.34E-20	7.196E-48
IGF1R_rs9920651	C/T	4.19E-38	3.09E-20	4.52716E-40

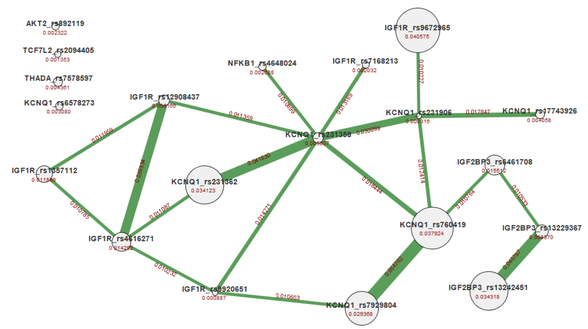
Table 3. Impact of Diabetes-related SNP pairs on PCa among PLCO participants using a Case-Control Analysis

Gene_dbSNP ID #1	Gene_dbSNP ID #2	p-value	FDR-adj p-value
IGF2BP3_rs12700428	KCNQ1_rs129074	1.22E-28	4.26E-25
IGF2BP3_rs12540730	IGF1R_rs12439656	3.106E-25	3.62E-22
KCNQ1_rs11523905	IGF1R_rs11854132	5.76E-24	5.03E-21
IGF1R_rs11854132	HNF1B_rs11263755	1.78E-22	7.77E-20
KCNQ1_rs736609	HNF4A_rs736824	3.705E-22	1.30E-19

Table 4. Impact of Diabetes-related SNP pairs on Aggressive PCa among PLCO participants using a Case-only Analysis

Gene_dbSNP ID #1	Gene_dbSNP ID #2	p-value	FDR-adj p-value
KCNQ1_rs739677	HNF1B_rs7407025	5.21E-36	1.30E-32
TCF7L2_rs12255372	KCNQ1_rs12287029	7.672E-36	9.56E-33
KCNQ1_rs129074	IGF1R_rs1319869	9.09E-34	5.66E-31
IGF1R_rs702497	HNF4A_rs6093978	1.36E-33	6.78E-31
NFKB1_rs4648135	KCNQ1_rs433052	2.187E-32	4.96E-30

Figure 2. Interaction entropy graph for diabetes-related gene variants and prostate cancer risk among the CGEMS participants using Statistical Epistasis Network (Case-Controls)



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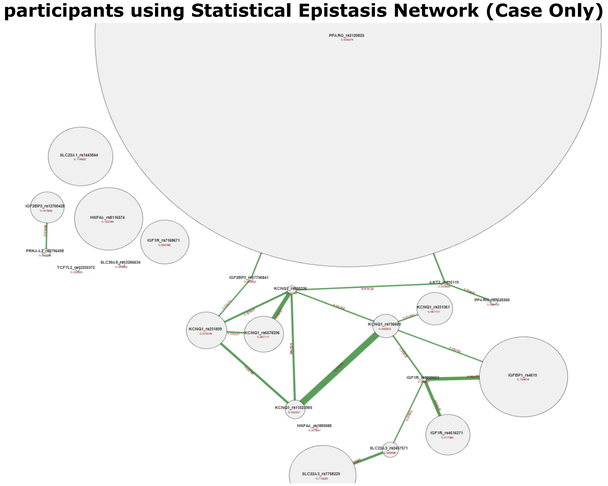

CONCLUSIONS

- 65%-75% of diabetes-related SNPs remained significantly related to PCa and disease severity under the overall, recessive, dominant and/or additive genetic models after adjusting for multiple hypothesis testing.
- PPARG_rs2120825 exhibits a strong link with aggressive PCa based on it's information gain (IG) score of 0.934. note, PPARG is protective against diabetes but plays a role in various prostate cancer pathways.
- The statistical epistasis network confirmed joint-modifying effects of SNP pairs along the IGF2BP3-KCNQ1 and KCNQ1-AKT2 axes in relation to PCa risk and aggressive disease, respectively. For instance, combined IG scores for the SNP pairs were larger than individual markers.
- The resulting markers may explain the genetic component of the protective effect of diabetes among PCa patients with non-lethal disease. Moreover, these genetic markers may lead to more effective treatment strategies against lethal PCa, especially among diabetic patients.

FUTURE DIRECTIONS

- The application of these findings in clinical trials to utilize diabetes treatment drugs to combat symptoms and severity of prostate and other cancers.
- Expansion of study to investigate findings in racially/ethnically diverse sub-populations.

CLINICAL RELEVANCE

- Seleected genetic markers can direct future pre-clinical and clinical trials as well as enhance early detection measures, treatment methods, and overall survival rates.
- The findings can prompt clinicians to screen prostate cancer patients for diabetes and encourage PCa patients to better manage their diabetes.

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