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THE ROLE OF GENETIC AND ENVIRONMENTAL OXIDATIVE STRESS FACTORS IN PROSTATE CANCER

By

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B.S., University of Louisville, 2005
M.S., University of Louisville, 2008

A Dissertation
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Doctor of Philosophy

Department of Pharmacology and Toxicology
University of Louisville
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A Dissertation Approved on

November 19, 2010

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DEDICATION

This dissertation is dedicated to my parents
Mr. Marvin D. Lavender, Sr. and Mrs. Sharon E. Lavender
who have always supported my educational endeavors
I also want to dedicate this dissertation to my late brother Marvin Jr.,
my fiancé Shawn P. Krupp,
and my son Dohnavan T. Lydian
for never giving up on me or letting me give up on myself.

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Special thanks to my family and friends for their confidence and encouragement of my success: Mary and the late Clifford Seger, Aunt Deborah, Aunt Kathy, Uncle Skip, Uncle Frank Lavender, Sr., Victor Lavender, Jr. Kelly Seger Fox, and Theresa Ladusaw.

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ABSTRACT

THE ROLE OF GENETIC AND ENVIRONMENTAL OXIDATIVE STRESS FACTORS IN PROSTATE CANCER

Nicole A. Lavender

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Prostate cancer (PCA) development may be influenced by genetic variations within oxidative stress response (OSR) related mechanisms, such as antioxidation (e.g., carcinogen metabolism/detoxification), DNA repair, and apoptotic regulation. Excessive oxidative stress can produce DNA base changes, damage tumor suppressors, enhance proto-oncogene expression, and induce malignant transformation of cells. Persistent oxidative stress may even trigger apoptosis. Environmental reactive oxygen species (ROS) exposure attributable to lifestyle factors may exacerbate this situation by increasing oxidative stress. Therefore, it is likely that genetic variation resulting in compromised ROS capacity combined with increased environmental ROS exposure may increase PCA risk and disease aggressiveness. Consequently, this research evaluated the individual and joint modifying effects of OSR 242 genetic and 27 environmental factors in relation to PCA development among men of European and African descents. This analysis utilized a combination of traditional and innovative advanced mathematical methodologies that provided an opportunity to visualize, verify, and evaluate the

predictive accuracy of higher-order interactions as indicators of disease risk and aggressiveness.

Our analysis identified several OSR sequence variants to individually associated PCA risk among MED. In addition, antioxidative- and apoptotic-related SNPs were linked to increased disease risk in MAD. Higher order interaction analyses for across both populations detected gene-gene combinations among antioxidative- and apoptotic-related sequence targets associated with increased risk. The potential functional consequences of these polymorphisms suggest that compromised detoxification and apoptotic induction may cause increased risk for PCA and more aggressive disease. Our results also indicate that environmental factors related to meat consumption and cooking methods may contribute to PCA mechanisms. Unfortunately, we were not able to characterize environmental factors alone or combined with gene variants that are involved in PCA. This may be attributed to MDR data filtering, small MAD sample size, or limitations in some study variables (e.g., meat-derived carcinogen exposure). However, future analysis within larger study populations, more accurate exposure variables, and improved computational power may allow us to identify and validate environmental factors relevant to PCA development.

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INTRODUCTION

Prostate cancer (PCA) ranks second highest in incidence and mortality among all cancers occurring in American men, but its etiology remains is poorly understood.[1] For instance, age and family history are the strongest risk factors for PCA, but men of African descent (MAD) are 1.5-2.0 times more likely to develop the disease than any other racial or ethnic group.[1] MAD have a greater chance of being diagnosed with PCA at a younger age, with more aggressive disease and poorer prognosis.[2-4] Despite increases in five year survival rates for African-American men over the last few decades; their rates still lag far behind other races.[1] In addition to age, family history and race, genetic factors are believed play an important role in PCA initiation and progression.[1, 3, 5] Also, lifestyle habits (e.g., cigarette smoking, diet) are suggested to increase risk; indicating that environmental factors may also influence PCA.[1, 3] Based on its complexity, prostate carcinogenesis and its disparity most likely involve a multifaceted interplay between genetic and environmental contributors. Unfortunately, characterization of these factors and how their interactions modify PCA risk and disease progression are largely unknown.[3, 5-6] Essential to overcoming gaps in understanding PCA and eliminating its disparities is identification and validation of genomic profiles in important biological pathways.[3, 7-8] These profiles, along with environmental factors may serve as effective predictors of PCA risk and disease progression.[3, 7-8]

Oxidative stress response (OSR) is one such biological pathway that is becoming increasingly important in prostate carcinogenesis.[9-12] PCA development may be influenced by genetic variations within OSR related mechanisms, such as antioxidation (e.g., carcinogen metabolism/detoxification), DNA repair, and apoptotic regulation, as shown in *Figure 1*.[2-3, 9, 13] Excessive oxidative stress can produce DNA base changes, damage tumor suppressors, enhance proto-oncogene expression, and induce malignant transformation of cells.[13-14] Persistent oxidative stress may even trigger apoptosis. Environmental reactive oxygen species (ROS) exposure attributable to lifestyle factors may exacerbate this situation by increasing oxidative stress. Therefore, it is likely that genetic variation resulting in compromised ROS capacity combined with increased environmental ROS exposure may increase PCA risk and disease aggressiveness. Consequently, this research evaluated the individual and joint modifying effects of genetic and environmental OSR factors in relation to PCA among a case control population of men of European and African descents.

Figure 1. Oxidative Stress Response Mechanisms

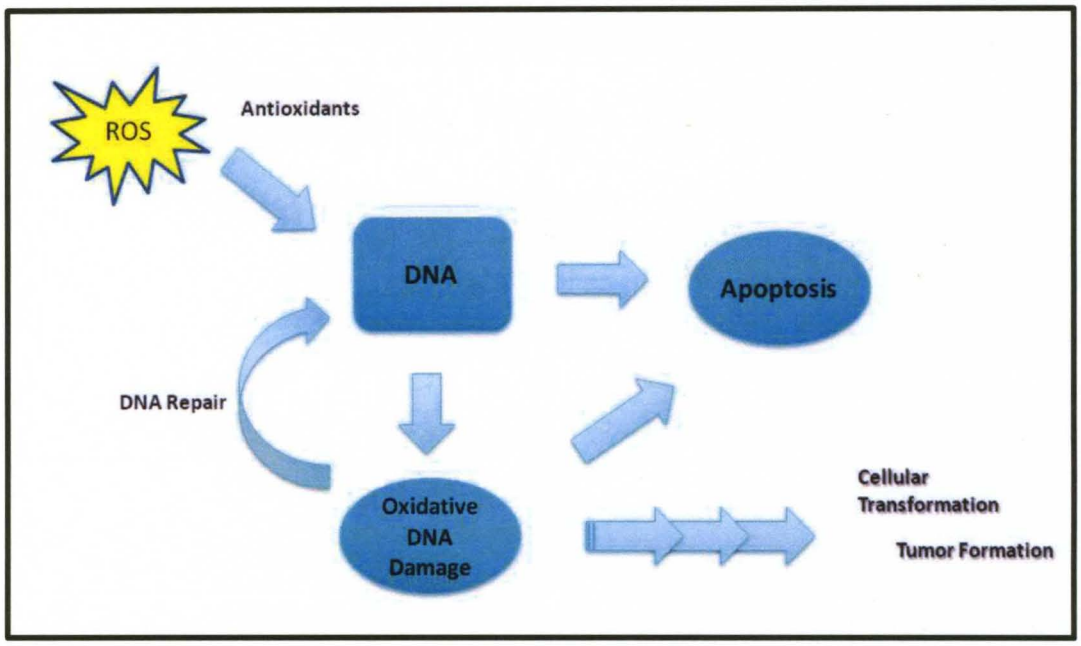


Figure 1: Oxidative Stress Response Mechanisms. Oxidative stress can result when the amount of reactive oxygen species produced exceeds that which can be removed. Prevention of oxidative stress involves multiple biological pathways, such as antioxidation (e.g., carcinogen metabolism/detoxification), DNA repair, and apoptotic regulation. Antioxidants function to remove or reduce reactive oxygen species and DNA repair corrects oxidative damage. However, excessive or persist oxidative damage may signal apoptosis to avoid induce malignant transformation of cells.

OXIDATIVE STRESS

Oxidative stress is a condition in which the amount of reactive oxygen species (ROS) produced exceeds the amount removed and can result from multiple endogenous and exogenous ROS-generating sources.[13-16] Therefore, maintenance of homeostatic ROS levels is critical to prevent these highly reactive electrophiles from interacting with biomolecules, interfering with cell signaling and promoting cellular transformation.[11, 14-17] This includes direct damage to nucleic acids and proteins, resulting in bulky adducts, oxidized DNA bases, and protein catalytic sites.[9, 14-15, 17-18] Reactive species can also modify secondary or tertiary protein structures, subsequently effecting protein function or activation.[15] In addition, ROS are capable of increasing intracellular calcium concentration, causing changes in calcium signaling that may ultimately affect protein activation states.[15] These effects can be manifested as altered gene and protein expression, cell proliferation or apoptosis.[15] Left unrepaired, accumulating ROS damage can lead to cellular transformation and ultimately progress into to cancer.[12, 15, 18-19]

CIGARETTE SMOKE AS A SOURCE OF REACTIVE OXYGEN SPECIES

Oxidative stress can arise from exogenous sources such as environmental toxins and contaminants.[13-14, 20] For example, cigarette smoke contains more than 60 known carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and aromatic amines.[21-23] Benzo[a]pyrene (BaP) is a prototypical and heavily studied PAH produced by combustion processes, such as smoke from cigarettes or grilled meats.[23-24] BaP is a suspected carcinogen capable of producing oxidative damage and bulky DNA adducts.[17] As shown in *Figure 2*, during its metabolism, BaP is bioactivated as more reactive metabolites are generated that can lead to oxidative DNA damage and possibly tumor formation. Exposure to PAHs, such as BaP, and other compounds in cigarette smoke result in higher ROS levels as a consequence of antioxidant metabolic reactions.[13, 25-26] Over time increased ROS exposure can lead to cellular oxidative stress as well as oxidative DNA damage.[13, 25-26] Inevitability, these conditions may contribute to increased cancer risk and progression.[13, 25-26]

Figure 2. Metabolism of benzo[a]pyrene[27]

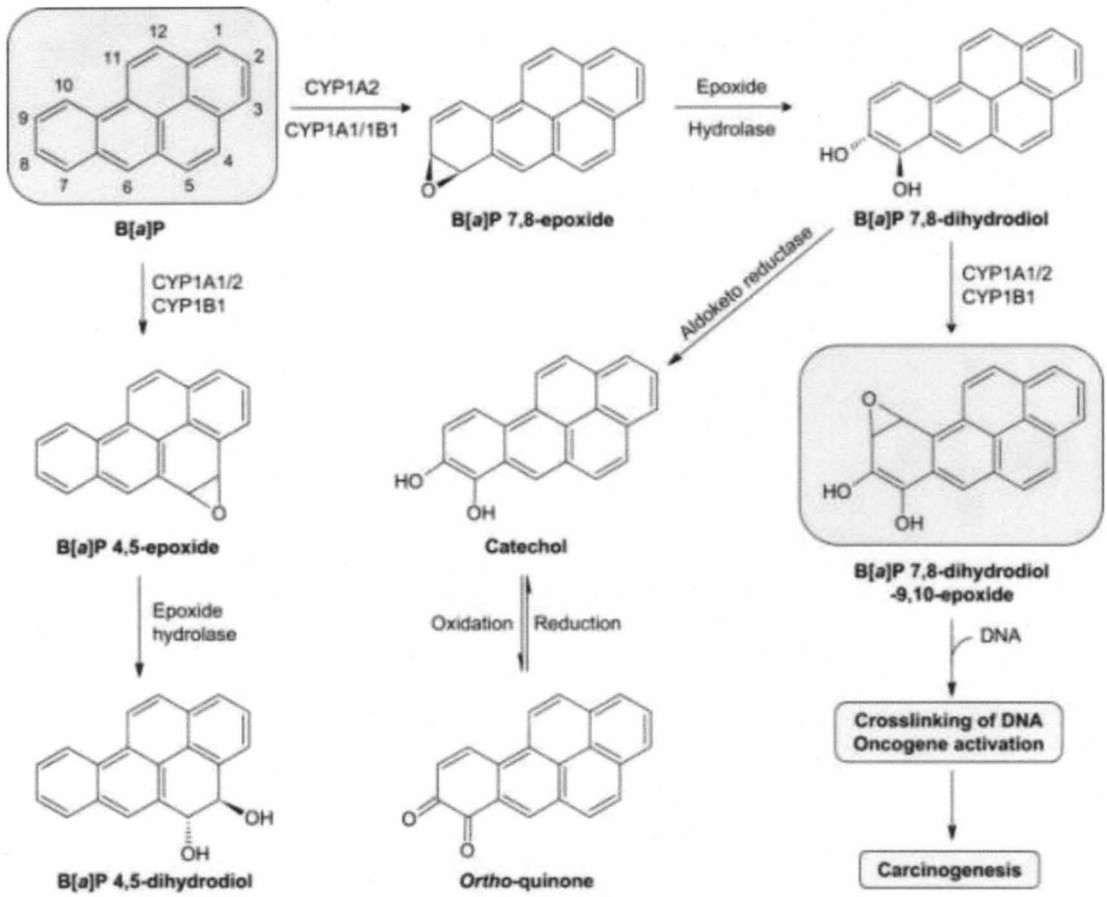


Figure 2: Metabolism of benzo[a]pyrene. The tobacco carcinogen benzo[a]pyrene can be converted to DNA-reactive compounds through its metabolism. This figure illustrates BaP metabolism by Cytochrome P450 (CYP) and Epoxide Hydrolase enzymes to generate either BaP 4,5-dihydrodiol or BaP 7,8-dihydrodiol. Although both mutagenic, stereoselectivity as well as CYPs or ROS support the generation of B[a]P 7,8-dihydrodiol-9,10-epoxide (BPDE). BPDE can ssubsequently react with DNA to produce stable guanosine adducts, ultimately leading to tumor formation. Alternatively, BaP 7,8-dihydrodiol can be reduced to catechol and further oxidized to reactive ortho-quinone.

Although cigarette smoke is a suspected contributor to carcinogenesis based on its chemical composition its role in PCA remains unclear. For example, a cohort study with over 22,000 men in the Physicians' Health Study (PHS) found no association between smoking and overall PCA risk.[28] In comparison to never smokers, the risk ratio (RR) and corresponding 95% Confidence Interval was 1.14 (1.00-1.30) for former smokers.[28] The number of cigarettes smoked per day also had no effect on risk: RR (95%CI) = 1.10 (0.78-1.55) for less than 20 cigarettes per day and RR (95%CI) = 1.10 (0.84-1.44) for 20 or more cigarettes.[28] This study also considered the number of years smoked, but found no significant effects between duration and risk [RR (95%CI) =1.69 (0.75-3.82) for 29-38 years and [RR (95%CI) = 1.05 (0.41-2.70)] for ≥ 39 years.[28] With respect to PCA mortality, smoking history [RR (95%CI) = 1.30 (0.87-1.95)], daily frequency [RR (95%CI) = 1.25 (0.87-1.95) for < 20 and 1.22 (0.54-2.74) ≥ 20 cigarettes/day] nor number of years smoked were associated with fatal PCA [RR (95%CI) = 1.69 (0.75-3.82) for 29-38 and 1.05 (0.41-2.70) ≥ 39 years].[28]

In contrast to the PHS cohort, a population-based case control study of 752 subjects found smoking at the time of diagnosis was associated with 2.7-fold increase in PCA mortality risk.[29] Another report observed a decrease in risk associated with smoking but an increase in fatality among participants of the NIH-AARP Diet and Health Study.[30] They found former and current smokers were less likely to be diagnosed with non-aggressive PCA [HR (95% CI) = 0.90 (0.87-0.93) and HR (95%CI) = 0.85 (0.80-0.90), respectively].[30] However, an increased risk of PCA mortality was associated with current and not former smokers [HR (95%CI) = 1.69 (1.25-2.27)].[30]

A recent meta-analysis cites that inconsistencies in published findings may be due to differences in study type (e.g., cohort, case-control) as well as clinical outcome (e.g., incidence versus mortality).[31] To address this issue, this analysis pooled data from 24 previous publications to evaluate role of smoking in PCA risk, progression and mortality.[31] They found former, but not current smokers were at increased risk of PCA development.[31] When the data was stratified by cigarettes smoked per day or years smoked, the increased use and duration translated to increased risk of disease and fatality.[31]

In addition to differences in study design and endpoints, conflicting results may be due to lack of considering multiple genetic and environmental factors along with smoking exposure. Biological evidence suggests that cigarette smoking may contribute to prostate carcinogenesis due to increased exposure to suspected carcinogenic and ROS-generating compounds.[13, 25-26, 30-31] However, genetic variation or other environmental oxidative stress factors can influence the detoxification and damaging effects of cigarette smoking. Therefore, our study evaluated cigarette smoking as part of a comprehensive OSR panel to characterization of the role of these factors in PCA development.

MEAT-DERIVED SOURCES OF REACTIVE OXYGEN SPECIES

HCAs such as, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP); 2-amino-3,8-dimethylimidazo[4,5-*b*]quinoxaline (MeIQx); and 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx), naturally form from creatinine or creatine, amino acids and sugar condensing when meats are cooked.[32-33] However, consumption of meat cooked at high temperatures or for prolonged periods (e.g., grilled or 'well-done'), has been found to produce high HCA exposure levels.[32, 34-36] Although these compounds are typically attributed to red meat, white (e.g., chicken, pork) and processed (e.g., cold cuts) meats are also sources of HCAs.[32-33] Since HCAs are produced during cooking, exposure is heavily influenced by method and duration used.[33] Total HCA concentration can vary, but cooked meat generally contains ≤ 100 ng/g, but can range between ≤ 1-500 ng/g.[33] Done or well-done chicken has been shown to have low or undetectable MeIQx (≤ 1) and PhIP concentrations (6-64ng/g).[37] Very well-done or grilled chicken has been shown to have high MeIQx (3ng/g) and PhIP concentrations (70-480ng/g).[37]

Similar to BaP, HCA are bioactivated by metabolic enzymes to highly reactive compounds capable of forming DNA adducts (*See Figures 3 & 4*).[11, 24, 27] Furthermore, processed meats containing nitrates/nitrites can produce nitrosamines that are also

potentially genotoxic.[33, 38] Once metabolically activated, nitrosamines function as alkylating agents capable of reacting with DNA bases.[39]

Figure 3. Major metabolism of PhIP[27]

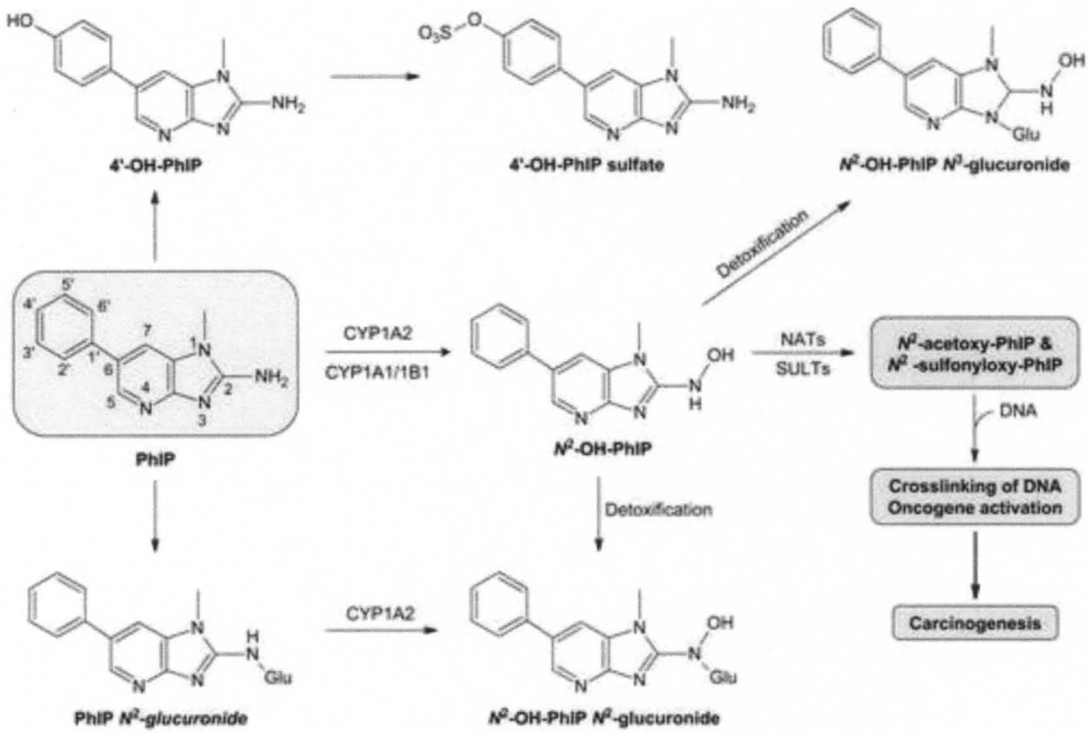


Figure 3: Major metabolism of PhIP. Cytochrome P450 enzymes bioactivate PhIP by catalyzing the *N*-oxidation of its exocyclic amine group. The resulting *N*-hydroxy-PhIP is subsequently acetylated or sulfated by acetyltransferases (NATs) or sulfotransferases (SULTs) to yield highly unstable esters that react with DNA to form adducts. Detoxification can occur via glucuronidation by UGT1A1 directly reacting with PhIP or *N*-hydroxy-PhIP. GSTA1 can also catalyze detoxification by reducing *N*-acetoxy-PhIP to PhIP.

Figure 4. MeIQx Metabolism[27]

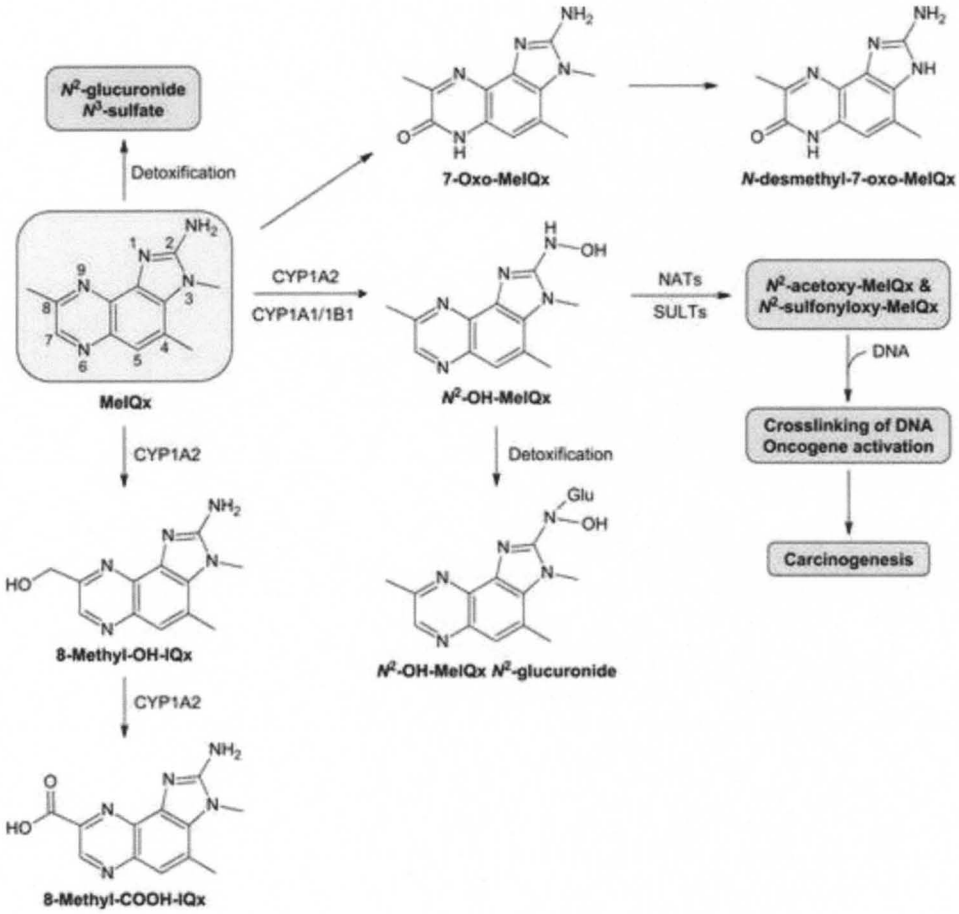


Figure 4: MeIQx metabolism. The metabolism of MeIQx is catalyzed by cytochrome P450 1A2 (CYP1A2). Subsequent acetylation or sulfation by acetyltransferases (NATs) or sulfotransferases (SULTs) produce N^2-acetoxy-MeIQx and N^2-sulfonyloxy-MeIQx. These esters can ultimately generate highly reactive arylnitrenium ions capable of cross-linking DNA molecules. Detoxification of MeIQx is achieved by either *N*-conjugation or oxidation of the C8 methyl group by CYP1A2.

