Impact of Mitogen-activated Protein Kinase (MAPK14/p38) Sequence Variant Partners on Aggressive Prostate Cancer

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INTRODUCTION

- Men diagnosed with metastatic prostate cancer (PCA) have 71% lower 5-year survival rate compared to men with local/regional disease (29% versus 100%).
- Once the cancer spreads to other organs, the disease becomes less responsive to conventional treatment strategies.
- Moreover, there is a 25% disease recurrence rate among PCA patients who undergo a radical prostatectomy.
- Consequently, new biomarkers are needed to: distinguish between lethal and non-lethal disease; and identify patients who will respond favorably to available treatment strategies.
- Apoptosis-related markers may serve as both prognostication as well as therapeutic targets for tumor classification as well as treatment strategies based on observational and pre-clinical studies.
- Apoptosis (aka, programmed cell death) is a biological process that moderates all the major hallmarks of cancer, including cell differentiation, proliferation, and whole body homeostasis. Failure to undergo this process permits survival of transformed cells, leading to genetic alteration, genomic instability, and a more severe cancer phenotype.
- Several studies have evaluated the link between apoptosis-related sequence variants and cancer outcomes.

Figure 1: Candidate Apoptosis Gene Products & Cancer

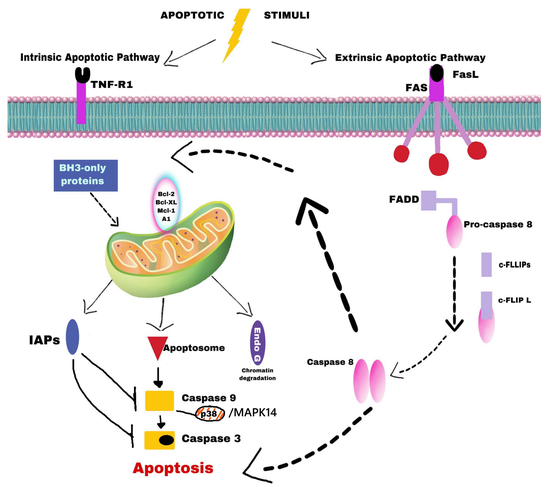

Table 1: Apoptosis gene-gene interactions in literature

Gene	Case/Control	Disease	Reference
TRAIL; DR4	91/139	Bladder Cancer	Timirci-Kahraman, 2015
FAS; FASL	91/101	Bladder Cancer	Verim, 2014
AKT3, PRKCQ	1,175/1,111	Prostate Cancer	Lavender, 2012

RESEARCH GAP

There are limited studies that focus on the impact of two sequence variants in apoptosis-related genes that jointly modify prostate cancer risk and aggressive disease.

RESEARCH OBJECTIVE

Evaluate the joint modifying effects of 10,878 single nucleotide polymorphism (SNP) pairs in relation to PCA susceptibility and aggressive disease among European-American men.

HYPOTHESIS

Apoptosis signaling Sequence variants → Changes in Macromolecules → ↑ Cell Proliferation, Cell Survival, Poorly differentiated cells → ↑ Prostate cancer risk/progression

STUDY DESIGN

- Cancer Genetics & Markers of Susceptibility (CGEMS)
  - Genome wide association study (GWAS) database
  - Access SNP data from CGEMS data portal: http://cgems.cancer.gov/ Houses SNP data for participants of the PCA screening trial of the PLCO study
  - 2277 European-Americans (1176 cases, 1101 controls)
  - Quality Control Analysis
    - •HWE p-value >0.05, genotype call rate ≥95%
    - •1168 cases (483 aggressive, 685 non aggressive), 1094 controls

METHODS

- Assess differences in the genotype frequency comparing cases and controls using Chi-square and Fisher's Exact Test
- Logistic Regression Analysis
  - Calculated risk estimates and corresponding 95% Confidence Intervals
  - Adjusted for potential confounders [Prostate-Specific Antigen (PSA) and family history of prostate cancer
- PLINK & Statistical Analysis Software (SAS) 9.4
  - Genome association analysis toolset http://zzz.bwh.harvard.edu/plink/
  - Analyzed > 10,878 pair-wise interactions
  - All p-values were adjusted for confounders and multiple hypothesis testing using the false-discovery rate (FDR)