Meat-derived PAHs, HCAs, and nitrosamines are all suspected carcinogens based on experimental evidence showing their ability to generate oxidative and DNA damage.[32-33] Unfortunately, studies examining the role of meat consumption and cooking methods in relation to PCA development have not yielded entirely consistent findings. For instance, a prospective study among more than 29,300 men from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial found no association between PCA risk and the consumption of red, white, or processed meats.[40] However, based on the population's median daily intake of 10g of well-done meat, men consuming more than this amount per daily had a 42% increase in disease risk [RR 1.42 (1.05-1.92; p = 0.02].[40] This study also considered the effect of meat-derived carcinogens (i.e., PhIP, DiMeIQx, MeIQx, BaP) on PCA; but only high levels of PhIP (>269.2 ng/day) was associated with an increase in risk [RR 1.22 (1.01-1.48; p = 0.04].[40]

A more recent study evaluated the effect of meat intake and these carcinogens on PCA risk, aggressiveness, and fatality among participants of the NIH-AARP Diet and Health Study.[38] Within a study cohort of more than 175,000 men, consumption of both red and processed meats was associated with an increased of PCA risk and advanced disease [hazard ratio(HR) = 1.13 (1.02-1.25); p_{trend} = 0.003 and HR = 1.45 (1.10-1.92); p_{trend} = 0.006, respectively.[38]

A 2009 review of published reports examining the role well-done meat and HCA on cancer risk concluded that most evidence suggests that high intake of well-done meat and exposure to meat-derived carcinogens increase PCA risk.[24] This included a 1999 population-based study of 317 cases and 480 controls that found well-done beef

and streak associated with an 1.7-fold increase in risk [OR (95%CI) = 1.7 (1.1-2.8)].[24] However, no associations were detected for other well-done meats or individual and total HCA exposure.[24] This review also referenced a 2008 cohort study of 613 cases (140 advanced) that observed an increase in PCA risk [RR (95%CI) = 1.26 (1.02-1.54)] and advanced [RR (95%CI) = 1.97 (1.26-3.08)] disease associated with well- / very-well done meat consumption.[24, 34]

Inconsistent findings from previous studies may be attributed to additional factors that may modify meat-carcinogen exposure or limited statistical power to model these effects. Carcinogenic dietary exposures are difficult to measure, since levels can fluctuate according to the type of meat, as well as cooking duration and temperature. Furthermore, exposure levels are also affected by genetic variants and other dietary habits (e.g., vegetable intake, vitamin/supplement use) that contribute to ROS metabolizing/ detoxifying capacity. To address this shortcoming, this study evaluated meat intake, cooking method and duration, meat-derived carcinogens; alone and combined with multiple genetic and environmental OSR factors.

DIETARY ANTIOXIDANTS

In contrast to meat consumption, a diet abundant in fruits and vegetables is presumed to reduce the risk of developing PCA.[32, 41-42] These foods contain dietary antioxidants, such as carotenoids, vitamins C & E, and selenium, capable of protecting cells from oxidative stress.[23, 32, 41] They have also been shown to possess certain anti-carcinogenic properties that may retard cancer-cell development and inhibit tumor promotion.[41] Compounds found in cruciferous vegetables (e.g., glucosinolates, isothiocyanates, flavonoids) have been shown to protect cells from DNA damage, induce apoptosis, and inhibit cell proliferation of PCA.[42] For example, some flavonoids have antioxidant properties capable of binding of free radicals, and consequently reducing oxidative DNA damage and possibly preventing cancer.[42] Vitamin E is a major lipid-soluble antioxidant in cell membranes; capable of scavenging free radicals; inducing apoptosis; and inhibiting expression of prostate specific antigen and androgen receptor mRNA as well as protein kinase C activity.[23, 41] Similarly, vitamin C is a potent ROS scavenger that can also induce apoptosis and reduce lipid peroxidation in cellular membranes.[23, 41] Selenium has been shown to induce apoptosis, inhibit cellular proliferation and angiogenesis as well.[42]

Based on their biological functions, dietary antioxidants are believed to protect against PCA development, but epidemiological research investigating this claim is largely

inconclusive.[42-44] For example, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study examined the effects of family history and lifestyle factors (e.g., micronutrient intake) on disease risk.[44] This placebo-controlled, double-blinded study was designed primarily as a prevention trial and consisted of more than 29,000 Finnish male smokers.[44] Study participants received either a placebo or a daily supplement of 50 mg α-tocopheryl acetate, 20 mg β-carotene or both α-tocopheryl acetate and β-carotene.[44] Among men with no family history of PCA, neither vitamin was significantly associated with disease risk [α-tocopheryl acetate: RR (95%CI) = 0.83 (0.74-0.94) and β-carotene: RR (95%CI) = 1.09 (0.97-1.23)].[44] There were also no statistically significant findings for subjects with a family history of PCA, however, their findings suggest that elevated β-carotene serum levels increase risk (interaction $p = 0.08$).[44] Low β-carotene serum levels nor α-tocopheryl/ β-carotene supplement use affected PCA risk among men with a family history of the disease.[44]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), investigated whether selenium and vitamin E, taken alone or combined could prevent PCA with little or no toxicity in relatively healthy men.[45] Among more than 35,500 men from multiple sites in the United States, Canada, and Puerto Rico, this project found that daily oral use of 200μg selenium or 400 IU vitamin E, individually or together did not prevent PCA.[45]

A study conducted within the Cancer Prevention Study Nutrition Cohort observed no protective effects against PCA from vitamin E use.[46] However, when only current smokers were considered, a decrease in risk was detected for those with regular or long-term supplement use compared to non-users.[46]

In a 2009 publication, Zhang et al. examined the use of multivitamins and supplements in relation to PCA among a hospital-based case-control population.[47] They found no statistically significant associations between single supplement and multivitamin use of vitamin E, selenium, zinc, and β-carotene in relation to disease risk or aggressiveness [$p \geq 0.089$].[47] In contrast to the Cancer Prevention Study findings, this report determined there was no impact of vitamin E on PCA risk in smokers.[47] The effects of 11 micronutrients [i.e., 7 carotenoids, retinol (vitamin A), vitamin E] on PCA was examined using plasma concentration collected from male subjects of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[48] Although no significant associations were observed in relation to risk ($p_{trend} \geq 0.50$), lycopene alone and the combined carotenoids were both shown to protect against advanced disease ($p_{trend} \leq 0.05$).[48]

The lack of consistent findings may be due to failure to consider multiple genetic and environmental factors along with dietary antioxidants that may jointly modify PCA susceptibility and aggressiveness. Consequently, this study investigated this multiple dietary factors (e.g., meat, vegetable, vitamin/supplement intake) as part of our unique panel OSR-related panel to elucidate their role in PCA development.

GENETIC OXIDATIVE STRESS RESPONSE PATHWAYS

As a consequence of the potentially damaging effects of ROS, cells have multiple protective OSR mechanisms to prevent excess ROS, oxidative stress and genetic damage.[15, 18-19] Several biological processes are relevant to oxidative stress status in prostate cells, including detoxification (via antioxidant enzymes), DNA repair, and apoptosis.[2-3, 9, 13]

Antioxidation Targets & Prostate Cancer

Antioxidant enzymes are a major cellular oxidative stress defense mechanism in the removal of ROS.[11, 14, 49-50] These enzymes reduce ROS to produce a less reactive species and thereby prevent cellular damage.[9, 14, 19, 49-51] For example, superoxide dismutases (SODs) scavenge superoxide radicals, converting them to hydrogen peroxide molecules.[50] Reactive hydrogen peroxide is then subsequently removed by either catalase (CAT) or glutathione peroxidases (GPX).[15, 19, 50] Other antioxidative-related enzymes important in detoxification and metabolism include, cytochrome P450s (CYPs), epoxide hydrolase (EPHX1), uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGTs), sulfotransferases (SULTs), *N*-acetyltransferases (NATs) and glutathione S-transferases (GSTs) [*See Table 1*].[17, 34, 52] CYPs are a diverse class of enzymes that catalyze the oxidation or reduction of endogenous and exogenous substrates.[17, 34] Ephx1 converts epoxides from aromatic compounds to dihydrodiols that can be conjugated and excreted.[52] There are two *NAT* genes (*NAT1* and *NAT2*) that function in the metabolism of arylamines by catalyzing the transfer of an acetyl group from acetyl-CoA.[17, 34] In contrast, other phase II metabolizing enzymes function by conjugating xenobiotics to less reactive, water soluble compounds that are more easily excreted.[17, 52] More specifically, ugt enzymes transfer a glucuronic acid; sults catalyze the sulfate conjugation; and gsts catalyze the conjugation of ROS to glutathione to produce less reactive, water soluble compounds that are more easily excreted.[19, 53]

Table 1. Phase I & II Metabolizing Enzymes[17, 52]

	Gene	Function
Phase I	Cytochrome P450 (CYP)	Catalyze oxidation or reduction of many xenobiotics, including PAHs that may be metabolized to carcinogenic intermediates.
	Epoxide hydrolase 1 (EPHX1)	Catalyzes conversion of epoxides to dihydrodiols to detoxify or bioactivate aromatic compounds
Phase II	Glutathione S-transferase (GSTs)	Catalyze the conjugation of reduced glutathione to electrophilic and hydrophobic compounds
	N-acetyltransferase (NATs)	Catalyze the transfer of an acetyl group from acetyl-CoA to detoxify or bioactivate xenobiotic substrates
	Sulfotransferases (SULTs)	Catalyze the sulfate conjugation of many xenobiotic compounds
	UDP-glucuronosyltransferase (UGTs)	Catalyze the conjugation of glucuronic acid to many xenobiotic compounds

Unfortunately, in some cases antioxidation reactions can convert compounds such as PAHs and HCAs derived from cigarette smoke or meat to more reactive intermediates.[27, 40, 54-56] As shown in figure 4, cyps catalyze the *N*-hydroxylation of MeIQx which can be further metabolized by *NATs* or *SULTs* to form N^2-acetoxy-MeIQx or N^2-sulfonyloxy-MeIQx.[27, 57] These highly reactive compounds can form DNA adducts that may lead to tumor formation if left unrepaired.[27, 57] This is also true for endogenous ROS generated from cellular processes (e.g., respiration, electron-transport chain) such as superoxide radicals.[13, 17, 58] Although, *SODs* scavenge these radicals, this reaction produces hydrogen peroxide which is a more unstable ROS.[13, 17, 58] Without intervention from *CAT* or *GPX*, hydrogen peroxide can interfere with cellular signaling.[13, 17, 58]

Due to their function in detoxification of potentially damaging ROS and carcinogens that may be critical to prostate carcinogenesis, antioxidant enzymes have been commonly studied in PCA risk.[3, 21, 59-60] It has been previously shown that men with PCA possess lower antioxidant enzyme levels in prostate tissues compared to both healthy controls and men with benign prostatic hyperplasia (BPH).[59] Several previous

studies have shown PCA tissues contain higher amounts of ROS and oxidative DNA damage.[21, 59-60] Also, *in vitro* studies have shown ROS to be associated with PCA progression and more aggressive phenotypes.[9, 61]

Although, genetic variation in polymorphic antioxidation-related genes has been implicated in the etiology of prostate cancer and other malignancies, the associations are not accepted across all observational studies.[53, 59, 62-66] For instance, a 2006 publication examined the effect of *GSTM1* and *T1* gene deletions as well as the *GSTP1* $Ile^{105}Val$ SNP on PCA susceptibility.[67] These variants are believed to increase disease risk due to decreased detoxification capacity.[67] This population-based study consisted of 590 cases (559 Caucasian, 31 African-American) and 538 controls (523 Caucasian, 15 African-American).[67] Among the Caucasian subjects, they found deletion of *GSTM1* was moderately associated with increased risk [OR (95%CI) = 1.54 (1.19-2.01)].[67] However, neither the *GSTT1* deletion nor *GSTP1* SNP modified risk in the Caucasians participants.[67] No associations were detected in the African-Americans, but this is most likely due to the limited sample size.[67] Although a larger study of 378 African-Americans (274 cases and 104 controls) investigated the *GSTP1* 105 variant and did not find any statistically significant effects in relation to PCA risk [OR (95%CI) = 1.30 (0.43-3.94); p = 0.65][68]

Nock et al. 2007 examined polymorphic PAH-metabolizing genes and cigarette smoking in PCA tumors collected from 210 Caucasian and 177 African-American subjects.[36] More specifically, this study evaluated the individual and joint effects of *CYP1A1* $Ile^{462}Val$; *CYP1B1* $Ala^{119}Ser$ and $Leu^{432}Val$; *EPHX1* $Tyr^{113}His$ and $His^{139}Arg$; *CYP3A4* $A^{-392}G$; *GSTM1* gene deletion; *GSTP1* $Ile^{105}Val$; and cigarette smoking in relation to PAH-

DNA adducts in PCA tumor and adjacent non-tumor cells.[36] Cigarette smoking was stratified by never- or ever-smokers with ever smokers including former and current smokers. They did not observe any significant effects in the total population, but Caucasian participants possessing *EPHX1* ^{139}Arg alleles had higher adduct levels in tumor and non-tumor cells compared to the *EPHX1* ^{139}His alleles ($p = 0.03$).[36] For Caucasian subjects with the heterozygous *GSTP1 105* genotype higher adducts were found in non-tumor cell compared to those with two *GSTP1* ^{105}Ile alleles ($p = 0.02$).[36] The *EPHX1* ^{139}Arg alleles were also associated with higher adduct levels in the African-American subjects, but only in non-tumor cells compared to the *EPHX1* ^{139}His alleles ($p = 0.07$).[36] In the African-Americans, possessing at least one variant *CYP1B1* 432Val allele was linked to higher adduct levels in tumor cells ($p \leq 0.04$).[36]

A more recent study evaluated gene-environment interactions between *CYP1A1* and *EPHX1* gene variants and cigarette smoking in relation to PCA risk among a case-control Indian population (130 cases, 140 controls).[69] No significant effects were observed in non-smokers possessing the variant *CYP1A1* or *EPHX1* ^{139}*Arg* alleles ($p \geq 0.54$).[69] However, the variant *EPHX1* ^{113}*His* allele, alone and combined with cigarette smoking was associated with an increase at least a 2.6-fold increase in risk ($p \geq 0.008$).[69] They found smokers carrying the *CYP1A1* polymorphism had a 1.2-to 1.6-fold increase in risk, while those with at least one variant *EPHX1* ^{139}*Arg* was associated with a 3.0-fold increase in risk.[69]

Although studies such as these may be limited by sample size or scope; investigating polymorphic xenobiotic metabolizing genes combined with environmental

ROS exposures in relation to PCA development has failed to produce consistent findings.[34-35, 43, 70] For instance, Koutros et al. 2009 evaluated 127 polymorphisms across multiple metabolizing genes (*CYP1A1, CYP1A2, CYP1B1, GSTA1, GSTM1, GSTM3, GSTP1, NAT1, NAT2, SULT1A1, SULT1A2*, and *UGT1A* locus) and meat-derived HCAs in relation to PCA susceptibility within a subset participants selected from the Prostate Lung Colorectal and Ovarian Cancer Screening Trial.[34] Meat-derived carcinogen exposures was estimated using questionnaire data regarding meat consumption and cooking method for a study population of 1126 cases (473 non-aggressive, 654 aggressive) and 1127 controls.[34] From this analysis, possession of at least one or more variant *GSTM3* ^{356}*Ser* was associated with increased risk among subjects in the highest percentile of DiMeIQx compared to subjects in the lowest percentile [OR (95%CI) = 2.3 (1.2 – 4.7). HCA-SNP analyses revealed significant interactions between *GSTM3* ^{356}*Ser* and MeIQx and DiMeIQx (p = 0.001). Although data generated from this study suggests joint risk effects may exist among *GSTP1* ^{105}*Val* or the *UGT1A* locus and meat-derived carcinogens, the interactions were no longer significance after adjusting for False Discovery Rate (FDR).[34]

More recently, Sharma et al. examined eight *NAT1* and seven *NAT2* SNPs, along with well-done red meat consumption in relation to PCA risk using a multi-ethnic cohort population (2106 cases, 2063 controls).[70] Individual and multivariate statistical analyses were conducted using possession of the *NAT1*10* or 'slow' *NAT2* phenotypes and frequent well-done red meat consumption designated as the high risk groups.[70] No

single or combined risk effects were observed between variant *NAT1* or *NAT2* acetylors and well-done red meat intake.[70]

Discrepancies across antioxidative gene variant study findings may be partially attributed to failure to consider interactions among antioxidation sequence variants along with downstream targets such as those involved in DNA repair and cell death.

Base Excision Repair (BER) & Prostate Cancer

In the event that antioxidant enzymes are not capable of removing ROS, DNA repair mechanisms help prevent replication of damaged nucleotides.[16, 18, 49, 71] ROS can damage DNA by oxidizing bases, resulting in mismatches or adducts and that can possibly lead to deletions, mutations and distortions in the helix.[18] One of the most important pathways for removing oxidative DNA damage is base excision repair (BER).[72] BER incorporates several enzymes which recognize and remove an erroneous base. The process, shown in *Figure 5*, is initiated by a glycosylase, such as 8-oxoguanine glycosylase (*OGG1*) or Thymine-DNA glycosylase (*TDG*).[73-75] The glycosylase catalyzes the cleavage of the helical backbone to liberate the damaged base, creating an abasic site.[73-75] Then the phosphodiester bond on the 5' side of the intact apurinic/apyrimidinic site is incised by either a glycosylase with lyase activity (bifunctional) or an apurinic/apyrimidinic endonuclease (*APEX1*).[73-75] Finally, repair is completed with the recruitment of DNA polymerase β and ligase (*LIG1*) by X-ray repair cross-complementing group 1 (*XRCC1*) along with poly (ADP-ribose) polymerase (*PARP1*).[73-75]

Figure 5. Base Excision DNA Repair[76]

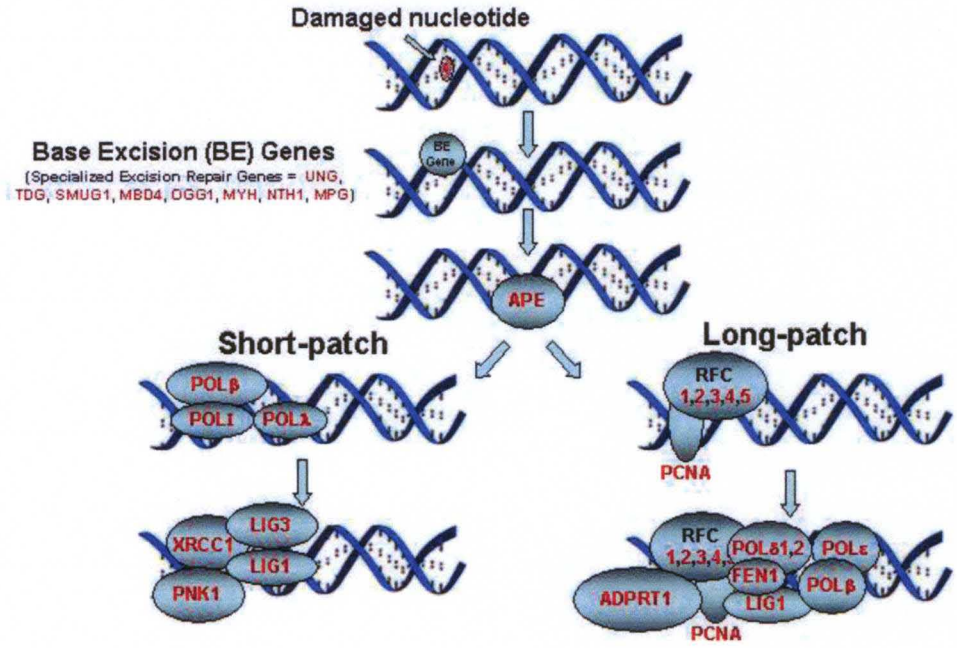


Figure 5: Base Excision DNA Repair. BER is initiated by a glycosylase which catalyzes the cleavage of the helical backbone to liberate the damaged base. The phosphodiester bond on the 5′ side of the abasic site is incised by either a glycosylase with lyase activity (bifunctional) or an apurinic/apyrimidinic endonuclease (APE). X-ray repair cross-complementing group 1 (*XRCC1*) or poly (ADP-ribose) polymerase (*PARP1*) recruit polymerase β and ligase (*LIG1*) to complete the repair process.

Several investigators have examined if non-sysnonymous BER variants (e.g., *OGG1, APEX1, XRCC1*) alter DNA repair capacity of encoded proteins and ultimately influence cancer risk.[77-83] Previous studies on the functional consequence of the *OGG1* Ser^{326}Cys polymorphism observed a decreased capacity to repair 8-hydroxydeoxyguanosine (8-OHdG) adducts linked with the ^{326}Cys allele.[84-86] Yamane et al. 2003 demonstrated that the *OGG1* ^{326}Cys allele had a significantly lower capacity to suppress spontaneous mutagenesis relative to the ^{326}Ser protein using complementation activity assay in *Escherichia coli*.[84] In addition, two reports found higher levels of 8-OHdG in biospecimens (e.g., peripheral blood lymphocyte DNA or cord blood) collected from individuals with the Cys/Cys genotype relative to those who were Ser/Ser carriers.[85-86] Another study revealed that the *OGG1* Cys/Cys genotype was predictive of prostate cancer at the time of biopsy among 2,088 predominantly Caucasian men prescreened with prostate-specific antigen and digital rectal exam.[87]

Although the *APEX1* Asp^{148}Glu amino acid change does not appear to influence endonuclease activity, it may reduce the ability for *APEX1* to communicate with other BER proteins (e.g., *XRCC1*), resulting in a reduced BER efficiency and thus a potential link to carcinogenesis.[88-90] When the *APEX1* ^{148}Glu allele was considered in combination with the *XRCC1* ^{399}Gln variant allele in Caucasians (258 cases and 215 controls), Chen et al. 2006 observed a 2-3 fold increase in the risk of developing PCA relative to those with the referent genotype.[91] The *XRCC1* Arg^{399}Gln polymorphism, located within the *PARP*-binding domain has been extensively examined and the presence of the Gln allele has been associated with reduced DNA repair capacity as reflected in the persistence of

bulky DNA adducts and genotoxic DNA damage.[92-94] However, when examined individually, no investigators have found any association between this polymorphism and DNA adducts.[92] Similar to Chen et al. 2006, other studies suggest the variant *XRCC1* allele may play a role in PCA risk when considered with other DNA repair targets.[79, 95-96] For instance, Rybicki et al. (2004) observed a 4.8-fold increase in the risk of developing PCA among individuals with both the *XRCC1* ^{399}Gln/Gln and *XPD* ^{312}Asn/Asn genotypes.[79]

Unfortunately, there are limited published reports on whether complex interactions among BER genes and up-/ downstream targets in relation to PCA susceptibility, particularly among high-risk MAD. To clarify the role of BER genes alone and in concert with other OSR targets, we evaluated their individual and joint modifying effects in relation to PCA development.

Apoptosis & Prostate Cancer

In cases of persistent, severe or unrepaired oxidative damage, cells will signal apoptosis as a protective measure to prevent the replication and advancement of cellular damage into tumorigenesis.[97-100] Apoptosis is an important biological process for cell differentiation, proliferation, death and overall whole body homeostasis.[98, 100-101] As shown in *Table 2*, this process is controlled by pro- and anti-apoptosis genes that function to induce or block apoptosis, respectively.[98-100, 102] Regulation of these genes is critical in prevention of tumor formation and carcinogenesis.[97-99] Clonal expansion and tumor growth are believed to result from increased cell proliferation and decreased apoptotic cell death.[98] Failure to undergo apoptosis may enable survival of transformed cells that are prone to undergo further genetic alteration and show genomic instability, leading to more invasive phenotypes.[100]

Table 2. Major genes involved in the regulation of Apoptosis[52]

	Gene	Function
Pro- & Anti-apoptotic	Tumor Protein 53 (TP53)	Transcriptionally regulates target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism in response to cellular stresses
	Tumor Protein p53 inducible nuclear protein 1 (TP53INP)	Regulates cell cycle progression and apoptosis, dependently & independently from TP53
	Tumor Necrosis Factor (TNF)	Binds and functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR to regulate cell proliferation, differentiation, apoptosis
	BCL2-like 1 (BCL2L1)	(AKA: BCL-XL); Outer mitochondrial membrane protein that regulates membrane potential, controlling ROS production and cytochrome c release. Exists in two isoforms: the longer isoform acts as an apoptotic inhibitor and the shorter is pro-apoptotic
Pro-apoptotic	Fas & FAS ligand (FASL)	Death domain-containing receptor, binding of FASL to FAS allows the formation of a death-inducing signaling complex
	Caspases (CASP)	Cysteine-aspartic acid protease (caspase) gene family involved in the execution of cell apoptosis
	Bcl2-associated X (BAX)	Forms a heterodimer with BCL2 and functions as an apoptotic activator involved mitochondrial release of cytochrome c
	BCL2-antagonist/killer 1 (BAK1)	Induces apoptosis by increasing cytochrome c release; interacts with the TP53 after exposure to cell stress
	BCL2-associated agonist of cell death (BAD)	Forming heterodimers with BCL-XL and BCL-2 to reverse their death repressor activity.
	BCL2-like 10 (BCL2L10)	Interact with BCL2 proteins (e.g., BCL2, BCL2L1/BCL-XL, and BAX)
	BCL2-like 11 (BCL2L11)	(AKA BIM); Interacts with other members of the BCL-2 protein family (e.g., BCL2, BCL2L1/BCL-XL), and MCL1) to act as an apoptotic activator
	BCL2-like 14 (BCL2L14)	apoptosis facilitator
	BH3 interacting domain death agonist (BID)	Induced by caspase-8 (CASP8); CASP8 cleaves this encoded protein, and the COOH-terminal part translocates to mitochondria and triggers cytochrome c release
	BCL2-interacting killer (BIK)	Interacts with survival-promoting proteins to enhance programmed cell death; possible target for anti-apoptotic proteins
Anti-apoptotic	B-cell CLL/lymphoma 2 (BCL2)	Blocks the release of pro-apoptotic cytochrome c from and block caspase activation.
	BCL2-related protein A1 (BCL2A1)	Reduces cytochrome c release from mitochondria and blocks caspase activation
	Baculoviral IAP repeat-containing 2 (BIRC2)	(AKA CIAP1); Inhibits apoptosis by binding to tumor necrosis factor receptor-associated factors TRAF1 and TRAF2
	BCL2/adenovirus E1B 19kDa interacting protein 3-like (BNIP3L)	(AKA NIX); BCL2/adenovirus E1B 19 kd-interacting protein (BNIP) gene that may function simultaneously with BNIP3 and play a role in tumor suppression

One of the key genes in apoptotic induction is *Tumor Protein 53* (*TP53*) which is regarded as "guardian of the genome" due to its multiple functions in regulating the cell cycle and supporting genomic stability.[103-104] As a transcription factor (TF) for apoptotic

genes, *TP53* can directly and indirectly trigger permanent or temporary arrest of the cell cycle as well as induce apoptosis when DNA repair cannot be achieved.[104-105] *TP53*'s cycle cell regulatory activity is dictated from intrinsic (cytotoxic stress) or extrinsic (outside the cell) signals that indicate the presence of oxidative damage.[104-105] Intrinsic signals initiated by cytotoxic damage or stress can activate *TP53* to arrest the cell cycle or induce apoptosis. [104-106] Extrinsic signals are mediated through the binding of ligands [e.g., tumor necrosis factor (tnf), fas ligand (fasl)], to their respective cellular membrane 'death' receptors.[106] [*See Figure 6*] This interaction can signal apoptosis or survival to downstream targets, such as *BCL2*-related genes.[100] The *BCL2* family consists of pro- and anti-apoptotic proteins capable of inducing or blocking cell death, respectively.[6, 107-109] *BCL2* regulates the transport of molecules and apoptotic transcription factors through mitochondria channels based on the oxidative state of the cell.[107] *BAK1* (BCL2 Antagonist Killer-1) and *BIM* (BCL2-Interacting Protein) help accelerate channel opening. These proteins, as well as *BAX* (BCL2 Associated X-protein), these are initially inactive and must translocate to mitochondria to induce apoptosis.[108-109] They can either forming pores in mitochondria directly or by binding to and antagonizing anti-apoptotic targets, such as *BCL2* or *BCL-XL* (*BCL2* Related Protein Long Isoform).[108-109]

BCL2 genes can activate additional apoptotic induction pathways, including the cysteine-dependent aspartate-specific proteases or caspases (casps).[97, 107] For example, cytochrome-C from the mitochondria binds to Apoptotic Protease Activating Factor-1 (APAF1) with dATP and Procaspase 9 to activate Caspase 9.[106] The activation of Caspase 9 leads to activation of the caspase cascade.[106] Casp proteins can activate downstream

apoptotic events by either extrinsic (receptor-mediated) or intrinsic (mitochondrial) cellular pathways.[100]

Figure 6. Apoptosis[110]

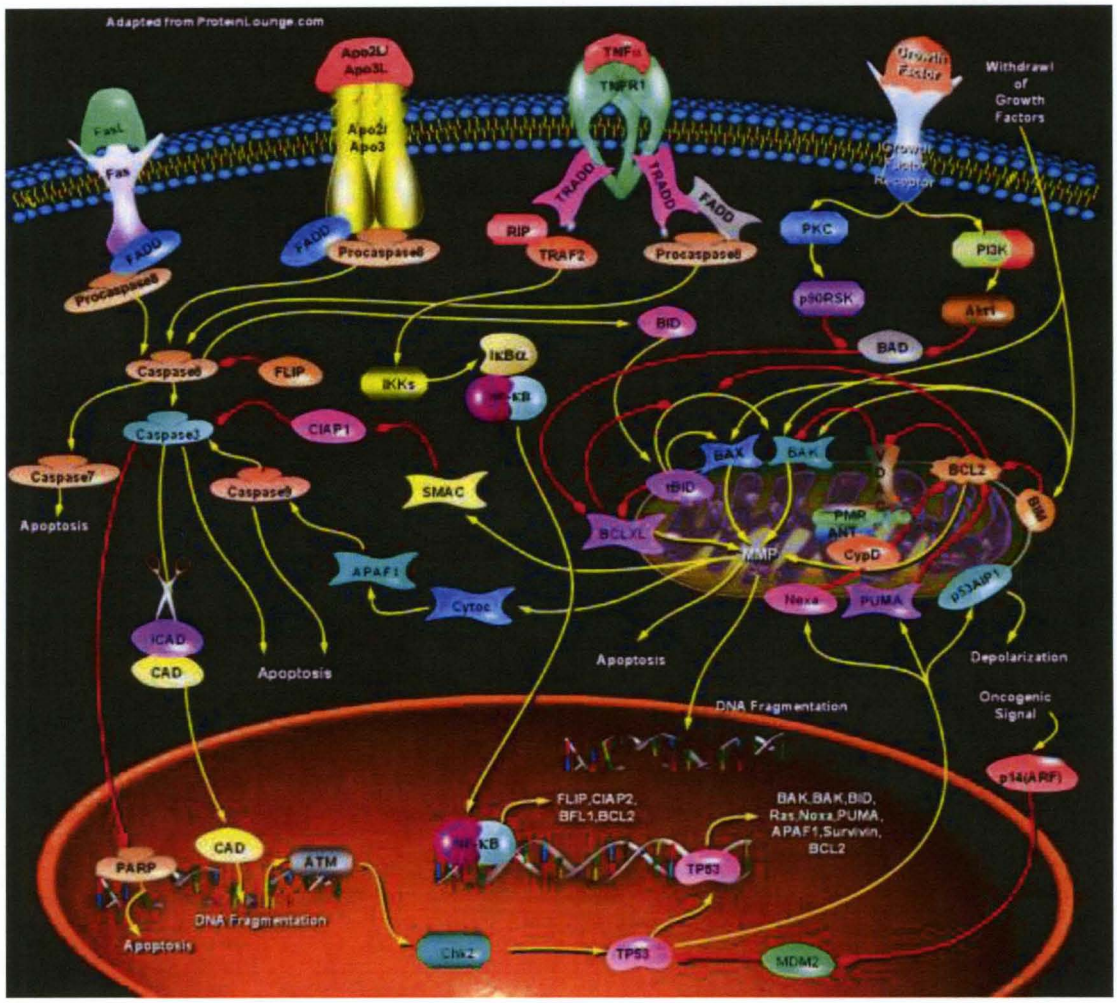


Figure 6: Apoptosis. Apoptosis is a complex process involving multiple proteins that can either block or induce cell death. Pro-apoptotic proteins can be activated by extrinsic or intrinsic signaling that indicate to the cell is no longer needed or damaged beyond repair. In the extrinsic pathway, signaling begins outside a cell, when conditions in the extracellular environment determine that a cell must die. This signaling activates cell surface receptors that in turn transmit the apoptotic signal to downstream targets, such as BID (Bcl2 Interacting Protein). The COOH-terminal part of BID translocates to the mitochondria and triggers the release of cytochrome-C. The released cytochrome-C binds to Apoptotic Protease Activating Factor-1 (APAF1) with dATP and Procaspase 9 to activate Caspase 9. The activation of Caspase 9 leads to activation of the caspase cascade. The intrinsic apoptosis pathway is initiated by cytotoxic stress or damage. TP53 (aka P53) is a sensor of cellular stress and is a critical activator of the intrinsic pathway. As a transcription factor, TP53 can initiate apoptosis by either activating pro-apoptotic (BAX) or suppressing anti-apoptotic (BAK1 aka BAK) BCL2-related targets.

Apoptotic targets play an important role in PCA progression as well as disease susceptibility. For instance, *TP53*, which is the most commonly mutated tumor suppressor in cancer, has a low mutation rate in primary PCA but is frequently mutated in metastatic PCA.[5] Nam et al. 2005 reported that the TNF promoter SNP at -308 associated with increased TNF transcription activity was linked to PCA risk in population of 996 cases and 1092 controls ($p = 0.04$).[87] Studies have also found that expression of the TNF receptor family member FAS is reduced in PCA tissues, suggesting SNPs decreasing FAS or FASL functionality may contribute to disease progression.[111-112] Also, overexpression of bcl-2 protein in prostate tumor epithelial cells has been correlated with tumor progression to androgen independent disease (e.g., more aggressive phenotypes).[6] In fact, increased expression of either *TP53 or BCL2* has each been linked to poorer PCA prognosis.[5-6] Another report found a decrease in the risk of developing PCA among African-American men harboring the low expressing *BCL2* -938 AA genotype.[97] Higher bcl-2 immunostaining has been associated with more advanced disease (i.e., higher Gleason grade), suggesting that an increase in this anti-apoptotic protein may occur during PCA progression.[113] McConkey et al. also revealed an increase in bcl-2 expression levels and loss of pro-apoptotic bax expression in prostatic carcinoma cells.[114]

Based on these studies, it is apparent that genetic alterations in apoptosis-related genes have an important role in the pathogenesis of PCA, presumably due to an accumulation of genetically altered and transformed cells. Previous studies indicate that in isolation, apoptotic SNPs may minimally influence PCA progression.[5-6, 87, 97, 113-115]

However, combinations of variants may have a joint modifying effect. To our knowledge, there are limited published reports on the relationship between apoptotic polymorphisms, alone or in combination with variations in other biological pathways, and their association with PCA development.

HYPOTHESIS STATEMENT

This research project hypothesizes that inheritance of alleles in oxidative stress response (OSR) genes associated with compromised OSR capacity, combined with exposure to environmental oxidative stress factors will increase prostate cancer susceptibility and aggressiveness.

SPECIFIC AIMS

The following three specific aims were executed to evaluate the hypothesis of this study:

Specific Aim 1: Determine the single- and joint-modifying effects of variations within oxidative stress response (OSR)-related genes in relation to PCA risk. Oxidative stress is a condition in which the amount of reactive oxygen species (ROS) produced exceeds the amount that can be removed.[13-16] Several biological processes have relevant effects on the oxidative stress status in prostate cells, including detoxification (via antioxidant enzymes), DNA repair, and apoptosis.[2-3, 9, 13] Polymorphisms in OSR genes may influence the capacity to suppress ROS, repair oxidative DNA damage, and regulate cell death signaling pathways. Hence, it is likely that genetic variation in OSR genes resulting in compromised ROS capacity may increase PCA risk.

Specific Aim 2: Evaluate the individual- and combined effects of apoptotic polymorphisms on PCA progression (e.g., disease aggressiveness, tumor grade). Genetic variations that disrupt cell death and cell cycle regulation pathways may result in more aggressive phenotypes in prostatic tumors.[2, 6] Regulation of the cell death is critical to maintain cellular homeostasis, proliferation, and differentiation by facilitating repair or induction of cell death.[98] This process involves multiple pathways and a balance

between pro- and anti-apoptotic genes that function to activate or block apoptosis.[16, 98] Decrease or loss of apoptotic induction can permit escape of transformed cells from programmed cell death, increase the accumulation of damaged cells, and lead to tumor formation and progression.[98] Therefore, genetic variations linked with decreased apoptosis and/or cell cycle arrest capacity may result in more aggressive disease.[100, 116]

Specific Aim 3: Identify Oxidative Stress Response-related genetic-environment interactions capable of serving as effective predictors of prostate cancer development. Endogenous and exogenous ROS sources can contribute to oxidative stress.[13-16] This includes normal cellular respiration and metabolic processes as well as polycyclic aromatic hydrocarbons and heterocyclic amines.[13-14] Excessive oxidative stress can produce DNA base changes, damage tumor suppressors, enhance proto-oncogene expression, and induce malignant transformation of cells.[13-16] Persistent oxidative stress may even trigger apoptosis.[13-14, 16] OSR mechanisms function to protect cells against oxidative stress damage, however genetic alterations may diminish the ability to maintain ROS.[3-4] Increased exposure to environmental ROS can exacerbate this effect. Consequently, OSR gene variants associated with decreased ROS capacity, combined with elevated ROS levels due to environmental factors may increase the risk of PCA disease and aggressiveness.

RESEARCH DESIGN AND METHODS

POPULATION DESCRIPTION

Cancer Genetic Markers of Susceptibility (CGEMS) subjects

Setting and Participant. This population consists of nationally available genetic data from 2,277 men of European-descent (488 non-aggressive cases, 688 aggressive cases and 1101 controls) collected through the NCI Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial.[117-118] Randomization for the PLCO Trial began in 1993 and ended in2001 among men ages 55-74 years to evaluate the effect of screening on disease specific mortality, relative to standard care.

Men were included in the current analysis if they had a baseline PSA measurement before October 1, 2003, completed a baseline questionnaire, returned at least one Annual Study Update (ASU), and had available SNP profile data through the CGEMS data portal. For PCA screening, blood samples were collected and men received a Prostate Specific Antigen (PSA) test and Digital Rectal Exam (DRE). Subsequent to the initial screen, participants received a PSA and DRE annually for three and five years, consecutively. Men who had PSA levels >4ng/ml or abnormal DRE were referred to their health care provider for follow-up care.

Identification of PCA Cases and Controls. The PLCO Trial identified 1172 incident PCA cases (484 non-aggressive and 688 aggressive) through various sources including: screening exams; reports from patients, physicians, or relatives; linkage with the National Death Index; or linkage with the state cancer registries. Incident PCA (non-aggressive) cases were pathologically confirmed (Gleason score <7 or tumor stage I/II). Cases were diagnosed with aggressive disease based on a Gleason score ≥7 or tumor stage III/IV (regional or metastatic disease). Incident cases were defined as men receiving a diagnosis after the first year of follow-up. Controls (n = 1157) were matched to cases based on age, time since initial screening, and year of blood draw using incidence density sampling. Incidence Density sampling accounts the dynamic nature of a cohort study.[119] Under this selection strategy, controls were selected independently for each case from those who were at risk at the time of the diagnosis of the case. Identification as a control for a given case set is independent of the following: future diagnosis as a case, selection as a control for other case sets, and the number of entry and exit times. Therefore, individuals may be included as both a case and a control. The genotype data for individuals who have been selected multiple times are taken into consideration for each selection. Other covariates that vary with time, such as age are defined differently each time, depending on the characteristics of the case set for which he was selected as a control.[119]

All participants signed informed consent documents approved by both the NCI and local institutional review boards. Access to clinical and background data collected through examinations and questionnaires was approved for use by the PLCO.

Demographic, Anthropometric and Lifestyle factors. Questionnaire data included information regarding age, family history of prostate cancer, as well as a comprehensive dietary and supplemental usage. For patient characteristics and lifestyle factors, risk categories were designated using guidelines recommended by the 2005 United States Department of Agriculture (USDA) Report of Dietary Guidelines and the NIH Office of Dietary Supplements.[120-121] For a male with median height and weight, a BMI less than 24.9 was considered normal or underweight.[120] The USDA also advises that adult men get at least 30 minutes of physical activity each day.[120] A BMI between 25 and 29.9 is overweight and men with a BMI greater than 30 are classified as obese.[120] Men over the age of 19, with a normal BMI should consume between 2000-3000 calories per day with at least 4 servings of fruits and 5 servings of vegetables, but no more than 5 servings of meat.[120] Total fat intake should be limited to 20-35% of daily calories and less than 10% percent of calories ought to come from saturated fatty acids.[120] Alcoholic consumption should be limited to no more than drinks per day.[120]

According to the NIH office of Dietary Supplements, each day adult men need approximately 90 mg of vitamin C, 900 μg or 3,000 IU (International Units) of vitamin A, and 15 mg or 22.4 IU of vitamin E.[121] It is also recommended than adult men intake at least 11 mg of zinc and 55 μg of selenium daily.[121]

For variables related to meat consumption and cooking methods, as well as exposure to meat-derived carcinogens were divided into quartiles using data for the control subjects. The 1st quartile was used as the low risk category. These categories included daily total meat intake as well the amount of white (i.e. chicken and fish), processed, or red meats. Red meat consumption was also stratified by type or cooking duration into non-processed, rare/medium-well, and well-/very-well done. The meat-derived carcinogens used in this analysis were MeIQx, DiMeIQx, PhIP, and BaP.

Men of African Descent subjects

Between 2001 and 2005, 774 unrelated male residents were recruited from the Washington, D.C. and Columbia, SC areas through the Howard University Hospital (HUH) Division of Urology or PCA screening programs. The study population of men of African descent (i.e., self-reported African-Americans, East African-Americans, West African-Americans, and Afro-Caribbean Americans) consisted of 219 incident PCA cases and 694 unrelated controls. PCA patients between the ages of 41 and 91 were diagnosed within one year of enrollment. Following a visit to the HUH Division of Urology for an annual PCA screening exam or urinary symptoms, incident PCA cases were identified by a urologist using a transrectal ultrasound-guided biopsy. Biopsy cores were reviewed by members of the Department of Pathology at the Howard University College of Medicine. PCA cases were classified according to a well-established Gleason scoring system.[122] Inclusion criteria of controls included men older than 45 with a low prostate specific

antigen (PSA) level ≤ 4.0 ng/ml and normal digital rectal exams (DREs) or biopsies. Clinical characteristics including age at diagnosis/enrollment, family history of PCA, PSA level (ng/ml), and Gleason score for PCA patients, were obtained from medical records. Histopathological grade was recorded as the Gleason score. Information on smoking history was also collected at the time of recruitment using a short questionnaire. Male residents from D.C. were classified as either never (n = 107) or ever smokers (n = 109), where 'ever' includes former and current smokers. All study participants had DNA extracted from whole blood and provided written informed consent for participation in genetic analysis studies under a protocol approved by Howard University, the HUH Division of Urology, and the University of Louisville Institutional Review Board.

Ancestry Markers. One hundred previously validated ancestry markers autosomal markers were included to account for potential population stratification among our admixed population of self-reported African-Americans, West African, East African, Afro-Caribbean, as previously described.[123] Study participants were grouped from lowest to highest genetic West African Ancestry (WAA), with scores ranging from 0-100%. These 100 markers were assembled using DNA from self-identified African-Americans (Coriell Institute for Medical Research, n = 96), Yoruban West Africans (HapMap, n = 60), West Africans (Bantu and Nilo Saharan speakers, n = 72), Europeans (New York City, n = 24), and CEPH Europeans (HapMap Panel, n = 60), as previously reported.[123] Individuals (n = 873) with a high degree of WAA greater than or equal to 25% were considered in the final analysis.

OSR GENE SELECTION

In an attempt to focus our investigation of OSR related genes in relation to PCA risk and disease progression, a panel of candidate SNPs was generated from genes involved in antioxidation, DNA repair and apoptotic mechanisms. A list of 118 OSR genes generated based on published PCA epidemiology studies as well as pathway databases and tools, including KEGG, *Kyoto Encyclopedia of Genes and Genomes* (www.genome.jp/kegg), Ingenuity (www.ingenuity.com), BioCarta (www.biocarta.com),and SNPs3D (www.SNPs3D.org), as summarized in *Figure 7*.[110, 124-128] More specifically, KEGG and BioCarta sites provide diagrams illustrating gene interactions within human biological pathways.[110, 124-126] Ingenuity is a pathway analysis software that allows researchers to model and investigate biological systems (e.g., genes, mechanisms, and diseases).[127] SNPs3D is a website which assigns molecular functional effects of non-synonymous SNPs (nsSNPs) based on structure and sequence analysis.[128] SNPs3D also allows users to generate candidate gene lists and interactive maps for various conditions based on published literature as well as other functional/pathway databases [e.g., KEGG and the Gene Ontology (GO)].[128] Together, these tools show important molecular interactions and genes not readily found by literature search or other traditional methods. In order to predict the functional effects of a SNP, this site considers factors such as, protein structure, gene regulation, splicing

and miRNA binding, and whether the alternative alleles are likely to have differential effects on function.[129]

SNP SELECTION

Phase I Selection of SNPs for men of European Descent. Prior to uploading our initial list (i.e., 118 OSR genes) into the CGEMS data portal, we secured the HUGO gene name equivalents for the targets of interest using National Center for Biotechnology Information (*NCBI*, http://www.ncbi.nlm.nih.gov) Entrez Gene. SNP profile data was available for more than 1516 SNPs [*Figure 7*].[119] However, the final analysis focused on 242 SNPs detected in 83 OSR genes collected from 2276 European-Americans CGEMS participants, as summarized in *Tables 3-8*. Emphasis was placed on sequence variants that were: (1) detected within all exons, 2.5kb upstream of the gene, 2.5kb downstream of intron 1, 2.5kb downstream of the gene; (2) had a minor allele frequency >1%. SNPs were discarded if the observed genotype frequency among controls significantly deviated from the Hardy-Weinberg Equilibrium (HWE $p < 0.005$). Over 240 sequence variants detected in 83 OSR genes fit the aforementioned selection criteria, following assessment using NCBI Entrez SNP, as detailed in figure 7.[52, 129]

Phase II Selection of SNPs for men of African Descent. 25 OSR SNPs were selected for analysis using one or more of following criteria: (1) epidemiological evidence from the CGEMS prostate cancer database or published reports indicating their involvement in cancer based on p values < 0.05; (2) commonly studied loci; (3)

marked disparities in genotype frequency comparing men of African descent to their Caucasian counterparts; (4) evidence demonstrating a link with alterations in mRNA expression/stability or protein expression/structure or function using *in silico* tools (e.g., SNPinfo, SNPs3D) or published reports; and (5) minor allele frequency >1%. The SNPs that were analyzed among men of African descent are indicated in tables 3-8 by magenta font.