Table 2. Clinical Utility of Apoptosis Markers as Therapeutic Targets

Gene	Treatment	Disease	Sponsor	Status	Trial Number
BRE	Everolimus; Fulvestrant	Breast Cancer	Mara Chambers	Phase I	NCT00570921
MAPK14	Regorafenib	Metastatic Colorectal Cancer	Gerald Batist	Phase II	NCT01949194
MAPK14	LY2228820; Carboplatin; Placebo; Gemcitabine	Epithelial Ovarian Cancer; Fallopian Tube Cancer; Primary Peritoneal Cancer	Eli Lilly and Company	Phase I	NCT01663857
MAPK14	LY2228820; Temozolomide; Radiotherapy	Adult Glioblastoma	Centre Jean Perrin	Phase I	NCT02364206
MAPK14	LY3007113	Metastatic Cancer	Eli Lilly and Company	Phase I	NCT01463631

RESULTS

Table 3. Impact of Individual Apoptosis-related Sequence Variants on Aggressive Prostate Cancer among study participants.

SNP Pair	Nucleotide Change	Predicted Function	hetero vs maj/maj	min/min vs maj/maj	recessive	p-trend
BNIP3L_rs2874670	G/A	--	0.521	0.004	0.0003	0.014
ABL1_rs10901291	C/T	--	0.106	0.011	0.009	0.980
TXNDC5_rs9328448	A/G	--	0.188	0.025	0.017	0.784
BCL2_rs4987786	G/T	--	0.943	0.526	0.019	0.022
BNIP3L_rs7813520	C/T	--	0.107	0.017	0.042	0.010
BRE_rs7578052	A/G	--	0.278	4.418	0.054	0.040
RET_rs2435347	A/G	--	0.021	0.545	0.062	0.986
RET_rs752978	C/T	--	0.027	0.556	0.071	0.975
RASSF5_rs7544370	A/G	--	0.256	0.044	0.089	0.042
CARD8_rs6509364	C/T	--	0.217	0.046	0.091	0.039
TNFRSF8_rs6541014	C/T	--	0.238	0.047	0.093	0.043
BNIP3L_rs3808577	T/C	--	0.132	0.048	0.131	0.033
TNFAIP8_rs1112247	G/T	--	0.010	0.014	0.155	0.007
TGFB2_rs1891467	A/G	--	0.024	0.124	0.223	0.011
RASSF5_rs11589	T/C	miRNA	0.011	0.087	0.236	0.007
FAIM_rs811322	A/G	Splicing; ESE or ESS	0.021	0.033	0.239	0.018
TNFSF12_rs4511593	C/T	--	0.072	0.112	0.296	0.045
CRADD_rs3858606	T/C	--	0.038	0.989	0.454	0.359
BRCA2_rs206115	T/C	TFBS	0.044	0.162	0.609	0.096
CASP3_rs4647693	T/C	--	0.028	0.350	0.626	0.045
BCL2L14_rs6488494	C/T	--	0.005	0.042	0.854	0.096
TNFRSF11B_rs3134057	A/G	--	0.019	0.416	0.912	0.141
TNFRSF11B_rs3134058	A/G	--	0.004	0.252	0.930	0.073

Table 4. Joint Modifying Effect of Apoptosis SNP pairs on Aggressive Prostate Cancer among PLCO study participants.