PREDICTED FUNTION OF SELECTED SNPS

Tools such as SNPinfo and SNPs3D aid investigators in annotating and/or predicting the functional consequence of selected SNP targets.[129] For instance, in the case of SNPs located in gene coding regions, the server identifies nonsense SNPs that lead to premature termination of translation or nsSNPs that lead to amino acid changes affecting protein function.[129] Sequence variants at transcription factor binding sites (TFBS) may affect the level or timing of gene expression.[129] Also, non-coding SNPs that are located in intronic or near gene regions may impact either splice- or microRNA-(miRNA) binding sites.[129] SNPs that are located within two base pairs of an intron–exon junction or at exonic splicing- enhancer (ESE)/ silencer (ESS) binding sites may disrupt messenger RNA (mRNA) splicing and severely affect protein function.[129] miRNA are 21–23-base single-stranded RNA molecules that are usually complementary to a site in the 3′ UTR region of an mRNA.[129] miRNA bound to the end of mRNA can inhibit protein translation.[129]

Figure 7. Gene and SNP Selection Flow Diagram

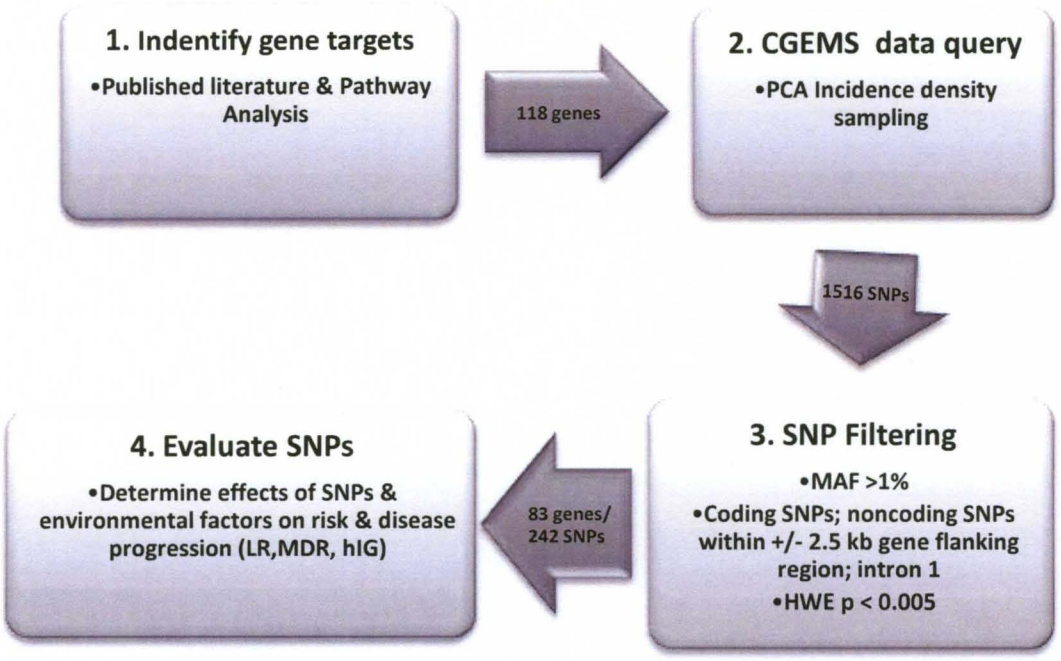


Figure 7: SNP Selection Flow Diagram. By exploring published literature and pathway analysis tools for genes involved in prostate cancer and oxidative stress response, an initial list of more than 100 genes was generated. Upon analyzing these genes in CGEMS association finding dataset, we found 1,516 SNPs had genotype data available in the CGEMS database. National Center for Biotechnology Information (NCBI) was reviewed to ensure that the selected targets were related to our pathways of interest, had a minor allele frequency >1%, resided in regions likely to modify mRNA expression/stability/splicing or protein expression/structure/function. The finalized panel consisting of 242 SNPs detected in 83 OSR genes was then analyzed by logistic regression analysis (LR), multifactor dimensionality reduction (MDR), and hierarchical interaction graphs (hIG)

Table 3. NCBI data for Antioxidative Polymorphisms[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs1001179	*CAT*	11	34416807	5'near gene (-206)	G>A	
rs564250	*CAT*	11	34415437	5'near gene (-1616)	C>T	
rs2470893	*CYP1A1*	15	72806502	3'near gene (-1540)	G>A	
rs4646903	*CYP1A1*	15	72828970	3'near gene (+1188)	G>A	
rs2069514	*CYP1A2*	15	75038220	5'region (-3859)	G>A	
rs2069522	*CYP1A2*	15	72826286	5'near gene (-1757)	T>C	
rs762551	*CYP1A2*	15	75041917	Intron 1	A>C	
rs1800440	*CYP1B1*	2	38209790	Exon 2	A>G	
rs11673270	*CYP2B6*	19	46212684	Intron 1	A>C	
rs2860840	*CYP2C18*	10	96485222	3'UTR (mRNA 1830)	C>T	
rs10509681	*CYP2C8*	10	96788739	Exon 8	T>C	Lys399Arg
rs1058932	*CYP2C8*	10	96786851	3'UTR (mRNA 1592)	C>T	
rs7909236	*CYP2C8*	10	96819420	5'near gene (-120)	G>T	
rs2480258	*CYP2E1*	10	135240981	Intron 1	G>A	
rs2515642	*CYP2E1*	10	135240894	Intron 1	T>C	
rs6413420	*CYP2E1*	10	135229710	5'near gene (+38)	G>T	
rs1051740	*EPHX1*	1	222326368	Exon 4	T>C	Tyr113His
rs1051741	*EPHX1*	1	222338964	Exon 2	C>T	Asn357Asn
rs2234922	*EPHX1*	1	222333141	Exon 5	A>G	His139Arg
rs6917325	*GSTA1*	6	52774232	Intron 1	C>T	
rs563464	*GSTA3*	6	52883831	5'near gene (-1387)	C>T	
	GSTM1			Gene deletion	*1>*0	
rs638820	*GSTM2*	1	109921948	5'near gene (+765)	C>T	
rs7483	*GSTM3*	1	109991743	Exon 7	G>A	Val224Ile
rs1695	*GSTP1*	11	67109265	Exon 5	A>G	Ile105Val
rs6591256	*GSTP1*	11	67106475	5'near gene (+1197)	A>G	
	GSTT1			Gene deletion	*1>*0	
rs10888150	*NAT1*	8	18110406	5'near gene(+1489)	C>T	
rs4921581	*NAT1*	8	18115375	Intron 1	G>A	
rs7003890	*NAT1*	8	18121590	Intron 1	T>C	
rs7017402	*NAT1*	8	18112354	Intron 1	G>A	
rs8190870	*NAT1*	8	18125552	3'near gene (-452)	C>T	
rs1112005	*NAT2*	8	18300156	Intron 1	C>T	
rs1208	*NAT2*	8	18302596	Exon 2	A>G	Lys268Arg
rs1390358	*NAT2*	8	18297035	Intron 1	T>C	
rs4646247	*NAT2*	8	18303188	3'near gene (-224)	G>A	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 3. NCBI data for Antioxidative Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs7832071	*NAT2*	8	18301560	Intron 1	C>T	
rs2758331	*SOD2*	6	160025060	Intron 1	C>A	
rs6717546	*UGT1A1*	2	234464119	3'near gene (-174)	G>A	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 4. NCBI data for Base Excision Repair Polymorphisms[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs1130409	*APEX1*	14	20925154	Exon 5	T>G	
rs1052133	*OGG1*	3	9798773	Exon 6	C>G	Ser326Cys
rs125701	*OGG1*	3	9765478	5'near gene (+1402)	G>A	
rs2445837	*POLD1*	19	55613084	3'near gene (-207)	A>G	
rs3087374	*POLG*	15	87660998	Exon 16	G>T	
rs3730814	*POLI*	18	50072899	Intron 1	G>T	
rs545979	*POLI*	18	50073748	Intron 1	C>T	
rs8305	*POLI*	18	50074803	Exon 1	A>G	
rs4135036	*TDG*	12	102883184	5'near gene (+587)	T>C	
rs3219243	*UNG*	12	108026775	Intron 1	T>C	
rs3890995	*UNG*	12	108017912	5'near gene (+1953)	T>C	
rs25487	*XRCC1*	19	44055726	Exon 10	G>A	Arg399Gln
rs2682585	*XRCC1*	19	48773128	5'near gene (-1518)	G>A	
rs2854496	*XRCC1*	19	48760033	Intron 1	G>A	
rs3213255	*XRCC1*	19	48769347	Intron 1	T>C	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs1885097	*ACIN1*	14	22619159	Exon 6	A>G	Ser467Pro
rs3751501	*ACIN1*	14	22619125	Exon 2	G>A	Ser478Phe
rs10157763	*AKT3*	1	240321082	Intron 1	C>T	
rs10803155	*AKT3*	1	240220823	Intron 1	G>A	
rs10927067	*AKT3*	1	240249285	Intron 1	G>A	
rs12031994	*AKT3*	1	240243350	Intron 1	T>C	
rs2034915	*AKT3*	1	240204544	Intron 1	C>T	
rs2125230	*AKT3*	1	240211889	Intron 1	G>A	
rs2125231	*AKT3*	1	240088340	Intron 1	G>A	
rs2345994	*AKT3*	1	240258316	Intron 1	C>T	
rs4132509	*AKT3*	1	240269125	Intron 1	C>A	
rs4614244	*AKT3*	1	240326915	Intron 1	T>C	
rs897960	*AKT3*	1	240259609	Intron 1	A>G	
rs10745834	*APAF1*	12	97562818	Intron 1	A>G	
rs10860361	*APAF1*	12	97631965	3'near gene (-298)	A>G	
rs1439123	*APAF1*	12	97578784	Intron 1	T>C	
rs1439124	*APAF1*	12	97622538	Intron 1	A>C	
rs2288714	*APAF1*	12	97610756	Intron 1	T>C	
rs4319556	*APAF1*	12	97579054	Intron 1	G>A	
rs7299536	*APAF1*	12	97603878	Intron 1	G>A	
rs7315397	*APAF1*	12	97552834	Intron 1	G>A	
rs919699	*APAF1*	12	97586794	Intron 1	C>T	
rs210134	*BAK1*	6	33648187	3'near gene (+212)	G>A	
rs5745568	*BAK1*	6	33656372	5'near gene (-265)	C>A	
rs11667351	*BAX*	19	54147966	5'near gene (-2477)	T>G	
rs4645878	*BAX*	19	49457938	5'near gene (-248)	C>T	
rs4645900	*BAX*	19	54156175	Intron 1	C>T	
rs905238	*BAX*	19	54157196	3'near gene (-85)	A>G	
rs1016860	*BCL2*	18	58946054	3'UTR (mRNA 1997)	G>A	
rs1564483	*BCL2*	18	58945634	3'UTR (mRNA 2417)	G>A	
rs3927911	*BCL2*	18	59084606	Intron 1	C>T	
rs1138357	*BCL2A1*	15	78050461	Exon 1	G>A	Cys19Tyr
rs1138358	*BCL2A1*	15	78050400	Exon 1	T>G	Asn39Lys
rs3826007	*BCL2A1*	15	78050272	Exon 1	G>A	Gly82Asp
rs13405741	*BCL2L11*	2	111629287	Intron 1	T>C	
rs3789068	*BCL2L11*	2	617170	Intron 5	T>C	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs616130	*BCL2L11*	2	111628912	Intron 1	C>A	
rs724710	*BCL2L11*	2	111623922	Exon 1	C>T	Ile95Ile
rs4488761	*BCL2L13*	22	16584167	Exon 1	A>G	Ser257Ser
rs10772530	*BCL2L14*	12	12157308	Intron 1	C>A	
rs10845479	*BCL2L14*	12	12135568	Intron 1	A>G	
rs11054704	*BCL2L14*	12	12191036	Intron 1	G>A	
rs1612841	*BCL2L14*	12	12136155	Intron 1	T>C	
rs1628766	*BCL2L14*	12	12142116	Intron 1	T>C	
rs1641729	*BCL2L14*	12	12142419	Intron 1	G>A	
rs2448050	*BCL2L14*	12	12140491	Intron 1	G>A	
rs2448063	*BCL2L14*	12	12113301	5'near gene (-1844)	G>T	
rs6488494	*BCL2L14*	12	12121219	Intron 4	C>T	
rs4763780	*BCL2L14*	12	12144858	Intron 1	T>G	
rs4763781	*BCL2L14*	12	12145743	Intron 1	G>A	
rs4763782	*BCL2L14*	12	12146023	Intron 1	A>C	
rs879732	*BCL2L14*	12	12131466	Exon 1	T>C	Tyr162Tyr
rs885637	*BCL2L14*	12	12139547	Intron 1	G>A	
rs885720	*BCL2L14*	12	12139366	Intron 1	G>A	
rs888152	*BCL2L14*	12	12131932	Intron 1	C>T	
rs1950252	*BCL2L2*	14	22848538	3'UTR (mRNA 1294)	G>A	
rs181402	*BID*	22	16604328	Intron 1	C>T	
rs181405	*BID*	22	16607554	Intron 1	G>A	
rs181408	*BID*	22	16609859	Intron 1	T>C	
rs181417	*BID*	22	16615528	Intron 1	G>A	
rs366542	*BID*	22	16632936	5'near gene (+1137)	C>T	
rs5746474	*BID*	22	16620486	Intron 1	T>C	
rs5747351	*BID*	22	16620929	Intron 1	A>G	
rs738095	*BID*	22	16630542	Intron 1	G>A	
rs9604787	*BID*	22	16609143	Intron 1	G>A	
rs1883263	*BIK*	22	41834115	Intron 1	A>C	
rs4988360	*BIK*	22	41829569	5'near gene (-1725)	C>T	
rs4988366	*BIK*	22	41830193	5'near gene (-1101)	A>G	
rs738276	*BIK*	22	41840163	Intron 1	G>A	
rs1042992	*BNIP3L*	8	26325108	3'UTR (mRNA 2047)	C>T	
rs10503786	*BNIP3L*	8	26325853	3'UTR (mRNA 2792)	C>T	
rs10405717	*CARD8*	19	53443620	Intron 1	C>T	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs10416565	*CARD8*	19	53434199	Intron 1	A>G	
rs11670259	*CARD8*	19	53435976	Intron 1	C>T	
rs11672725	*CARD8*	19	53438493	Intron 1	C>T	
rs6509364	*CARD8*	19	53433879	Intron 2	C>T	
rs6509366	*CARD8*	19	53435389	Intron 2	G>A	
rs1049216	*CASP3*	4	185550089	3'UTR (mRNA 1267)	T>C	
rs2019978	*CASP3*	4	185932730	Intron 1	T>G	
rs507879	*CASP5*	11	104383137	Exon 2	A>G	Thr106Ala
rs537093	*CASP5*	11	104371256	Intron 5	G>A	
rs3181187	*CASP6*	4	110980514	Intron 1	G>A	
rs3212153	*CASP6*	4	110967085	3'near gene (+337)	C>T	
rs768063	*CASP6*	4	110978060	Intron 1	G>A	
rs12415607	*CASP7*	10	115428194	5'near gene (-740)	C>A	
rs10931934	*CASP8*	2	201945295	Intron	C>T	
rs6747918	*CASP8*	2	201923081	5'near gene (+751)	A>G	
rs1052571	*CASP9*	1	15595919	Exon 1	C>T	Ala28Val
rs1052576	*CASP9*	1	15832543	Exon 5	G>A	Arg221Gln
rs4645989	*CASP9*	1	15595649	Intron 1	T>C	
rs12817549	*CRADD*	12	92645445	Intron 2	T>C	
rs3858606	*CRADD*	12	92760016	Intron 2	G>A	
rs11588734	*DFFA*	1	10467247	5'near gene (-419)	A>G	
rs12738235	*DFFB*	1	3809402	Exon 2	G>A	Arg196Lys
rs3205087	*DFFB*	1	3823399	Exon 1	G>A	Pro318Pro
rs4074709	*DFFB*	1	3820105	Intron 1	G>T	
rs4648426	*DFFB*	1	3796246	5'near gene (+756)	T>C	
rs12870	*DIABLO*	12	121217700	3'UTR (mRNA 1633)	G>A	
rs7972948	*HRK*	12	115774919	Intron 1	C>T	
rs9669553	*HRK*	12	115778069	Intron 1	C>T	
rs1048906	*IKBIP*	12	97531754	Exon 1	G>A	Gly265Ser
rs12371097	*IKBIP*	12	97531767	Intron 1	A>G	
rs12821083	*IKBIP*	12	97533519	Intron 1	G>T	
rs11578093	*IKBKE*	1	203059049	3'near gene (-495)	T>G	
rs1539243	*IKBKE*	1	203036182	Exon 4	C>T	Ile67Ile
rs1930438	*IKBKE*	1	203031501	5'near gene (+710)	G>A	
rs944775	*IKBKE*	1	203056988	Intron 1	A>G	
rs11688	*JUN*	1	58960014	Exon 1	G>A	Gln250Gln

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs13096	*KRAS*	12	25251108	3'UTR (mRNA 3636)	A>G	
rs9266	*KRAS*	12	25253484	3'UTR (mRNA 1260)	T>C	
rs1609798	*NFKB1*	4	103894643	Intron 1	C>T	
rs230547	*NFKB1*	4	103893462	Intron 1	C>T	
rs4648135	*NFKB1*	4	103893871	Intron 1	A>G	
rs1056890	*NFKB2*	10	104152760	3'near gene (-523)	C>T	
rs696	*NFKBIA*	14	34940844	3'UTR (mRNA 1190)	G>A	
rs8904	*NFKBIA*	14	34940968	3'UTR (mRNA 1066)	C>T	
rs2230365	*NFKBIL1*	6	31633427	Exon 2	C>T	Ser126Ser
rs1607237	*PIK3CA*	3	180432999	Intron 1	T>C	
rs500687	*PIK3CB*	3	139942901	Intron 1	T>C	
rs4727666	*PIK3CG*	7	106099429	5'near gene (+473)	A>G	
rs4730205	*PIK3CG*	7	106123200	Intron 1	C>T	
rs11656099	*PRKCA*	17	62224124	Intron 1	G>A	
rs8074995	*PRKCA*	17	62222593	Intron 1	G>A	
rs9890506	*PRKCA*	17	62214645	Intron 1	C>T	
rs1530668	*PRKCE*	2	46318270	Intron 1	T>C	
rs17034455	*PRKCE*	2	46225132	Exon 4	C>T	His524His
rs2594489	*PRKCE*	2	46319722	Intron 1	C>T	
rs281472	*PRKCE*	2	46315488	Intron 1	T>C	
rs281476	*PRKCE*	2	46312255	Intron 1	T>C	
rs281505	*PRKCE*	2	46327196	3'near gene (+417)	T>C	
rs281508	*PRKCE*	2	46322858	Intron 1	G>T	
rs3820729	*PRKCE*	2	46304426	Intron 1	G>A	
rs608139	*PRKCE*	2	45789207	5'near gene (+1360)	T>C	
rs935672	*PRKCE*	2	45957610	Intron	C>T	
rs935673	*PRKCE*	2	46034008	Intron	A>G	
rs951012	*PRKCE*	2	46309282	Intron 1	C>A	
rs2236379	*PRKCQ*	10	6567149	Exon 3	C>T	Pro330Leu
rs2236380	*PRKCQ*	10	6509823	3'UTR (mRNA 2458)	C>T	
rs519951	*PRKCQ*	10	6598346	5'near gene (-1243)	C>T	
rs571715	*PRKCQ*	10	6596560	Intron 1	T>C	
rs574521	*PRKCQ*	10	6596860	Intron 1	T>C	
rs585881	*PRKCQ*	10	6598275	5'near gene (-1172)	T>C	
rs11128607	*RAF1*	3	12648275	Intron 1	A>G	
rs11709504	*RAF1*	3	12649199	Intron 1	T>C	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs11710163	*RAF1*	3	12671288	Intron 1	A>G	
rs13060691	*RAF1*	3	12653013	Intron 1	T>G	
rs6442322	*RAF1*	3	12664858	Intron 1	A>G	
rs6792773	*RAF1*	3	12643726	Intron 1	C>T	
rs7643321	*RAF1*	3	12638233	Intron 1	A>G	
rs7956	*RAF1*	3	12599763	5'near gene (+468)	A>G	
rs904453	*RAF1*	3	12679894	Intron 1	C>A	
rs9817675	*RAF1*	3	12651113	Intron 1	C>T	
rs7101916	*RELA*	11	65187936	5'near gene (-883)	C>T	
rs281505	*PRKCE*	2	46327196	3'near gene (+417)	T>C	
rs7739011	*RIPK1*	6	3057529	Intron 1	T>C	
rs11247963	*RPS6KA1*	1	26539543	5'near gene (+722)	G>A	
rs1865077	*RRAS*	19	54831904	Exon 3	T>C	Asn111Asn
rs1000294	*TNFRSF10A*	8	23136080	Intron 1	C>T	
rs13255394	*TNFRSF10A*	8	23139491	5'near gene (-890)	C>T	
rs13278062	*TNFRSF10A*	8	23138916	5'near gene (-386)	G>T	
rs2230229	*TNFRSF10A*	8	23105237	Exon 7	A>G	Arg441Lys
rs6557634	*TNFRSF10A*	8	23116201	Exon 4	T>C	His141Arg
rs7842021	*TNFRSF10A*	8	23135149	Intron 1	A>G	
rs1001793	*TNFRSF10B*	8	22956894	Intron 1	G>A	
rs1047266	*TNFRSF10B*	8	22956646	Exon 2	C>T	Ala67Val
rs11135693	*TNFRSF10B*	8	22981099	Intron 1	C>A	
rs9644062	*TNFRSF10B*	8	22976094	Intron 1	C>T	
rs1133782	*TNFRSF10D*	8	23057933	Exon 6	C>T	Ser310Leu
rs6651394	*TNFRSF10D*	8	23078565	5'near gene (-957)	T>C	
rs7463799	*TNFRSF10D*	8	23075599	Intron 1	T>C	
rs7957	*TNFRSF10D*	8	23049312	3'UTR (mRNA 3269)	T>C	
rs1860545	*TNFRSF1A*	12	6317038	Intron 1	C>T	
rs4149570	*TNFRSF1A*	12	6321851	5'near gene (+222)	G>T	
rs4149576	*TNFRSF1A*	12	6319376	Intron 1	A>G	
rs4149577	*TNFRSF1A*	12	6317783	Intron 1	T>C	
rs4149578	*TNFRSF1A*	12	6317698	Intron 1	G>A	
rs1061622	*TNFRSF1B*	1	12187221	Exon 4	T>G	Met196Arg
rs2270418	*TNFSF10*	3	173723701	Intron 1	T>G	
rs231983	*TNFSF10*	3	173719142	Intron 1	A>C	
rs365238	*TNFSF10*	3	173724568	5'near gene (-544)	A>G	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 5. NCBI data for Apoptosis-related Polymorphisms, *continued*[52]

dbSNP ID	Gene	Chr	Chr position	Location	Nucleotide change	Amino Acid Change
rs4894559	*TNFSF10*	3	173716071	Intron 1	G>A	
rs9859259	*TNFSF10*	3	173705843	3'near gene (+356)	C>A	
rs2078486	*TP53*	17	7523808	Intron 1	G>A	
rs2909430	*TP53*	17	7519370	5'UTR (mRNA 167)	A>G	
rs4735334	*TP53INP1*	8	96024468	Intron 1	A>G	
rs896849	*TP53INP1*	8	96011420	3'UTR (mRNA 1570)	T>C	
rs896854	*TP53INP1*	8	96029687	Intron 1	A>G	
rs3750512	*TRAF2*	9	137096905	3'near gene (-2)	T>C	
rs4880073	*TRAF2*	9	137093190	Intron 1	G>A	

Abbreviations: Chr, chromosome; Cau, Caucasians; AA, African-Americans

Table 6. NCBI Prevalence Data for Variant Antioxidative Targets[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs1001179	*CAT*	54.9-85.7	14.3-40.9	3.2-9.1	88.9-95.8	4.2-11.1	0.0
rs564250	*CAT*	51.7-72.7	22.7-46.7	1.7-4.5	72.7	27.3	0.0
rs2470893	*CYP1A1*	53.3-55.6	38.3-40.7	3.7-8.3	83.3	16.7	0.0
rs4646903	*CYP1A1*	62.1	37.9	0.0	56.6	30.4	13.0
rs2069514	*CYP1A2*	83.9	16.1	0.0	29.2	62.5	8.3
rs2069522	*CYP1A2*	83.3-100.0	16.7	0.0	75.0-78.3	20.8-21.7	4.2
rs762551	*CYP1A2*	45.5-54.2	33.3-41.9	6.5-13.6	26.1-54.2	45.8-69.2	17.4
rs1800440	*CYP1B1*	64.5-70.0	25.0-32.3	3.2-5.0	91.3-100.0	4.3	4.3
rs11673270	*CYP2B6*	51.7	43.3	5.0	n/a	n/a	n/a
rs2860840	*CYP2C18*	23.3-39.7	48.4-63.3	8.6-13.3	98.5-100.0	1.3-4.2	0.0
rs10509681	*CYP2C8*	75.2-80.6	16.1-25.0	1.7-4.2	95.7-100.0	1.3-9.4	0.0
rs1058932	*CYP2C8*	58.3-66.7	28.3-41.7	5.0	52.2	34.8	13.0
rs7909236	*CYP2C8*	56.7-57.6	39.0-40.0	3.3-3.4	n/a	n/a	n/a
rs2480258	*CYP2E1*	50.0-60.0	37.5-50.0	1.7-4.2	17.4-20.0	40.0-43.5	39.1-40.0
rs2515642	*CYP2E1*	50.0-58.3	39.1-50.0	1.7-4.3	18.2-20.0	40.0-40.9	40.0-40.9
rs6413420	*CYP2E1*	81.8-88.3	8.3-18.2	4.2	100.0	0.0	0.0
rs1051740	*EPHX1*	41.7-45.0	38.7-45.8	10.0-19.4	39.1-83.3	16.7-47.8	1.6-13.0
rs1051741	*EPHX1*	76.3-76.7	23.3-23.7	0.0	78.3	17.4	4.3
rs2234922	*EPHX1*	64.3-70.0	25.0-28.6	5.0-7.1	41.7	54.2	4.1
rs6917325	*GSTA1*	33.3-33.9	50.0-50.8	15.3-16.7	n/a	n/a	n/a
rs563464	*GSTA3*	93.2-100.0	6.8	0.0	33.3	46.7	20.0
	GSTM1	3.2	35.5	61.3	37.5	50.0	12.5
rs638820	*GSTM2*	36.7	33.3	30.0	n/a	n/a	n/a
rs7483	*GSTM3*	38.3-54.5	27.3-100.0	6.5-18.2	58.4-82.6	17.4-33.3	8.3
rs1695	*GSTP1*	33.3-47.8	30.4-55.5	11.7-21.7	33.3	52.4	14.3
rs6591256	*GSTP1*	30.0-37.5	37.5-54.2	15.3-25.0	34.8-41.0	47.5-56.5	8.7-11.5
	GSTT1	51.6	38.7	9.7	33.3	45.8	20.8
rs10888150	*NAT1*	31.7-33.9	46.7-51.7	16.7-20.0	1.6	35.5	62.9
rs4921581	*NAT1*	70.0	23.3	6.7	14.5	38.7	46.8
rs7003890	*NAT1*	23.3-29.2	37.5-50.0	26.7-33.3	34.8-53.2	35.5-43.5	11.3-21.7
rs7017402	*NAT1*	81.0-81.7	18.3-19.0	0.0	43.5	45.2	11.3
rs8190870	*NAT1*	70.0-76.7	20.0-26.7	3.3	54.8-73.9	26.1-40.3	4.8
rs1112005	*NAT2*	50.0-60.0	20.0-37.5	11.7-20.0	50.0-56.5	43.5-50.0	0.0
rs1208	*NAT2*	23.5-35.5	48.3-55.9	16.1-20.6	37.5-49.2	25.0-37.7	13.1-37.5
rs1390358	*NAT2*	36.7-45.8	37.5-49.2	13.6-16.7	43.5	47.8	8.7
rs4646247	*NAT2*	45.5-61.8	29.4-40.9	8.8-13.6	33.3-41.9	51.6-61.1	5.6-6.5
rs7832071	*NAT2*	35.0-45.8	37.5-50.0	15.0-16.7	36.4	45.5	18.2
rs2758331	*SOD2*	90.0	8.3	1.7	95.2	4.8	n/a

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 6. NCBI Prevalence Data for Antioxidative Targets, *continued*[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs6717546	*UGT1A1*	36.4-41.7	41.7-59.1	4.5-16.7	26.1-33.3	46.7-52.2	20.0-21.7

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 7. Prevalence Data for Variant Base Excision Repair Targets[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs1130409	*APEX1*	26.7	45.0-33.3	28.3-40.0	25.0-53.2	40.3-54.2	6.5-20.3
rs1052133	*OGG1*	51.1-63.3	30.0-38.9	6.7-6.9	79.2	20.8	0.0
rs125701	*OGG1*	74.6-77.3	22.7-23.7	1.7	87.0-88.0	12.0-13.0	0.0
rs2445837	*POLD1*	88.3	11.7	0.0	19.4	43.5	37.1
rs3087374	*POLG*	81.7-87.5	8.3-18.3	4.2	100.0	0.0	0.0
rs3730814	*POLI*	58.3-65.0	33.3	1.7-8.3	91.3	8.7	0.0
rs545979	*POLI*	51.7-58.3	33.3-41.7	6.7-8.3	78.3	21.7	0.0
rs8305	*POLI*	45.8-51.7	41.7-45.0	3.3-12.5	78.3-80.6	17.7-21.7	1.6
rs4135036	*TDG*	90.0	8.3	1.7	95.2	4.8	0.0
rs3219243	*UNG*	66.1	30.5	3.4	n/a	n/a	n/a
rs3890995	*UNG*	65.2-67.8	30.5-34.8	1.7	68.2	31.8	0.0
rs25487	*XRCC1*	25.8-47.9	12.5-43.7	8.5-19.4	83.3	12.5	4.2
rs2682585	*XRCC1*	63.3	31.7	5.0	n/a	n/a	n/a
rs2854496	*XRCC1*	73.3	23.3	3.3	n/a	n/a	n/a
rs3213255	*XRCC1*	25.0-38.3	48.3-70.8	4.2-13.3	38.7-39.1	43.5-51.6	9.7-17.4

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 8. Prevalence Data for Variant Apoptotic Targets[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs1885097	*ACIN1*	26.7-41.7	33.3-45.0	25.0-28.3	13.0	60.9	26.1
rs3751501	*ACIN1*	41.7-88.3	11.7-46.7	11.7	n/a	n/a	n/a
rs10157763	*AKT3*	50.8	39.0	10.2	n/a	n/a	n/a
rs10803155	*AKT3*	71.7	26.7	1.7	n/a	n/a	n/a
rs10927067	*AKT3*	71.7-72.9	25.4-26.7	1.7	n/a	n/a	n/a
rs12031994	*AKT3*	71.7	26.7	1.7	n/a	n/a	n/a
rs2034915	*AKT3*	50.0-60.0	25.0-40.0	10.0-20.8	0.0	26.1	73.9-100.0
rs2125230	*AKT3*	66.7-72.9	25.0-26.7	1.7-8.3	30.4	60.9	8.7
rs2125231	*AKT3*	50.0	40.0	10.0	n/a	n/a	n/a
rs2345994	*AKT3*	51.8	39.3	8.9	n/a	n/a	n/a
rs4132509	*AKT3*	62.5-71.7	26.7-29.2	1.7-8.3	56.5	34.8	8.7
rs4614244	*AKT3*	76.7-100.0	20.7-21.7	1.7	n/a	n/a	n/a
rs897960	*AKT3*	71.7-73.9	26.1-26.7	1.7	60.9	34.8	4.3
rs10745834	*APAF1*	36.2-36.7	55.0-55.2	8.3-8.6	n/a	n/a	n/a
rs10860361	*APAF1*	23.3	53.3	23.3	n/a	n/a	n/a
rs1439123	*APAF1*	71.7-75.0	25.0-26.7	1.7	73.9	26.1	0.0
rs1439124	*APAF1*	62.7-66.7	29.2-36.2	1.7-4.2	73.9	21.7	4.3
rs2288714	*APAF1*	23.7	59.3	16.9	n/a	n/a	n/a
rs4319556	*APAF1*	90.0	10.0	0.0	n/a	n/a	n/a
rs7299536	*APAF1*	38.3	53.3	8.3	n/a	n/a	n/a
rs7315397	*APAF1*	78.3	18.3	3.3	n/a	n/a	n/a
rs919699	*APAF1*	70.8-78.3	18.3-29.2	3.3	87.0	13.0	0.0
rs210134	*BAK1*	52.2-53.3	30.0-34.8	13.0-16.7	47.8-50.0	34.8-41.9	8.1-13.0
rs5745568	*BAK1*	68.3-70.0	25.9-26.7	3.3-5.2	74.2	25.8	0.0
rs11667351	*BAX*	73.3	25.0	1.7	n/a	n/a	n/a
rs4645878	*BAX*	78.8	19.2	1.9	81.8	13.6	4.5
rs4645900	*BAX*	90.0	10.0	0.0	n/a	n/a	n/a
rs905238	*BAX*	22.0-28.8	47.5-52.5	23.3-25.4	27.4	51.6	21.0
rs1016860	*BCL2*	85.0-95.8	4.2-15.0	0.0	50.0	31.8	18.2
rs1564483	*BCL2*	45.8-58.3	35.0-50.0	4.2-6.7	67.7-69.6	25.8-26.1	4.3-6.5
rs3927911	*BCL2*	50.0	41.7	8.3	n/a	n/a	n/a
rs1138357	*BCL2A1*	53.3-70.8	29.2-43.3	3.3	65.2	30.4	4.3
rs1138358	*BCL2A1*	53.3-70.8	29.2-43.3	3.3	21.7	52.2	26.1
rs3826007	*BCL2A1*	53.3-70.8	29.2-43.3	3.3	91.3	8.7	0.0
rs13405741	*BCL2L11*	81.4-81.7	16.7-16.9	1.7	n/a	n/a	n/a
rs3789068	*BCL2L11*	25.0-41.9	41.9-54.2	16.1-23.3	48.3-65.2	26.1-46.7	5.0-12.5
rs616130	*BCL2L11*	12.5-31.7	2.4-55.0	13.3-87.5	40.0	20.0	40.0
rs724710	*BCL2L11*	25.0-57.1	35.7-65.0	5.0-10.0	52.2-66.0	32.0-53.5	3.8-5.0

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 8. Prevalence Data for Variant Apoptotic Targets, *continued*[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs4488761	*BCL2L13*	26.7-33.3	33.3-58.3	15.0-33.3	13.0	52.2	34.8
rs10772530	*BCL2L14*	26.7	48.3	25.0	n/a	n/a	n/a
rs10845479	*BCL2L14*	48.3-54.2	45.0-45.8	6.7	43.5	56.5	0.0
rs11054704	*BCL2L14*	73.3	26.7	0.0	n/a	n/a	n/a
rs1612841	*BCL2L14*	50.0	39.7	10.3	0.0	0.0	0.0
rs1628766	*BCL2L14*	53.3-70.8	25.0-36.7	4.2-10.0	65.2	34.8	0.0
rs1641729	*BCL2L14*	52.5-70.8	25.0-37.3	4.2-10.2	82.6	17.4	0.0
rs2448050	*BCL2L14*	48.3-51.7	45.0-46.7	3.3-5.0	n/a	n/a	n/a
rs2448063	*BCL2L14*	48.3-51.7	43.1-48.3	3.3-5.2	n/a	n/a	n/a
rs6488494	*BCL2L14*	27.1-33.3	39.0-45.8	20.8-31.7	30.4	52.2	17.4
rs4763780	*BCL2L14*	48.3-63.6	27.3-50.0	4.2-9.1	26.1	30.4-33.3	43.5-66.7
rs4763781	*BCL2L14*	35.2	37.0	27.8	n/a	n/a	n/a
rs4763782	*BCL2L14*	28.8-30.0	45.0-45.8	25.0-25.4	n/a	n/a	n/a
rs879732	*BCL2L14*	20.8-40.4	43.9-46.7	15.0-33.3	17.4	43.5	39.1
rs885637	*BCL2L14*	42.4-44.8	43.1-45.8	11.9-12.1	n/a	n/a	n/a
rs885720	*BCL2L14*	52.2-74.5	23.6-47.8	1.7-1.8	30.4	43.5	26.1
rs888152	*BCL2L14*	36.4-100.0	16.7-50.0	4.2-14.3	66.7-75.0	25.0-33.3	0.0
rs1950252	*BCL2L2*	85.0-87.5	12.5-13.6	1.7	91.3	8.7	0.0
rs181402	*BID*	16.7-73.7	26.3-61.7	1.7-21.7	65.0	30.0	5.0
rs181405	*BID*	25.0-35.0	50.0-100.0	13.3-25.0	87.0	8.7	4.3
rs181408	*BID*	12.5-31.7	50.0-50.8	18.3-37.5	21.7	47.8	30.4
rs181417	*BID*	73.3	26.7	0.0	n/a	n/a	n/a
rs366542	*BID*	25.0	51.7	23.3	n/a	n/a	n/a
rs5746474	*BID*	29.1	63.6	7.3	n/a	n/a	n/a
rs5747351	*BID*	35.0-45.8	45.8-58.3	6.7-8.3	13.0	30.4	56.5
rs738095	*BID*	82.4-88.3	11.7-17.6	0.0	58.1	37.1	4.8
rs9604787	*BID*	73.3-81.1	18.9-26.7	0.0	n/a	n/a	n/a
rs1883263	*BIK*	39.0	55.9	5.1	n/a	n/a	n/a
rs4988360	*BIK*	66.7	30.0	3.3	93.5	6.5	0.0
rs4988366	*BIK*	76.7	23.3	0.0	36.1	59.0	4.9
rs738276	*BIK*	42.1-54.2	41.7-53.3	4.2-10.5	52.2-65.2	28.3-39.1	6.5-8.7
rs1042992	*BNIP3L*	62.5-100.0	20.3-36.4	1.7-4.2	502-60.9	39.1-50.0	0.0
rs10503786	*BNIP3L*	54.4-58.3	25.0-45.6	8.5-16.7	100.0	0.0	0.0
rs10405717	*CARD8*	71.7	25.0	3.3	n/a	n/a	n/a
rs10416565	*CARD8*	100.0	0.0	0.0	60.9	34.8	4.3
rs11670259	*CARD8*	38.3-56.5	30.4-48.3	13.0-13.3	73.9	26.1	0.0
rs11672725	*CARD8*	58.3-61.7	33.3-37.5	4.2-5.0	65.2	21.7	13.0
rs6509364	*CARD8*	41.7-45.0	40.0-41.7	15.0-16.7	60.9	30.4	8.7

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 8. Prevalence Data for Variant Apoptotic Targets, *continued*[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs6509366	*CARD8*	41.7-45.0	45.8-46.7	8.3-12.5	52.2	39.1	8.7
rs1049216	*CASP3*	41.9-61.8	26.5-45.8	8.3-12.9	67.7-69.9	26.1-41.7	1.6-4.3
rs2019978	*CASP3*	58.3-100.0	28.3-41.7	6.7-8.7	75.0	25.0	0.0
rs507879	*CASP5*	23.3-42.9	28.6-63.6	4.5-28.6	7.1-16.7	50.0-64.3	28.6-33.3
rs537093	*CASP5*	23.8-25.0	38.1-55.0	20.0-38.1	46.7-54.5	36.4-40.0	9.1-13.3
rs3181187	*CASP6*	33.3-33.9	45.8-58.3	8.3-20.8	54.5-66.1	29.0-31.8	4.8-13.6
rs3212153	*CASP6*	61.7-66.7	29.2-36.7	1.7-4.2	91.3	8.7	0.0
rs768063	*CASP6*	86.7-88.3	11.7-13.3	0.0	n/a	n/a	n/a
rs12415607	*CASP7*	57.6	37.3	5.1	n/a	n/a	n/a
rs10931934	*CASP8*	33.3-45.5	42.4-45.5	9.1-23.7	6.7	46.7	46.7
rs6747918	*CASP8*	12.5-31.8	41.9-58.3	18.2-29.2	43.5-60.0	13.3-30.4	3.4-26.7
rs1052571	*CASP9*	30.0-30.5	42.4-43.3	23.7-26.7	8.2	45.9	45.9
rs1052576	*CASP9*	29.8-34.5	41.4-43.9	26.3-27.6	4.2-8.2	41.7-45.9	45.9-54.1
rs4645989	*CASP9*	63.0	35.2	1.9	n/a	n/a	n/a
rs12817549	*CRADD*	35.0-50.0	41.7-43.3	8.3-21.7	47.8	43.5	8.7
rs3858606	*CRADD*	45.8-46.7	37.5-41.7	11.7-16.7	26.1	47.8	26.1
rs11588734	*DFFA*	71.7	26.7	1.7	n/a	n/a	n/a
rs12738235	*DFFB*	53.3-86.7	13.3-40.0	6.7	n/a	n/a	n/a
rs3205087	*DFFB*	25.9	53.4	20.7	n/a	n/a	n/a
rs4074709	*DFFB*	76.7-85.7	13.2-20.0	3.3-3.8	78.3	17.4	4.3
rs4648426	*DFFB*	49.1	49.1	1.8	n/a	n/a	n/a
rs12870	*DIABLO*	33.3	45.0	21.7	n/a	n/a	n/a
rs12870	*DIABLO*	71.7	26.7	1.7	n/a	n/a	n/a
rs7972948	*HRK*	51.7	41.7	6.7	n/a	n/a	n/a
rs9669553	*HRK*	51.7	41.7	6.7	n/a	n/a	n/a
rs1048906	*IKBIP*	40.0-50.0	37.5-53.3	6.7-12.5	26.1	52.2	21.7
rs12371097	*IKBIP*	63.3-66.7	33.3-34.8	3.3-4.2	n/a	n/a	n/a
rs12821083	*IKBIP*	53.3-60.9	30.4-41.7	5.0-8.7	30.4	65.2	4.3
rs11578093	*IKBKE*	36.7	45.0	18.3	n/a	n/a	n/a
rs1539243	*IKBKE*	71.4-100.0	20.8-28.6	1.7-4.2	83.3-87.0	13.0-16.7	0.0
rs1930438	*IKBKE*	65.2-69.5	28.8-34.8	1.7	n/a	n/a	n/a
rs944775	*IKBKE*	25.9-30.4	39.1-60.9	13.0-32.8	17.4	56.5	26.1
rs11688	*JUN*	86.7	13.3	0.0	n/a	n/a	n/a
rs13096	*KRAS*	25.4-54.5	27.3-49.2	18.2-25.4	68.2	27.3	4.5
rs9266	*KRAS*	23.7-52.2	30.4-49.2	17.4-27.1	65.2	30.4	4.3
rs1609798	*NFKB1*	41.7-44.1	45.8-50.0	8.3-10.2	73.9	26.1	0.0
rs230547	*NFKB1*	89.8-96.7	3.3-8.5	1.7-4.2	62.5-73.9	26.1-33.3	1.6-4.2
rs1056890	*NFKB2*	45.0	38.3	16.7	0.0	0.0	0.0

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 8. Prevalence Data for Variant Apoptotic Targets, *continued*[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs696	*NFKBIA*	31.7-40.0	50.0-55.0	5.0-18.3	17.4	43.5	39.1
rs8904	*NFKBIA*	31.7-48.4	38.7-50.0	12.5-18.6	6.7-20.8	40.9-58.3	20.8-46.7
rs2230365	*NFKBIL1*	58.1-75.0	25.0-38.7	3.2	90.0-95.8	4.2-10.0	0.0
rs11656099	*PRKCA*	55.0-56.7	36.7-38.3	6.7	n/a	n/a	n/a
rs8074995	*PRKCA*	80.0	20.0	0.0	n/a	n/a	n/a
rs9890506	*PRKCA*	86.4-86.7	11.7-11.9	1.7	n/a	n/a	n/a
rs1530668	*PRKCE*	93.3	6.7	0.0	n/a	n/a	n/a
rs17034455	*PRKCE*	78.3-100.0	10.3-17.4	3.4-4.3	95.7	4.3	0.0
rs2594489	*PRKCE*	41.4-41.7	37.5-50.0	8.3-20.8	4.3	26.1	69.6
rs281472	*PRKCE*	83.1-83.3	15.0-15.3	1.7	n/a	n/a	n/a
rs281476	*PRKCE*	53.3-66.7	28.8-33.3	16.7-16.9	56.5	34.8	8.7
rs281505	*PRKCE*	32.8-33.3	50.0	16.4-17.2	n/a	n/a	n/a
rs281508	*PRKCE*	40.7-75.0	16.7-43.3	8.3-12.5	17.4-50.0	50.0-78.3	4.3
rs3820729	*PRKCE*	80.0	16.7	3.3	n/a	n/a	n/a
rs608139	*PRKCE*	63.3	31.7	5.0	n/a	n/a	n/a
rs935672	*PRKCE*	33.3-49.2	32.2-54.2	12.5-18.3	4.3	47.8	47.8
rs935673	*PRKCE*	31.7-37.5	50.0-60.0	8.3-12.5	12.5	50.0	37.5
rs951012	*PRKCE*	35.0-50.0	36.7-45.8	8.3-21.7	21.7-35.0	50.0-60.9	8.3-15.0
rs2236379	*PRKCQ*	61.7	35.0	3.3	47.2	43.4	9.4
rs2236380	*PRKCQ*	45.0-54.2	41.7-50.0	4.2-5.1	8.7	26.1	65.2
rs519951	*PRKCQ*	58.3-68.3	30.0-37.5	1.7-4.2	39.1	43.5	17.4
rs571715	*PRKCQ*	58.3-85.7	14.3-37.5	1.7-4.2	43.5-77.8	11.1-39.1	10.0-17.4
rs574521	*PRKCQ*	58.3-66.7	31.7-37.5	1.7-4.2	43.5	39.1	17.4
rs585881	*PRKCQ*	58.3-66.7	31.7-37.5	1.7-4.2	39.1	43.5	17.4
rs11128607	*RAF1*	65.0	31.7	3.3	n/a	n/a	n/a
rs11709504	*RAF1*	66.7-69.5	27.1-29.2	3.4-4.2	39.1	43.5	17.4
rs11710163	*RAF1*	83.3	16.7	0.0	n/a	n/a	n/a
rs13060691	*RAF1*	88.7	11.3	0.0	n/a	n/a	n/a
rs6442322	*RAF1*	33.3	50.0-51.7	15.0-16.7	56.5	39.1	4.3
rs6792773	*RAF1*	65.0	31.7	3.3	n/a	n/a	n/a
rs7643321	*RAF1*	68.3-79.6	16.7-28.3	3.3-3.7	n/a	n/a	n/a
rs7956	*RAF1*	61.0-62.5	33.3-33.9	4.2-5.1	52.4	33.3	14.3
rs904453	*RAF1*	31.7-42.9	45.5-57.1	15.0-18.2	28.6-35.5	43.5-45.5	14.3-21.0
rs9817675	*RAF1*	56.7-69.6	26.1-40.0	3.3-4.3	50.0	38.9	11.1
rs7101916	*RELA*	71.7	25.0	3.3	n/a	n/a	n/a
rs7739011	*RIPK1*	86.7	13.3	0.0	n/a	n/a	n/a
rs11247963	*RPS6KA1*	66.7-67.9	23.2-23.3	8.9-10.0	n/a	n/a	n/a