Gene_dbSNP ID	gene_dbSNP ID2	adj_gen FDR	adj_dom FDR	adj_rec FDR
RASSF5_rs11589	CASP4_rs666723	0.924	0.070	0.046
BRE_rs4666052	MAPK14_rs3804454	0.428	0.037	0.099
BIK_rs1883263	RAB15_rs2277501	1.00	0.048	0.137
CASP5_rs507879	TNFRSF1B_rs1061624	1.00	0.050	0.173

Figure 2: Predicted Functional Partners of Mitogen-activated Protein Kinase (MAPK14/p38) using string-db.org

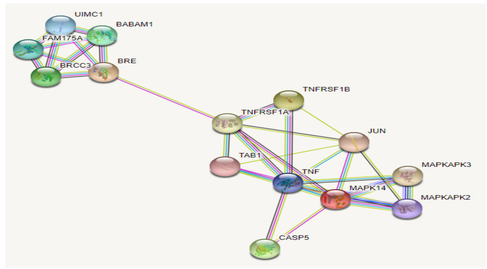

Table 5. Role of Apoptosis-related Sequence Variants in Prostate Cancer among men of European descent using an Additive Scale

Gene_dbSNP ID	# of variant Alleles	Agg (%)	Non-agg (%)	OR_{adj} (95% CI)	Unadj P-values	P-trend
RASSF5_rs11589	0	114 (16.6)	97 (20.1)	1.00 (referent)	--	0.070
CASP4_rs666723	1	244 (35.6)	201 (41.6)	1.04 (0.75, 1.45)	0.847	--
	2	253 (36.9)	117 (24.2)	1.86 (1.31, 2.64)	0.001	--
	3-4	74 (10.8)	68 (14.1)	0.93 (0.61, 1.43)	0.724	--
BRE_rs4666052	0	150 (21.9)	131 (27.1)	1.00 (referent)	--	0.579
MAPK14_rs3804454	1	303 (44.2)	191 (39.5)	1.38 (1.02, 1.85)	0.031	--
	2	186 (27.2)	117 (24.2)	1.36 (0.98, 1.90)	0.051	--
	3-4	46 (6.7)	44 (9.1)	0.91 (0.57, 1.47)	0.707	--
BIK_rs1883263	0	143 (20.9)	87 (18.1)	1.00 (referent)	--	0.422
RAB15_rs2277501	1	260 (38.0)	203 (42.1)	0.77 (0.56, 1.07)	0.131	--
	2	195 (28.5)	160 (33.2)	0.75 (0.54, 1.06)	0.084	--
	3-4	86 (12.6)	195 (28.5)	1.60 (0.98, 2.61)	0.047	--
CASP5_rs507879	0	28 (4.2)	36 (7.6)	1.00 (referent)	--	0.068
TNFRSF1B_rs1061624	1	148 (22.4)	119 (25.1)	1.63 (0.94, 2.83)	0.094	--
	2	261 (39.4)	163 (34.4)	2.06 (1.21, 3.50)	0.008	--
	3-4	225 (34.0)	156 (33.0)	1.84 (1.08, 3.14)	0.024	--

CONCLUSIONS

- Approximately 1% of the apoptosis SNP pairs were significantly associated with PCA risk (n =121) and aggressive disease (n = 117) under the overall, dominant, recessive and additive genetic models using Plink & SAS.
- 67-75% of the aforementioned SNP pairs remained significantly linked to PCA risk (n = 81) and aggressive disease (n = 88) statistical after adjusting for confounders (i.e., PSA, family history of disease).
- Four apoptosis-related SNP pairs were uniquely related to aggressive PCA on the multiplicative scale. For example, the MAPK14-BRE SNP pair was significantly associated with prostate cancer even after adjusting for confounders and multiple comparison bias.
- Inheritance of at least 3 minor alleles detected within the CASP5-TNFRSF1B axes was linked to a 1.8 fold increase in the risk of developing aggressive prostate cancer.

CLINICAL RELEVANCE

- These research findings may help to identify new genetic signatures to inform future pre-clinical and clinical trial studies.
- Validated genetic markers may help to improve or replace prostate cancer prognostication and treatment strategies.

FUTURE DIRECTIONS

- Additional studies are needed to assess whether our 4 apoptosis-related SNP pairs are predictive of aggressive disease above and beyond standard clinic-pathological parameters.
- Identify and evaluate the impact of additional apoptosis-related SNP pairs on aggressive prostate cancer, disease relapse, survival, and response to treatment using Statistical Epistasis Network (SEN) and Genetic Architecture Model Emulator for Testing & Evaluating Software (GAMETES).
- Validate or expand study findings in racially/ethnically diverse sub-populations.

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