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

Table 8. Prevalence Data for Variant Apoptotic Targets, *continued*[52]

dbSNP ID	Gene	Cau WT/WT	Cau WT/VT	Cau VT/VT	AA WT/WT	AA WT/VT	AA VT/VT
rs1865077	*RRAS*	43.3-43.5	34.8-48.3	8.3-21.7	54.5	40.9	4.5
rs1000294	*TNFRSF10A*	60.0	38.3	1.7	n/a	n/a	n/a
rs13255394	*TNFRSF10A*	22.4	58.6	19.0	n/a	n/a	n/a
rs13278062	*TNFRSF10A*	16.9	67.8-100.0	15.3	n/a	n/a	n/a
rs2230229	*TNFRSF10A*	68.3-71.7	25.0-28.3	3.3	71.7	28.3	0.0
rs6557634	*TNFRSF10A*	29.2-38.3	41.4-54.2	16.7-20.3	34.8	56.5	8.7
rs7842021	*TNFRSF10A*	31.7	46.7	21.7	n/a	n/a	n/a
rs1001793	*TNFRSF10B*	56.7	40.0	3.3	n/a	n/a	n/a
rs1047266	*TNFRSF10B*	95.0	5.0	0.0	n/a	n/a	n/a
rs11135693	*TNFRSF10B*	33.3	51.7	15.0	n/a	n/a	n/a
rs9644062	*TNFRSF10B*	62.1	36.2	1.7	n/a	n/a	n/a
rs1133782	*TNFRSF10D*	40.0	45.0	15.0	n/a	n/a	n/a
rs6651394	*TNFRSF10D*	76.7	20.0	3.3	n/a	n/a	n/a
rs7463799	*TNFRSF10D*	75.9	20.7	3.4	n/a	n/a	n/a
rs7957	*TNFRSF10D*	60.0	36.7	3.3	n/a	n/a	n/a
rs1860545	*TNFRSF1A*	14.3-30.0	46.7-66.7	19.0-23.3	73.9	26.1	n/a
rs4149570	*TNFRSF1A*	45.5-50.9	40.4-47.8	4.3-9.1	78.3-80.6	19.4-21.7	0.0
rs4149576	*TNFRSF1A*	28.3-33.3	43.3-57.1	9.5-28.3	1.6	25.8-31.6	68.4-72.6
rs4149577	*TNFRSF1A*	35.0-40.9	45.5-50.0	13.6-15.0	75.0	25.0	0.0
rs4149578	*TNFRSF1A*	78.0-86.4	13.6-18.6	1.7	58.3-61.3	35.5-41.7	3.2
rs1061622	*TNFRSF1B*	52.5-62.5	37.5-44.1	3.3-3.4	68.4-75.8	17.7-29.2	5.3-6.5
rs2270418	*TNFSF10*	64.4-66.7	30.0-33.3	5.0-5.1	82.6	17.4	0.0
rs231983	*TNFSF10*	35.0-37.5	45.0-58.3	4.2-21.1	12.5-21.7	34.8-54.2	32.2-43.5
rs365238	*TNFSF10*	78.3-79.2	17.4-21.7	0.0	n/a	n/a	n/a
rs4894559	*TNFSF10*	55.9-58.3	36.7-41.7	6.7-6.8	87.0	13.0	0.0
rs9859259	*TNFSF10*	33.3	55.0	11.7	n/a	n/a	n/a
rs2078486	*TP53*	83.3-90.0	7.7-13.3	3.3-3.8	52.2-65.2	30.4-46.7	4.3-6.5
rs2909430	*TP53*	67.7-84.7	15.3-22.6	9.7	50.0	45.8	4.2
rs4735334	*TP53INP1*	48.3	45.0	6.7	n/a	n/a	n/a
rs896849	*TP53INP1*	70.8-100.0	10.0-29.2	3.4-10.0	30.4-33.3	52.2-66.7	17.4
rs896854	*TP53INP1*	25.0-91.7	8.3-45.0	25.0	n/a	n/a	n/a
rs3750512	*TRAF2*	33.3-43.5	50.0-56.5	16.7	72.7	27.3	0.0
rs4880073	*TRAF2*	38.3	36.7	25.0	n/a	n/a	n/a

Abbreviations: Cau, Caucasians; AA, African-Americans, WT, wild-type; VT, variant

GENETIC ANALYSIS OF VARIANT OSR MARKERS

To evaluate interactions among candidate OSR related genetic alterations in relation to PCA development we used genetic profile data collected from participants within our study populations. The CGEMS project has genotyped nearly 550,000 common genetic variants (SNPs) among 2,277 men of European descent (488 non-aggressive cases, 688 aggressive cases and 1101 controls).[119] Genetic profiling was performed using the Illumina Human HapMap500 chips (Illumina, Inc, San Diego, CA). Access to clinical and background data collected through examinations and questionnaires was approved for use by PLCO. UofL IRB approval is not required for the use of nationally available de-identified data.

Candidate SNPs were detected among MAD subjects using TaqMan®- PCR allelic discrimination assays (Applied Biosystems, Foster City, CA) and 48-Plex GenomeLab™ SNPstream® Genotyping System (Beckman Coulter, Brea, CA). Based on 24 non-DNA template controls per batch analysis (n = 384), the percent cross-contamination during sample handling was minimal (<4.0%). Duplicate genotyping was performed for 72 randomly selected samples for quality control purposes, resulting in concordance rates >98%.

SINGLE & MULTIPLE OSR FACTORS IN RELATION TO PROSTATE CANCER OUTCOMES

Logistic Regression Analysis. Logistic regression analysis was used to evaluate 219 and 25 OSR associated SNPs among men of European and African descent, respectively, in relation to prostate cancer outcomes. To assess whether individuals possessing at least one variant (i.e., minor) oxidative stress allele have an elevated risk of developing PCA, we tested for significant differences in the distribution of homozygous wildtype, heterozygous, and homozygous minor genotypes between cases and controls using the chi-square test of heterogeneity. Case-control and case-case analyses were used to evaluate variant OSR related alleles in relation to PCA risk and aggressive disease (Gleason score < 7 and tumor stage ≥3 versus Gleason score >7 and tumor stage ≤2). The associations between PCA and candidate polymorphic genes, expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs), were estimated using unconditional multivariate LR models adjusted for potential confounders. LR analysis for genetic variants and PCA development were conducted using the wild-type or common genotype as referent category. Risk estimates for MED were adjusted for age and family history of prostate cancer. Whereas, risk estimates for MAD were adjusted for age and WAA. All chi-square tests and LR analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was assessed using a p value < 0.05.

Analysis of SNP pairwise interactions using LR. Two-way (i.e., gene-gene and gene-environment) interactions were evaluated by the significance of the coefficient of the product term $\beta_3 factor\_1 * factor\_2$ in the following model: $Logit = \beta_0 + \beta_1 factor\_1 + \beta_2 factor\_2 + \beta_3 factor\_1 * factor\_2$. Interaction models were adjusted for potential confounders.

Reduction. To evaluate the single- and joint- modifying effects of hundreds of candidate SNPs within a large dataset, such as CGEMS is computationally challenging.[130-131] In order to overcome this problem, Multifactor Dimensionality Reduction (MDR) 2.0 (SourceForge, Inc, Sourceforge.net) was used to prioritize OSR sequence variants. The MDR software is open-source and freely available online.[132] MDR is a method for detecting and characterizing high-order interactions in case-control studies, one remaining effective with relatively small sample sizes.[80] With MDR, multi-locus genotypes are pooled into high-risk and low-risk groups, reducing high-dimensional data to a single variable dimension and permitting an investigation of gene-gene and gene-environment interactions. Concisely, this one-dimensional multi-locus genotype variable was evaluated for its ability to classify and predict disease susceptibility through cross-validation and permutation testing. Among all of the gene-gene and gene-environment combinations, a single model was selected that maximized the case-to-control ratio of the high-risk groups while minimizing classification and prediction errors.

The current version of MDR used in this project allows for the incorporation and adjustment of multiple covariates.[133] To remove the covariate effect, we integrated two sampling methods (i.e., over- and under-sampling). This approach is computationally efficient, thus allowing for adjustment of multiple covariates without significantly increasing computational burden. Inclusion of covariates allows estimates of specificity, sensitivity, and overall predictive accuracy with and without the genetic factors, to assess the gains in predictive ability afforded by the genetic factors.

To evaluate how many times the same MDR model is identified in each possible $9/10^{ths}$ of the data and repeats this 10-fold cross-validation 10 times until the entire dataset is evaluated.[134] Therefore, CVC values can range from 1/10 up to 10/10, with a CVC = 10/10 indicating that a model was selected as the best predictor 10 out 10 times.[134] The prediction error is calculated as the average of prediction errors across each of the 10 cross-validation subsets.[134-135] The model with the greatest CVC (e.g. ≥ 7/10) and lowest prediction error [e.g., Average Testing Accuracy (ATA) values between 0.540-0.600] is selected as the best predictor of disease outcome.[134-135] MDR models are validated by comparing the average CVC to the distribution of the average consistencies under the null hypothesis of no association, to be derived empirically from 1,000 permutations. The null hypothesis is rejected when the upper-tail Monte Carlo p value is ≤ 0.05. LR was used to calculate risk estimates of the joint modifying effects of two or more factors identified by MDR.

Most data mining methods, including MDR, are by nature nonparametric, model free, and data-driven. Determining the statistical significance of these models requires

rigorous permutation testing to evaluate statistical significance while accounting for multiple testing issues. With permutation testing, the data relationships are randomized in a way consistent with the null hypothesis of no association. With many such datasets, the distribution of the statistical measure of association under the null hypothesis can be generated and used to calculate an empirical p value for the statistic calculated in the original dataset. This approach accounts for multiple testing issues as long as the entire model-fitting procedure is repeated for each randomized dataset to provide an opportunity to identify false-positives.

MDR with Covariate Adjustment. A newly updated version of the MDR software allows for the incorporation and adjustment of covariates in evaluating gene-gene interactions. To remove the covariate effect, we will incorporate two sampling methods (i.e, over- and under-sampling). The approach is computationally efficient, thus allowing for adjustment of multiple covariates without significantly increasing computational burden.

with Spatially Uniform ReliefF (SURF) & Tuned ReliefF (TuRF) Filtering. Filtering options, such as RefliefF, built into MDR that rank and select factors most likely to be associated with the outcome of interest.[130-131] Since the filter removes SNPs possessing the lowest predictive value, the "background noise" is typically reduced.[130-131] Hence, using a filtered dataset improves the likelihood of detecting relevant interactions associated

with a particular outcome.[130-131] For this study, a combinatorial version of Relief called Spatially Uniform ReliefF (SURF) & Tuned ReliefF (TuRF) was used to filter the large candidate SNP list in order to select the most promising targets.[130-131] With respect to genetic association studies, ReliefF assigns a weight to each SNP using multiple individuals that are genetically similar.[130-131] TuRF repeats the ReliefF algorithm and with each repetition of SNPs with the lowest predictive values are removed; while SURF adjusts the weights of all the SNPs using all neighbors within a fixed distance (i.e., similarity threshold).[130] The combined effect of combining both approaches as SURF & TuRF essentially iterates SURF, but substantially improves detection of epistatic interactions compared to using either method individually.[130]

To minimize any interactions that could potentially be removed by filtering, the OSR candidate panel was analyzed separately by each pathway in additional to analyzing the entire panel with the SURF & TuRF. Hence, there were a total of four MDR analyses conducted for the genetic factors, one combined analysis that was filtered, as well as separate analyses for all the antioxidative-, BER- and apoptosis-related SNPs.

SPECIALIZED VISUALIZATION TOOLS (INTERACTION ENTROPY ALGORITHMS & HIERARCHICAL GRAPHS

Interaction entropy algorithm, based on information theory, is a method to verify, visualize, and interpret combination effects identified by LR and MDR.[80, 136-138] Orange software was used to perform interaction entropy analysis among candidate OSR factors and PCA development. This strategy will help to interpret multi-locus interactions identified by parametric and non-parametric modeling. Interaction entropy uses information gain (IG) to gauge whether interactions between two or more factors provide more information about PCA outcomes relative to each factor considered independently.[80, 136-138]

Individual and all possible pairwise loci are assigned an IG percentage score in relation to disease risk or aggressiveness (scores < 5% are typical).[80, 136-138] Explain why IG scores <5% are reasonable. Pairwise SNP combinations are deemed important if the pairwise IG is greater than the IG for each individual locus ($IG_{FACTOR\_1+\ FACTOR\_2} > IG_{FACTOR\_1}$ and $IG_{FACTOR\_1+\ FACTOR\_2} > IG_{FACTOR\_2}$).[80, 137-139] Interactions can be further visualized using an interaction graph. Strongly interacting factors are coded either red or orange, indicating high and medium levels of synergistic effects on outcomes, respectively [*See Figure 8*].[80, 136-139] Weakly interacting factors are coded either blue or green to denote high or modest levels of redundancy between markers, respectively. Gold colored branches are neither redundant nor synergistic.[137-139] Similarly, this tool can also be

used to visualize whether single or multi-markers have a stronger outcome prediction capacity relative to gold standard demographic and clinic-pathological parameters.[137-139]

Figure 8. Interaction Entropy Graph

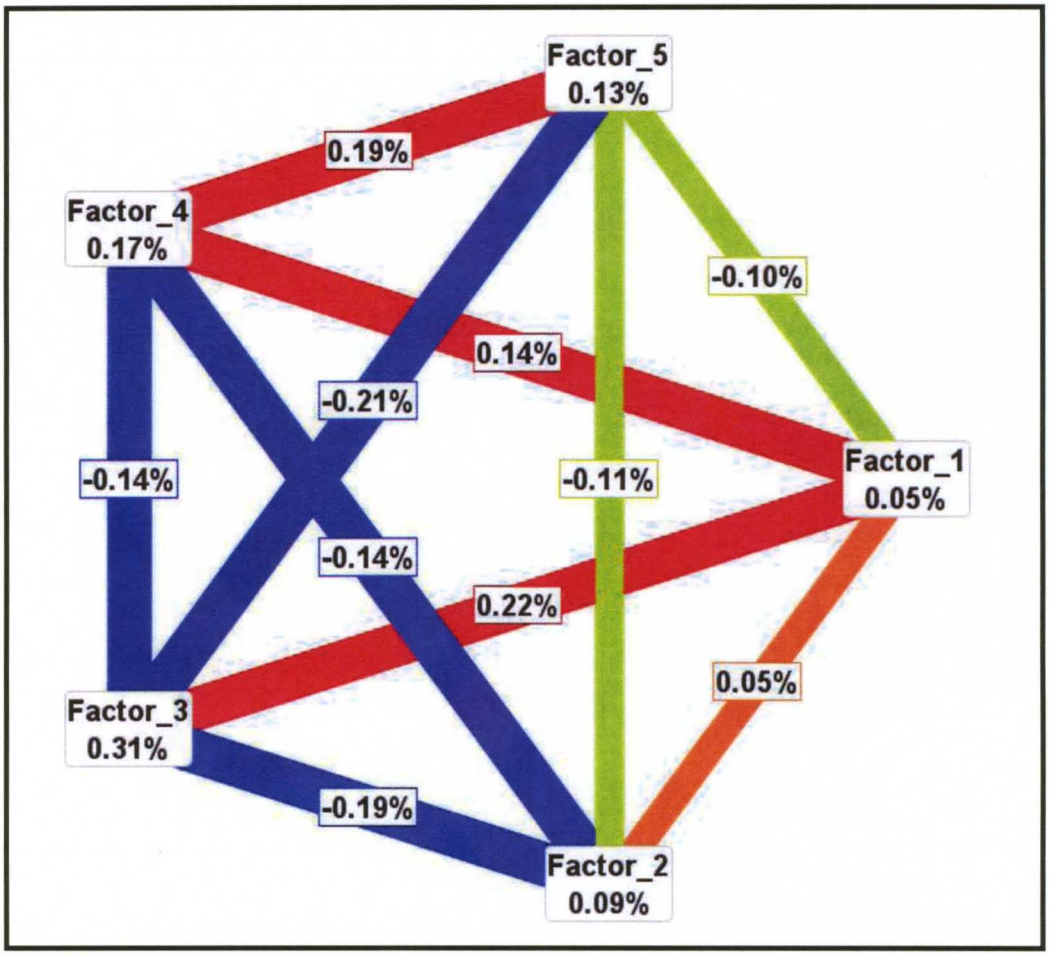


Figure 8: Interaction Entropy Graph. Interaction entropy uses information gain (IG) to gauge whether interactions between two or more factors provide more information about PCA outcomes relative to each factor considered independently. The strongest interacting factors are coded in red indicating a high level of synergy. As shown in this figure, the strongest interaction detected is between Factors 4 and 5 evidenced by an IG score of 0.19%. Factors 4 and 5 provide more information about the outcome of interest relative to either factor when considered alone based on individual IG scores of 0.13% and 0.17%, respectively. A moderately synergistic interaction exists between Factor 1 and 2, as shown in orange. Weakly interacting factors are coded either blue (i.e., Factor 2-4, Factor 3-4, and Factor 3-5) or green (i.e., Factor 1-5 and Factor 2-5) to denote high or modest levels of redundancy between markers, respectively. Gold colored branches are neither redundant nor synergistic.

RESULTS

Population Description among CGEMS Participants. CGEMS study participants consisted of middle aged non-Hispanic Caucasian men (MED), ranging in ages between 55 and 81. A large portion of the study participants consumed adequate amounts of fruits (>4 servings/day) and vegetables (>5 servings/day), vitamins, and supplements. Despite these healthy eating practices, a majority of the men were overweight/obese (61.1%), as delineated in *Tables 9 & 13*. Men diagnosed with prostate cancer were more likely to have a family history of prostate cancer (11.4% versus 6.3%), PSA levels > 4ng/ml (49.8% versus 6.5%), and irregular DRE exams (64% versus 48.9%) relative to controls, as depicted in table 8. However there were no marked differences in smoking status, body mass index (BMI), lifestyle characteristics (i.e, meat intake, fruit/vegetable intake, vitamin supplement usage, physical activity, usage, alcohol consumption), daily total caloric intake, comparing cases to controls or aggressive and non-aggressive cases, as depicted in *Tables 9 & 11-15*.

Population Description among men of African Descent. Descriptive information for the men of African Descent (MAD) study participants is summarized in *Table 10*. Cases were significantly older and had higher PSA levels relative to controls. There was

a significant difference in median West African genetic ancestry estimates comparing cases and controls (p = 0.004).

Table 8. Patient and Tumor Characteristics by disease status among European-American male participants of the CGEMS Study

Characteristics	Cases	Controls	p value[a]
Number of Participants, n	1176	1101	---
Age at diagnosis (yrs), median (range)	67 (55-81)	67 (55-80)	0.299
Age at enrollment (yrs), median (range)	65 (55-74)	64 (55-74)	0.094
Family History of Prostate Cancer, n (%)			
Yes	133 (11.4)	70 (6.3)	<0.0001
No	1031 (88.6)	1043 (93.7)	
PSA (ng/ml), n (%)			
< 4	569 (50.2)	1022 (93.5)	<0.0001
≥ 4	564 (49.8)	71 (6.5)	
Missing	31 (1.4)	20 (0.8)	
DRE results, n (%)			
Normal	398 (36.0)	537 (51.1)	<0.0001
Abnormal, suspicious	472 (42.8)	438 (41.8)	
Abnormal, non-suspicious	234 (21.2)	75 (7.1)	
Missing	60 (2.6)	63 (0.3)	
Gleason Score,[b] n (%)			
4	49 (4.2)		
5	151 (13.0)		
6	357 (30.7)		
7	467 (40.2)		
8	69 (5.9)		
9	44 (3.8)		
10	3 (0.3)		
Body Mass Index (BMI),[c] n (%)			
Underweight or normal	305 (26.2)	271 (24.4)	0.244
Overweight	612 (52.6)	574 (51.7)	0.648
Obese	246 (21.2)	266 (23.9)	0.111
Missing	1 (0.4)	2 (0.9)	
Tobacco Use, n (%)			
Never	477 (41.0)	421 (37.9)	0.045
Former	593 (51.0)	570 (51.3)	0.880
Current	93 (8.0)	120 (10.8)	0.022
Ever (Former & Current)	686 (59.0)	690 (62.1)	0.128

Abbreviations: PSA, prostate specific antigen; DRE, digital rectal examination; [a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test; [b]Underweight or normal: BMI <24.9; Overweight: BMI 25-29.9; Obese: BMI >30 based on values established by the 2005 USDA Dietary Guidelines;[120]

Table 10. Patient and Tumor Characteristics for Men of African Descent

Characteristics	Cases	Controls	p value[a]
Number of Participants, n	219	694	---
Age at diagnosis (yrs), median (range)	65 (41-91)	53 (26-89)	0.0001
PSA (ng/ml), n (%)			
< 4	45 (20.5)	636 (91.6)	< 0.0001
≥ 4	174 (79.5)	58 (8.4)	
Gleason Score, n (%)			
4	18 (13.1)		
5	16 (11.7)		
6	35 (25.6)		
7	41 (29.9)		
8	7 (5.1)		
9	16 (11.7)		
10	4 (2.9)		
Tobacco Use, n (%)			
Current	26 (12.0)	11 (2.0)	0.825
Former	53 (24.5)	20 (3.6)	
Never	71 (32.9)	33 (6.0)	
Missing	66 (30.6)	491 (88.4)	
Global WAA, mean (SD)	0.734 (0.253-0.937)	0.716 (0.255-0.946)	0.004

Abbreviations: PSA, prostate specific antigen; WAA, West African Ancestry; *Differences in frequencies were tested by a Chi-square test of heterogeneity, differences in age and Global West African Ancestry between cases and controls were tested using the Wilcoxon sum Rank test.

Table 11. Lifestyle Characteristics by disease status among European-American male participants of the CGEMS Study

Dietary Factor	Cases	Controls	p value[a]
Meat Consumption (g/day), median (IQR)			
Total meat	173.9 (118.4-254.2)	174.5 (129.3-252.9)	0.166
White Meat (chicken & fish)	42.6 (25.1-71.9)	44.6 (26.2-71.8)	0.478
Processed meat	11.4 (6.1-21.0)	11.4 (6.1-21.0)	0.646
Red Meat group	80.9 (47.6-125.0)	82.7 (53.9-124.2)	0.278
Red meat not processed	62.1 (38.6-95.7)	62.1 (38.6-95.7)	0.396
Red meat rare/med done	15.0 (3.8-33.6)	16.0 (3.9-32.4)	0.567
Red meat well/very well done	9.3 (4.1-19.8)	9.8 (4.9-19.8)	0.141
Fruit (servings/day),[b] n (%)			
≥ 4	975 (83.8)	952 (85.7)	0.219
< 4	188 (16.2)	159 (14.3)	
Missing	1 (0.4)	2 (0.9)	
Vegetables (servings/day),[b] n (%)			
≥ 5	907 (78.0)	831 (74.8)	0.073
< 5	256 (22.0)	280 (25.2)	
Missing	1 (0.4)	2 (0.9)	
Kcal from diet (g/day),[b] n (%)			
2000-3000	559 (48.1)	522 (47.0)	0.821
< 2000	395 (33.9)	391 (35.2)	0.538
> 3000	209 (18.0)	198 (17.8)	0.926
Missing	1 (0.4)	2 (0.9)	
Fat from diet (g/day), median (IQR)			
Fat	73.1 (95.5-56.4)	72.7 (99.2-55.7)	0.884
Saturated	25.0 (32.4-18.6)	24.6 (34.0-18.5)	0.790
Missing	1 (0.4)	2 (0.9)	
Physically Active (at least 30 min/day),[c] n (%)			
Currently	556 (47.8)	494 (44.5)	0.177
Since age 40	559 (50.3)	620 (53.3)	0.224
Missing	1 (0.4)	2 (0.9)	
Alcohol Consumption (drinks/day),[b] n (%)			
≤ 2	960 (82.6)	923 (83.1)	0.736
> 2	203 (17.4)	188 (16.9)	
Missing	1 (0.4)	2 (0.9)	

Abbreviations: IQR, Interquartile range; [a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test

Table 12. Vitamin and supplement by disease status among European-American male participants of the CGEMS Study

Vitamin/Mineral	Cases	Controls	p value[a]
Vitamin A (µg/day),[b] n (%)			
≥ 900	1054 (90.6)	1008 (90.6)	0.990
< 900	110 (9.4)	105 (9.4)	
Missing	0 (0.0)	0 (0.0)	
Vitamin C (mg/day),[b] n (%)			
≥ 75	1103 (94.8)	1042 (93.6)	0.245
< 75	61 (5.2)	71 (6.4)	
Missing	0 (0.0)	0 (0.0)	
Vitamin E (IU/day),[b] n (%)			
≥ 15	1014 (87.1)	952 (87.1)	0.273
< 15	150 (12.9)	161 (14.5)	
Missing	0 (0.0)	0 (0.0)	
Zinc (mg/day),[b] n (%)			
≥ 11	838 (72.0)	775 (69.6)	0.215
< 11	326 (28.0)	338 (30.4)	
Missing	0 (0.0)	0 (0.0)	
Selenium (µg/day),[b] n (%)			
≥ 55	1128 (97.0)	1085 (97.7)	0.324
< 55	35 (3.0)	26 (2.3)	
Missing	1 (0.4)	2 (0.9)	

[a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test; [b]Risk categories are based on values established in the 2005 USDA dietary guidelines & NIH office of dietary supplements

Table 13. Patient and Tumor Characteristics among CGEMS participants diagnosed with Prostate Cancer

Characteristics	Aggressive Cases	Non-Aggressive Cases	p value[a]
Number of Participants, n	688	488	---
Age at diagnosis (yrs), Median (range)	67 (55-81)	66 (55-78)	0.083
Age at enrollment (yrs), Median (range)	64 (55-74)	65 (55-74)	0.080
Family History of Prostate Cancer, n (%)			
Yes	605 (87.9)	435 (89.1)	0.525
No	83 (12.1)	53 (10.9)	
PSA (ng/ml), n (%)			
< 4	347 (52.1)	230 (48.0)	0.173
≥ 4	319 (47.9)	249 (52.0)	
Gleason Score,[b] n (%)			
4	4 (0.6)	45 (9.8)	< 0.0001
5	18 (2.6)	133 (29.0)	
6	86 (12.6)	271 (59.2)	
7	459 (67.3)	8 (1.8)	
8	68 (10.0)	1 (0.2)	
9	44 (6.5)	0 (0.0)	
10	3 (0.4)	0 (0.0)	
DRE results, n (%)			
Normal	241 (36.9)	159 (34.4)	0.435
Abnormal, suspicious	282 (43.2)	197 (42.6)	
Abnormal, non-suspicious	130 (19.9)	106 (23.0)	
Body Mass Index (BMI),[b] n (%)			
Underweight or normal	180 (26.2)	127 (26.0)	0.126
Overweight or normal	350 (51.0)	272 (55.8)	0.105
Obese	157 (22.8)	89 (18.2)	0.055
Missing			
Tobacco Use, n (%)			
Never	296 (43.1)	186 (38.1)	0.169
Former	335 (48.8)	265 (54.3)	0.061
Current	56 (8.1)	37 (7.6)	0.722
Ever (Former & Current)	391 (56.9)	302 (61.9)	0.088

Abbreviations: PSA, prostate specific antigen; DRE, digital rectal examination; [a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test; [b]Underweight or normal: BMI <24.9; Overweight: BMI 25-29.9; Obese: BMI >30 based on values established by the 2005 USDA Dietary Guidelines;[120]

Table 14. Lifestyle characteristics for CGEMS participants diagnosed with Prostate Cancer

Characteristics	Aggressive Cases	Non-Aggressive Cases	p-value[a]
Meat Consumption (g/day), median (IQR),			
Total meat	174.5 (124.3-24.7)	174.5 (118.1-245.6)	0.918
White Meat (chicken & fish)	44.6 (25.6-66.6)	44.6 (27.6-71.4)	0.129
Processed meat	11.4 (5.9-21.4)	11.4 (5.2-23.5)	0.928
Red Meat group	82.7 (50.8-122.8)	82.7 (50.2-119.8)	0.992
Red meat not processed	62.1 (36.2-93.6)	62.1 (36.7-91.9)	0.831
Red meat rare/med done	16.0 (3.9-32.7)	16.0 (3.8-31.6)	0.838
Red meat well/very well done	9.8 (4.7-19.4)	9.8 (4.2-16.9)	0.496
Fruit (servings/day),[b] n (%)			
< 4	584 (85.0)	403 (82.6)	0.264
≥ 4	103 (15.0)	85 (17.4)	
Missing	1 (0.9)	0 (0.0)	
Vegetables (servings/day),[b] n (%)			
< 5	547 (79.6)	370 (75.8)	0.121
≥ 5	140 (20.4)	118 (24.2)	
Missing	1 (0.9)	0 (0.0)	
Kcal from diet (g/day),[b] n (%)			
2000-3000	336 (48.9)	230 (47.1)	0.352
< 2000	237 (34.5)	161 (33.0)	0.591
> 3000	114 (16.6)	97 (19.9)	0.149
Missing	1 (0.9)	0 (0.0)	
Fat from diet (g/day), median (IQR)			
Fat	73.1 (57.7-94.6)	73.1 (56.4-98.2)	0.196
Saturated	25.0 (19.2-32.5)	25.0 (18.9-34.2)	0.114
Missing	1 (0.9)	0 (0.0)	
Physically Active (at least 30 min/day),[c] n (%)			
Currently	333 (48.5)	229 (46.9)	0.601
Since age 40	371 (54.0)	254 (52.1)	0.508
Missing			
Alcohol Consumption (drinks/day),[b] n (%)			
≤ 2	579 (84.3)	390 (79.9)	0.053
> 2	108 (15.7)	98 (20.1)	
Missing	0 (0.0)	0 (0.0)	

Abbreviations: IQR, Interquartile range; [a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test; [b]Risk categories are based on values established in the 2005 USDA Dietary Guidelines & NIH Office of Dietary Supplements[120-121]

Table 15. Vitamin and supplement use for among CGEMS participants diagnosed with Prostate Cancer

Vitamin/Mineral	Cases	Controls	p value[a]
Vitamin A (µg/day),[b] n (%)			
≥ 900	620 (90.1)	444 (91.0)	0.636
< 900	68 (9.9)	44 (9.0)	
Missing	0 (0.0)	0 (0.0)	
Vitamin C (mg/day),[b] n (%)			
≥ 75	40 (5.8)	22 (4.5)	0.324
< 75	648 (94.2)	466 (95.5)	
Missing	0 (0.0)	0 (0.0)	
Vitamin E (IU/day),[b] n (%)			
≥ 15	93 (13.5)	59 (12.1)	0.472
< 15	595 (13.6)	429 (87.9)	
Missing	0 (0.0)	0 (0.0)	
Zinc (mg/day),[b] n (%)			
≥ 11	491 (71.5)	351 (71.9)	0.876
< 11	196 (28.5)	137 (28.1)	
Missing	0 (0.0)	0 (0.0)	
Selenium (µg/day),[b] n (%)			
≥ 55	24 (3.5)	11 (2.3)	0.218
< 55	663 (96.5)	477 (97.7)	
Missing	0 (0.0)	0 (0.0)	

[a]Differences in frequencies were tested by a Chi-square test of heterogeneity; Differences in continuous variables between cases and controls were tested using the Wilcoxon sum Rank test; [b]Risk categories are based on values established in the 2005 USDA Dietary Guidelines & NIH Office of Dietary Supplements[120-121]

SPECIFIC AIM 1 FINDINGS - MED SUBJECTS

To determine the single- and joint-modifying effects of variations within oxidative stress response (OSR)-related genes in relation to PCA risk, we evaluated 219 genetic variations across 80 OSR genes in relation to disease risk among 2277 MED (1176 cases, 1101 controls). LR analysis revealed two antioxidative-related SNPs were associated with an increase in PCA risk [*See Table 16*]. Possession of at least one minor *CYP2C8_rs7909236* T allele was associated with an increase in risk [OR (95%CI) = 1.24 (1.05-1.47); p = 0.011]. The *EPHX1_rs1051741* TT genotype was linked with 2.5-fold increase in risk compared to wild-type CC genotype. In contrast, possession of two minor *NAT1_rs4921581* AA alleles was associated with a decrease in PCA risk [OR (95%CI) = 0.75 (0.56-0.99); p = 0.042;

We also observed a 1.2-fold increase in risk linked to possession of at least one minor T allele in the BER polymorphisms *OGG1_rs125701* [OR (95%CI) = 1.22 (1.02-1.45); p = 0.030; *See Table 17*]. However, we found a decrease in risk associated with men whom had one or more variant *POLI_rs8305* T alleles [OR (95%CI) = 0.84 (0.71-0.99); p = 0.036].

Among our apoptotic targets, we found four SNPs were linked with a 18-27% decrease in PCA risk (*BIK_rs4988366, BNIP3L_rs10503786, IKBKE_rs1539243*, or *TNFRSF1A_rs4149576*) [*See Table 18*].

Table 16. Association between Antioxidative-related polymorphisms and Prostate Cancer Risk among MED

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs11673270	*CYP2B6*	AA	690 (59.7)	660 (59.7)	1.00 (reference)	1.00 (reference)			
		AC	404 (34.9)	375 (33.9)	1.03 (0.86-1.23)	1.02 (0.86-1.22)	0.808		
		CC	62 (5.4)	71 (6.4)	0.84 (0.59-1.19)	0.79 (0.55-1.13)	0.188	0.674	0.342
		AC+CC	466 (40.3)	446 (40.3)	1.00 (0.85-1.18)	0.98 (0.83-1.17)	0.853		
rs7909236	*CYP2C8*	GG	626 (54.2)	659 (59.6)	1.00 (reference)	1.00 (reference)			
		TG	468 (40.5)	386 (35.0)	1.28 (1.07-1.52)	1.27 (1.07-1.52)	0.007		
		TT	61 (5.3)	60 (5.4)	1.07 (0.74-1.55)	1.06 (0.73-1.54)	0.779	0.036	0.107
		TG+TT	529 (45.8)	446 (40.4)	1.25 (1.06-1.48)	1.24 (1.05-1.47)	0.011		
rs1051741	*EPHX1*	CC	947 (81.4)	898 (80.7)	1.00 (reference)	1.00 (reference)			
		TC	199 (17.1)	208 (18.7)	0.91 (0.73-1.13)	0.91 (0.73-1.13)	0.391		
		TT	18 (1.5)	7 (0.6)	2.44 (1.01-5.86)	2.50 (1.04-6.02)	0.042	0.892	0.300
		TC+TT	217 (18.6)	215 (19.3)	0.96 (0.78-1.18)	0.96 (0.78-1.19)	0.711		
rs638820	*GSTM2*	CC	298 (25.6)	294 (26.4)	1.00 (reference)	1.00 (reference)			
		TC	555 (47.8)	553 (49.7)	0.99 (0.81-1.21)	1.00 (0.82-1.22)	0.998		
		TT	309 (26.6)	266 (23.9)	1.15 (0.91-1.44)	1.16 (0.92-1.46)	0.204	0.249	0.196
		TC+TT	864 (74.4)	819 (73.6)	1.04 (0.86-1.26)	1.05 (0.87-1.27)	0.596		
rs1695	*GSTP1*	AA	513 (44.1)	495 (44.5)	1.00 (reference)	1.00 (reference)			
		AG	505 (43.4)	491 (44.1)	0.99 (0.83-1.18)	0.98 (0.83-1.17)	0.854		
		GG	145 (12.5)	127 (11.4)	1.10 (0.84-1.44)	1.10 (0.84-1.44)	0.493	0.616	0.326
		AG+GG	650 (55.9)	618 (55.5)	1.02 (0.86-1.20)	1.01 (0.85-1.19)	0.932		
rs6591256	*GSTP1*	AA	390 (33.6)	384 (34.5)	1.00 (reference)	1.00 (reference)			
		AG	567 (48.8)	544 (48.9)	1.03 (0.85-1.23)	1.02 (0.85-1.23)	0.839		
		GG	205 (17.6)	185 (16.6)	1.09 (0.86-1.39)	1.09 (0.85-1.39)	0.510	0.502	0.380
		AG+GG	772 (66.4)	729 (65.5)	1.04 (0.88-1.24)	1.04 (0.87-1.23)	0.690		

*Adjusted OR are adjusted for age & family history

Table 16. Association between Antioxidative-related polymorphisms and Prostate Cancer Risk among MED, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs10888150	*NAT1*	CC	387 (33.2)	357 (32.1)	1.00 (reference)	1.00 (reference)			
		TC	578 (49.7)	563 (50.6)	0.95 (0.79-1.14)	0.94 (0.78-1.13)	0.522		
		TT	199 (17.1)	193 (17.3)	0.95 (0.75-1.22)	0.94 (0.74-1.21)	0.637	0.624	0.296
		TC+TT	777 (66.8)	756 (67.9)	0.95 (0.80-1.13)	0.94 (0.79-1.12)	0.502		
rs4921581	*NAT1*	GG	554 (48.0)	512 (46.3)	1.00 (reference)	1.00 (reference)			
		AG	493 (42.7)	463 (41.9)	0.98 (0.83-1.17)	0.98 (0.82-1.16)	0.779		
		AA	108 (9.3)	131 (11.8)	0.76 (0.58-1.01)	0.75 (0.56-0.99)	0.042	0.137	0.207
		AG+AA	601 (52.0)	594 (53.7)	0.94 (0.79-1.10)	0.92 (0.78-1.09)	0.353		
rs7003890	*NAT1*	TT	239 (20.5)	205 (18.4)	1.00 (reference)	1.00 (reference)			
		TC	598 (51.4)	582 (52.3)	0.88 (0.71-1.10)	0.88 (0.70-1.09)	0.237		
		CC	327 (28.1)	326 (29.3)	0.86 (0.68-1.10)	0.86 (0.67-1.09)	0.210	0.251	0.202
		TC+CC	925 (79.5)	908 (81.6)	0.87 (0.71-1.08)	0.87 (0.71-1.07)	0.187		
rs1208	*NAT2*	AA	382 (32.8)	340 (30.5)	1.00 (reference)	1.00 (reference)			
		AG	547 (47.0)	556 (50.0)	0.88 (0.73-1.06)	0.88 (0.73-1.07)	0.199		
		GG	235 (20.2)	217 (19.5)	0.96 (0.76-1.22)	0.97 (0.76-1.23)	0.781	0.595	0.216
		AG+GG	782 (67.2)	773 (69.5)	0.90 (0.76-1.08)	0.91 (0.76-1.08)	0.282		
rs1390358	*NAT2*	TT	395 (34.2)	352 (31.8)	1.00 (reference)	1.00 (reference)			
		TC	557 (48.2)	557 (50.4)	0.89 (0.74-1.07)	0.90 (0.75-1.08)	0.259		
		CC	204 (17.6)	197 (17.8)	0.92 (0.72-1.18)	0.93 (0.73-1.19)	0.558	0.392	0.271
		TC+CC	761 (65.8)	754 (68.2)	0.90 (0.76-1.07)	0.91 (0.76-1.08)	0.274		
rs7832071	*NAT2*	TT	386 (33.2)	344 (30.9)	1.00 (reference)	1.00 (reference)			
		TC	550 (47.2)	559 (50.2)	0.88 (0.73-1.06)	0.88 (0.73-1.07)	0.199		
		CC	228 (19.6)	210 (18.9)	0.97 (0.76-1.23)	0.97 (0.76 (1.23)	0.797	0.604	0.218
		TC+CC	778 (66.8)	769 (69.1)	0.90 (0.76-1.08)	0.91 (0.76-1.08)	0.283		

*Adjusted OR are adjusted for age & family history

Table 17. Association between Base Excision Repair polymorphisms and Prostate Cancer Risk among MED

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs125701	*OGG1*	GG	770 (66.2)	781 (70.2)	1.00 (reference)	1.00 (reference)			
		TG	354 (30.4)	304 (27.3)	1.18 (0.98-1.42)	1.20 (1.00-1.44)	0.055		
		TT	40 (3.4)	28 (2.5)	1.45 (0.89-2.37)	1.44 (0.88-2.36)	0.150	0.028	0.140
		TG+TT	394 (33.9)	332 (29.8)	1.20 (1.01-1.44)	1.22 (1.02-1.45)	0.030		
rs2445837	*POLD1*	AA	1020 (87.6)	955 (85.8)	1.00 (reference)	1.00 (reference)			
		AG	137 (11.8)	152 (13.7)	0.84 (0.66-1.08)	0.84 (0.66-1.08)	0.176		
		GG	7 (0.6)	6 (0.5)	1.09 (0.37-3.26)	1.11 (0.37-3.32)	0.857	0.245	0.284
		AG+GG	144 (12.4)	158 (14.2)	0.85 (0.67-1.09)	0.85 (0.67-1.09)	0.200		
rs545979	*POLI*	CC	566 (48.7)	529 (47.6)	1.00 (reference)	1.00 (reference)			
		TC	485 (41.7)	480 (43.1)	0.94 (0.79-1.12)	0.94 (0.79-1.12)	0.505		
		TT	112 (9.6)	104 (9.3)	1.01 (0.75-1.35)	0.98 (0.73-1.31)	0.891	0.756	0.291
		TC+TT	597 (51.3)	584 (52.4)	0.96 (0.81-1.13)	0.95 (0.81-1.12)	0.536		
rs8305	*POLI*	AA	601 (51.6)	526 (47.3)	1.00 (reference)	1.00 (reference)			
		AG	462 (39.7)	496 (44.6)	0.82 (0.69-0.97)	0.81 (0.68-0.97)	0.018		
		GG	101 (8.7)	90 (8.1)	0.98 (0.72-1.34)	0.98 (0.72-1.33)	0.898	0.163	0.109
		AG+GG	563 (48.4)	586 (52.7)	0.84 (0.71-0.99)	0.84 (0.71-0.99)	0.036		
rs4135036	*TDG*	TT	1010 (86.8)	962 (86.4)	1.00 (reference)	1.00 (reference)			
		TC	148 (12.7)	148 (13.3)	0.95 (0.75-1.22)	0.96 (0.75-1.23)	0.760		
		CC	6 (0.5)	3 (0.3)	1.91 (0.48-7.64)	1.76 (0.43-7.13)	0.430	0.952	0.391
		TC+CC	154 (13.2)	151 (13.6)	0.97 (0.76-1.24)	0.98 (0.77-1.25)	0.863		
rs2682585	*XRCC1*	GG	747 (64.9)	680 (61.7)	1.00 (reference)	1.00 (reference)			
		AG	355 (30.9)	375 (34.0)	0.86 (0.72-1.03)	0.85 (0.71-1.02)	0.078		
		AA	48 (4.2)	48 (4.3)	0.91 (0.60-1.38)	0.88 (0.58-1.33)	0.541	0.149	0.138
		AG+AA	403 (35.1)	423 (38.3)	0.87 (0.73-1.03)	0.85 (0.72-1.02)	0.073		

*Adjusted OR are adjusted for age & family history

Table 17. Association between Base Excision Repair polymorphisms and Prostate Cancer Risk among MED, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs3213255	*XRCC1*	TT	380 (32.7)	348 (31.3)	1.00 (reference)	1.00 (reference)			
		TC	579 (49.7)	546 (49.1)	0.97 (0.81-1.17)	0.97 (0.81-1.17)	0.763		
		CC	205 (17.6)	219 (19.7)	0.86 (0.68-1.09)	0.85 (0.67-1.08)	0.187	0.240	0.245
		TT+CC	784 (67.3)	795 (68.8)	0.94 (0.79-1.12)	0.94 (0.79-1.12)	0.470		

*Adjusted OR are adjusted for age & family history

Table 18. Association between Apoptotic polymorphisms and Prostate Cancer Risk among MED

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs12031994	*AKT3*	TT	853 (73.3)	802 (72.1)	1.00 (reference)	1.00 (reference)			
		TC	284 (24.4)	277 (24.9)	0.96 (0.80-1.17)	0.98 (0.81-1.19)	0.828		
		CC	27 (2.3)	34 (3.0)	0.75 (0.45-1.25)	0.75 (0.45-1.25)	0.267	0.363	0.391
		TC+CC	311 (26.7)	311 (27.9)	0.94 (0.78-1.13)	0.95 (0.79-1.15)	0.613		
rs10860361	*APAF1*	AA	332 (28.6)	345 (31.0)	1.00 (reference)	1.00 (reference)			
		AG	597 (51.3)	519 (46.6)	1.20 (0.99-1.45)	1.20 (0.99-1.45)	0.063		
		GG	234 (20.1)	249 (22.4)	0.98 (0.77-1.23)	0.97 (0.77-1.23)	0.828	0.947	0.133
		AG+GG	831 (71.4)	768 (69.0)	1.12 (0.94-1.35)	1.13 (0.94-1.35)	0.195		
rs905238	*BAX*	AA	315 (27.1)	302 (27.1)	1.00 (reference)	1.00 (reference)			
		AG	554 (47.6)	550 (49.4)	0.97 (0.79-1.18)	0.96 (0.79-1.17)	0.666		
		GG	295 (25.3)	261 (23.5)	1.08 (0.86-1.36)	1.07 (0.85-1.35)	0.564	0.513	0.335
		AG+GG	849 (72.9)	811 (72.9)	1.00 (0.83-1.21)	0.99 (0.83-1.20)	0.946		
rs616130	*BCL2L11*	CC	313 (26.9)	336 (30.2)	1.00 (reference)	1.00 (reference)			
		AC	603 (51.8)	527 (47.3)	1.23 (1.01-1.49)	1.21 (0.99-1.47)	0.058		
		AA	248 (21.3)	250 (22.5)	1.07 (0.84-1.35)	1.07 (0.84-1.35)	0.598	0.470	0.153
		AC+AA	851 (73.1)	777 (69.8)	1.18 (0.98-1.41)	1.16 (0.97-1.40)	0.109		
rs10845479	*BCL2L14*	AA	635 (54.6)	630 (56.6)	1.00 (reference)	1.00 (reference)			
		AG	445 (38.2)	420 (37.8)	1.05 (0.88-1.25)	1.06 (0.89-1.26)	0.518		
		GG	84 (7.2)	62 (5.6)	1.34 (0.95-1.90)	1.39 (0.98-1.97)	0.064	0.148	0.155
		AG+GG	529 (45.4)	482 (43.4)	1.09 (0.92-1.29)	1.10 (0.93-1.30)	0.257		
rs366542	*BID*	CC	275 (23.6)	264 (23.7)	1.00 (reference)	1.00 (reference)			
		TC	597 (51.3)	535 (48.1)	1.07 (0.87-1.32)	1.08 (0.88-1.33)	0.450		
		TT	292 (25.1)	314 (28.2)	0.89 (0.71-1.13)	0.90 (0.72-1.14)	0.391	0.308	0.169
		TC+TT	889 (76.4)	849 (76.3)	1.01 (0.83-1.22)	1.02 (0.84-1.23)	0.870		

*Adjusted OR are adjusted for age & family history

Table 18. Association between Apoptotic polymorphisms and Prostate Cancer Risk, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs4988366	*BIK*	AA	944 (81.1)	855 (76.8)	1.00 (reference)	1.00 (reference)			
		AG	208 (17.9)	244 (21.9)	0.77 (0.63-0.95)	0.78 (0.64-0.96)	0.020		
		GG	12 (1.0)	14 (1.3)	0.78 (0.36-1.69)	0.79 (0.36-1.71)	0.545	0.015	0.154
		AG+GG	220 (18.9)	258 (23.2)	0.77 (0.63-0.95)	0.78 (0.64-0.96)	0.017		
rs10503786	*BNIP3L*	CC	556 (48.9)	477 (43.9)	1.00 (reference)	1.00 (reference)			
		TC	480 (42.1)	489 (44.9)	0.84 (0.71-1.00)	0.85 (0.71-1.01)	0.061		
		TT	103 (9.0)	122 (11.2)	0.72 (0.54-0.97)	0.73 (0.55-0.98)	0.036	0.011	0.055
		TC+TT	583 (51.1)	611 (56.1)	0.82 (0.69-0.97)	0.82 (0.70-0.97)	0.022		
rs12870	*DIABLO*	GG	386 (33.2)	360 (32.4)	1.00 (reference)	1.00 (reference)			
		AG	568 (48.8)	540 (48.5)	0.98 (0.82-1.18)	098 (0.82-1.18)	0.850		
		AA	210 (18.0)	213 (19.1)	0.92 (0.72-1.17)	0.91 (0.71-1.15)	0.426	0.516	0.322
		AG+AA	778 (66.8)	753 (67.7)	0.96 (0.81-1.15)	0.96 (0.81-1.15)	0.656		
rs1539243	*IKBKE*	CC	837 (71.9)	740 (66.6)	1.00 (reference)	1.00 (reference)			
		TC	291 (25.0)	325 (29.2)	0.79 (0.66-0.95)	0.78 (0.65-0.95)	0.011		
		TT	36 (3.1)	47 (4.2)	0.68 (0.43-1.06)	0.68 (0.43-1.06)	0.085	0.005	0.072
		TC+TT	327 (28.1)	372 (33.4)	0.78 (0.65-0.93)	0.77 (0.64-0.92)	0.004		
rs11688	*JUN*	GG	1043 (89.6)	999 (89.8)	1.00 (reference)	1.00 (reference)			
		AG	120 (10.3)	110 (9.9)	1.05 (0.80-1.37)	1.06 (0.80-1.39)	0.692		
		AA	1 (0.1)	3 (0.3)	0.32 (0.03-3.08)	0.33 (0.03-3.19)	0.340	0.970	0.406
		AG+AA	121 (10.4)	113 (10.2)	1.03 (0.78-1.34)	1.04 (0.79-1.36)	0.789		
rs4727666	*PIK3CG*	AA	741 (64.2)	685 (62.1)	1.00 (reference)	1.00 (reference)			
		AG	364 (31.5)	366 (33.2)	0.92 (0.77-1.10)	0.91 (0.76-1.09)	0.317		
		GG	49 (4.3)	52 (4.7)	0.87 (0.58-1.30)	0.88 (0.59-1.32)	0.537	0.288	0.277
		AG+GG	413 (35.8)	418 (37.9)	0.91 (0.77-1.08)	0.91 (0.77-1.08)	0.274		

*Adjusted OR are adjusted for age & family history

Table 18. Association between Apoptotic polymorphisms and Prostate Cancer Risk, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs281508	*PRKCE*	GG	640 (55.0)	583 (52.4)	1.00 (reference)	1.00 (reference)			
		TG	445 (38.2)	438 (39.4)	0.93 (0.78-1.10)	0.92 (0.77-1.10)	0.347		
		TT	79 (6.80	91 (8.2)	0.79 (0.57-1.09)	0.77 (0.56-1.07)	0.117	0.136	0.216
		TG+TT	524 (45.0)	529 (47.6)	0.90 (0.77-1.06)	0.89 (0.76-1.06)	0.187		
rs571715	*PRKCQ*	TT	755 (65.0)	720 (64.8)	1.00 (reference)	1.00 (reference)			
		TC	353 (30.4)	354 (31.8)	0.95 (0.80-1.14)	0.95 (0.80-1.14)	0.594		
		CC	53 (4.6)	38 (3.4)	1.33 (0.87-2.04)	1.36 (0.89-2.10)	0.159	0.715	0.267
		TC+CC	406 (35.0)	392 (35.2)	0.99 (0.83-1.17)	0.99 (0.83-1.18)	0.925		
rs585881	*PRKCQ*	TT	765 (65.7)	723 (65.0)	1.00 (reference)	1.00 (reference)			
		TC	349 (30.0)	352 (31.6)	0.94 (0.78-1.12)	0.94 (0.78-1.12)	0.485		
		CC	50 (4.3)	38 (3.4)	1.24 (0.81-1.92)	1.28 (0.83-1.98)	0.265	0.960	0.255
		TC+CC	399 (34.3)	390 (35.0)	0.97 (0.81-1.15)	0.97 (0.82-1.16)	0.738		
rs6442322	*RAF1*	AA	342 (29.6)	361 (32.7)	1.00 (reference)	1.00 (reference)			
		AG	568 (49.1)	529 (48.0)	1.13 (0.94-1.37)	1.14 (0.94-1.37)	0.192		
		GG	247 (21.3)	213 (19.3)	1.22 (0.97-1.55)	1.21 (0.96-1.54)	0.110	0.082	0.216
		AG+GG	815 (70.4)	742 (67.3)	1.16 (0.97-1.39)	1.16 (0.97-1.38)	0.110		
rs11135693	*TNFRSF10B*	CC	574 (49.4)	510 (45.8)	1.00 (reference)	1.00 (reference)			
		AC	484 (41.6)	486 (43.7)	0.89 (0.74-1.05)	0.89 (0.75-1.06)	0.199		
		AA	105 (9.0)	117 (10.5)	0.80 (0.60-1.07)	0.80 (0.60-1.07)	0.126	0.069	0.170
		AC+AA	589 (50.6)	603 (54.2)	0.87 (0.74-1.02)	0.87 (0.74-1.03)	0.109		
rs4149576	*TNFRSF1A*	AA	234 (20.3)	183 (16.6)	1.00 (reference)	1.00 (reference)			
		AG	545 (47.2)	545 (49.4)	0.78 (0.62-0.98)	0.79 (0.63-0.99)	0.038		
		GG	375 (32.5)	376 (34.0)	0.78 (0.61-0.99)	0.79 (0.62-1.01)	0.056	0.076	0.167
		AG+GG	920 (79.7)	921 (83.4)	0.78 (0.63-0.97)	0.79 (0.63-0.98)	0.029		

*Adjusted OR are adjusted for age & family history

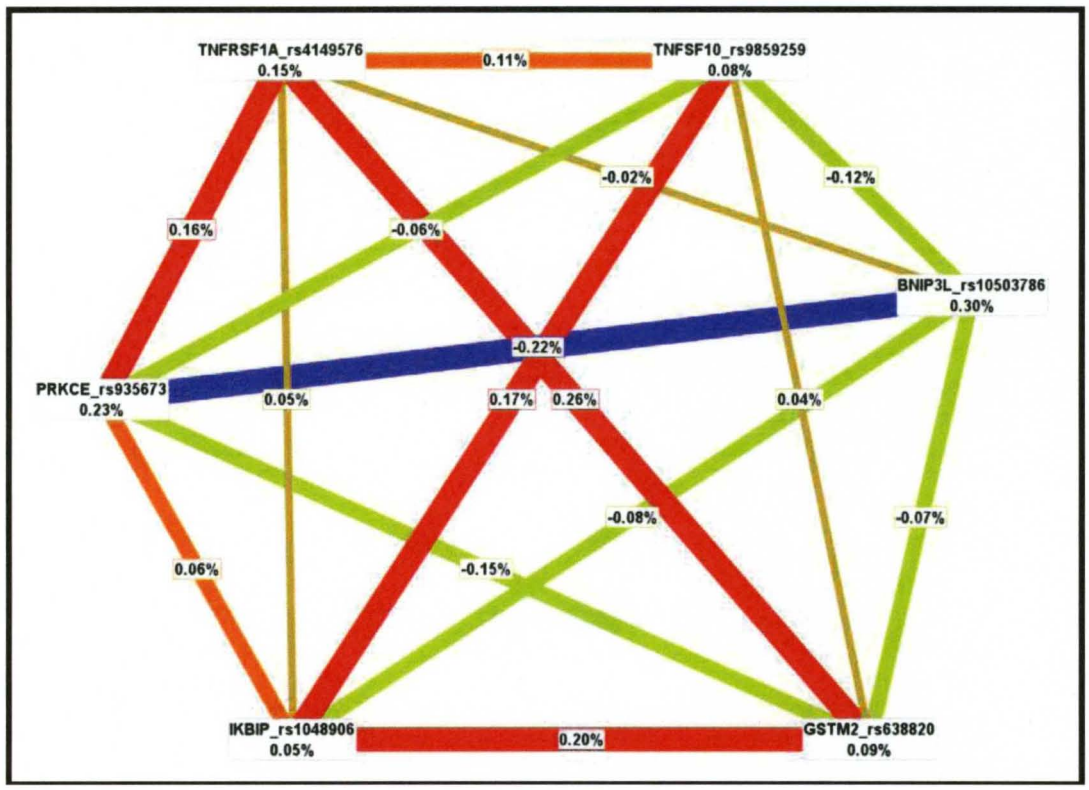
Based on the size of the entire OSR SNP panel (i.e., 219), MDR modeling would require analysis of more than 14 million one-, two-, and three-way combinations. Since it is not computationally feasible to analyze all 219 SNPs in MDR, we used the SURF & TuRF filter for the top 75 percentile OSR factors. This feature allows MDR to rank and select SNPs most likely to be associated with PCA risk and reduces the number of pair-wise and three-way combinations to amount that is possible to analyze (i.e., approximately 160,400).

Unfortunately, MDR modeling for the top 25th percentile of the OSR SNP panel did not reveal any statistically significant models associated with PCA risk (permutation testing p value ≥ 0.114) [*See Table 19*]. However, hIG revealed synergistic interactions: *TNFRSF1A_rs4149576-GSTM2_rs638820* (IG = 0.26%), *IKBIP_rs1048906-GSTM2_rs638820* (IG = 0.20%), *IKBIP_rs1048906-TNFSF10_rs9859259* (IG = 0.17%), and *TNFRSF1A_rs4149576-PRKCE_rs935673* (IG = 0.16%) [*See Figure 9*]. Although, LR did not show any statistically significant effects when these SNPs were examined individually, two-way analysis their combined effects confirmed the *TNFRSF1A-PRKCE* interaction [*See Table 20*]. We found possession of ≥3 minor *TNFRSF1A-PRKCE* alleles was associated with decreased risk [OR (95%CI) = 0.58 (0.42-0.81); p = 0.001].

Table 19. Top 25th Percentile MDR models for OSR polymorphisms and prostate cancer risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
<u>One Factor</u> *BNIP3L_rs10503786*	54	7/10	0.501	0.433
<u>Two Factor</u> *PRKCE_rs935673* *TNFRSF1A_rs4149576*	2916	3/10	0.485	0.800
<u>Three Factor</u> *GSTM2_rs638820* *IKBIP_rs1048906* *TNFRSF1A_rs4149576*	157464	7/10	0.522	0.114

Figure 1. Interaction entropy graph for OSR polymorphisms and prostate cancer risk among MED subjects



This graphical model describes the percent entropy that is explained by each OSR SNP or a combination of two loci within our MED study population. The joint effects of *GSTM2_rs638820-TNFRSF1A_rs4149576* yield an information gain of 0.14%, comparing to either *GSTM2* or *TNFRSF1A* loci alone (IG = 0.09% and 0.15%, respectively).

Table 20. Association between OSR gene-gene interactions & PCA risk among MED

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
TNFRSF1A_rs 4149576	AA	0	1.00 (reference)	1.00 (reference)		
GSTM2_rs638820	TT	1	0.82 (0.54-1.24)	0.81 (0.53-1.22)	0.308	
		2	0.74 (0.50-1.10)	0.74 (0.50-1.10)	0.141	0.383
		≥3	0.87 (0.58-1.29)	0.87 (0.59-1.30)	0.505	
IKBIP_rs1048906	AA	0	1.00 (reference)	1.00 (reference)		
GSTM2_rs638820	TT	1	1.27 (0.96-1.67)	1.28 (0.97-1.69)	0.081	
		2	1.13 (0.86-1.49)	1.14 (0.87-1.51)	0.344	0.399
		≥3	1.18 (0.87-1.60)	1.20 (0.88-1.63)	0.250	
IKBIP_rs1048906	AA	0	1.00 (reference)	1.00 (reference)		
TNFSF10_rs9859259	AA	1	1.06 (0.82-1.37)	1.07 (0.83-1.39)	0.589	
		2	0.83 (0.64-1.07)	0.83 (0.64-1.08)	0.164	0.121
		≥3	0.91 (0.67-1.23)	0.92 (0.68-1.24)	0.576	
TNFRSF1A_rs 4149576	AA	0	1.00 (reference)	1.00 (reference)		
PRKCE_rs935673	GG	1	0.75 (0.55-1.04)	0.77 (0.56-1.06)	0.112	
		2	0.84 (0.62-1.15)	0.86 (0.63-1.17)	0.332	0.363
		≥3	0.57 (0.41-0.79)	0.58 (0.42-0.81)	0.001	

*Adjusted OR are adjusted for age & family history

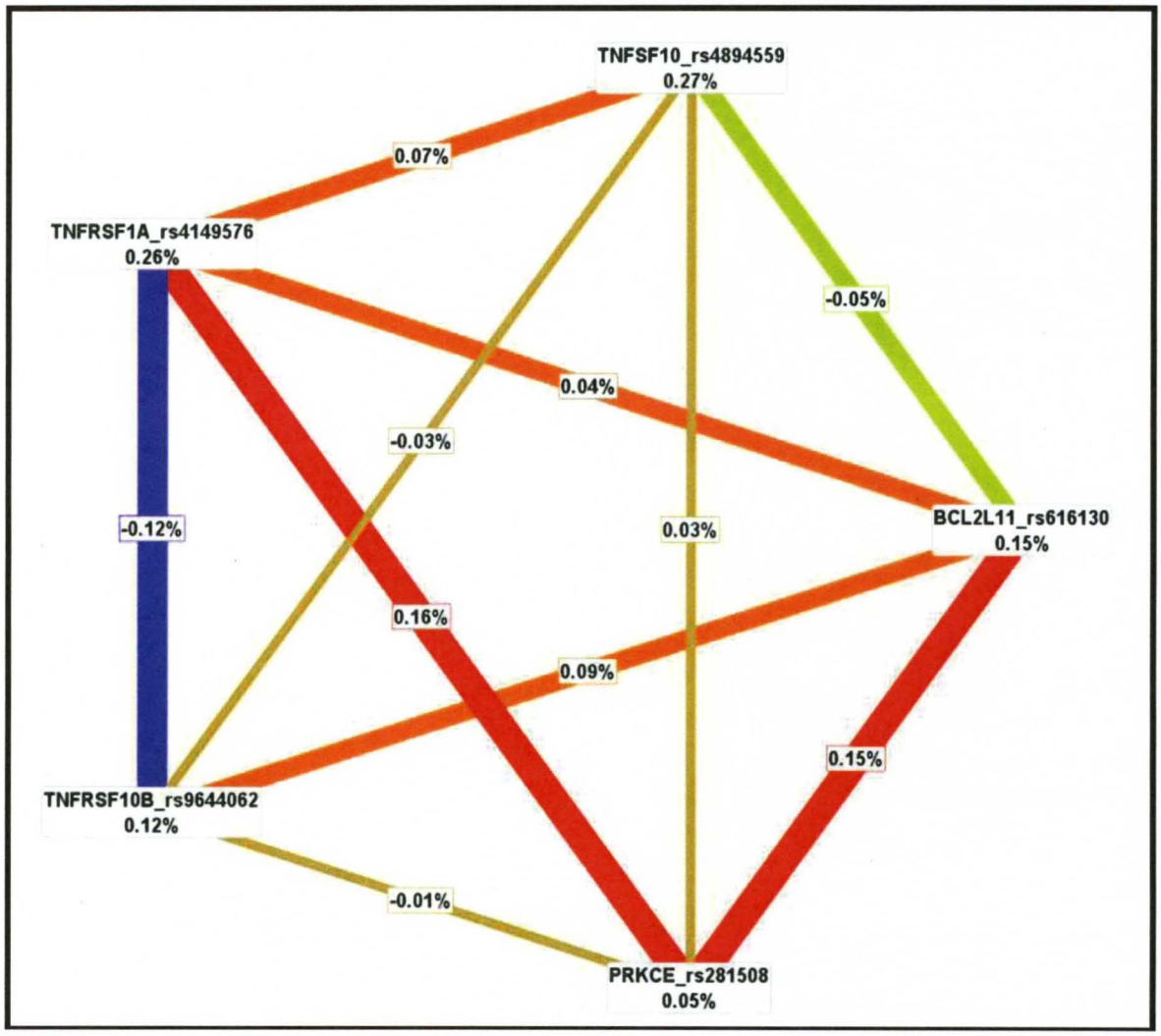
In order to verify that no interactions were missed by filtering the OSR SNP datafile, we performed additional analyses for all the SNPs separated by their respective biological pathway. Due to the large number of apoptosis-related markers, this panel was subjected to SURF & TuRF filtering. By selecting the top 50% of the apoptotic SNPs, the number of possible combinations was reduced from 5,177,717 to 636,056. However, no filtering was needed to analyze the antioxidative and BER SNP panels in MDR.

From these analyses, we did not observe any significant MDR models for the top 50th percentile apoptotic SNPs (permutation p value ≥ 0.062) [*Table 21*]. The entropy diagram showed synergistic effects involving *TNFRSF1A_rs4149576-PRKCE_rs281508* and *PRKCE_rs281508-BCL2L11_rs616130* [*See Figure 10*]. However, LR two-way risk analysis did not validate either interaction (p ≥ 0.093) [*Table 24*].

Table 21. Top 50th Percentile MDR models for apoptotic polymorphisms and prostate cancer risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***TNFSF10_rs4894559***	**86**	**5/10**	**0.505**	**0378**
Two Factor ***TNFRSF1A_rs4149576*** ***TNFSF10_rs4894559***	**7396**	**4/10**	**0.497**	**0.508**
Three Factor ***BCL2L11_rs616130*** ***PRKCE_rs281508*** ***TNFRSF1A_rs4149576***	**636056**	**7/10**	**0.529**	**0.062**

Figure 2. Interaction entropy graph for top 50th percentile apoptotic polymorphisms and PCA risk among MED subjects

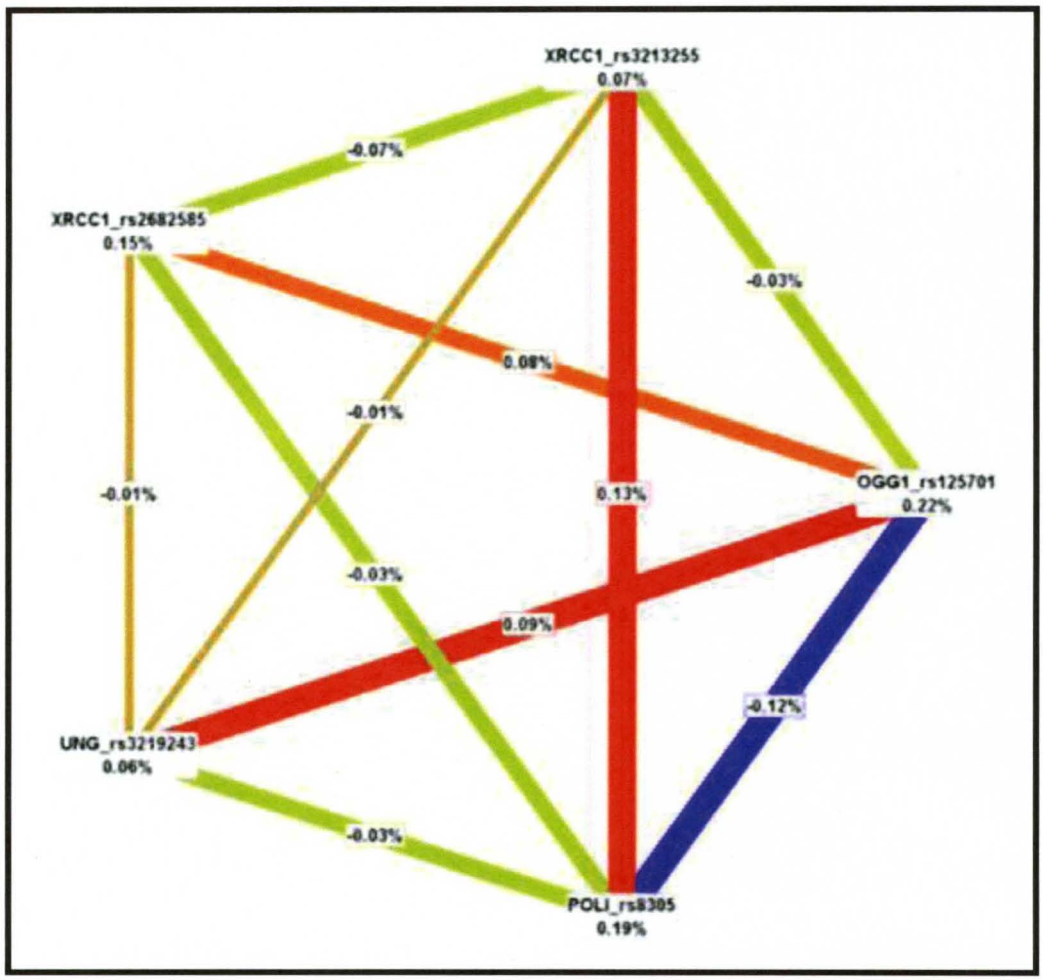


MDR did not detect any statistically significant models among the unfiltered BER SNP panel (permutation p value ≥ 0.182) [*Table 22*]. hIG revealed synergistic interactions between *XRCC1_rs3213255-POLI_rs8305* and *UNG_rs3219243-OGG1_rs125701* [*See Figure 11*]; however these combinations were not associated with risk when analyzed by LR [*See Table 24*].

Table 22. Unfiltered MDR models for BER polymorphisms and prostate cancer risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***POLI_rs8305***	**12**	**5/10**	**0.499**	**0.531**
Two Factor ***POLI_rs8305*** ***XRCC1_rs3213255***	**144**	**6/10**	**0.500**	**0.468**
Three Factor ***OGG1_rs125701*** ***POLI_rs8305*** ***XRCC1_rs2682585***	**1728**	**7/10**	**0.516**	**0.182**

Figure 3. BER polymorphisms and prostate cancer risk among MED



MDR analysis for the unfiltered antioxidative-related SNP panel confirmed the LR single effect finding for the antioxidative *CYP2C8_rs7909236* (CVC = 10/10) [*See Table 23*]. Although this model was identified as the best single predictor of risk, the permutation p value was not significant (p = 0.085). However, *CYP2C8* combined with *NAT1_rs4951581* was selected as the best two-factor predictor of risk (CVC = 10/10; p = 0.011). This interaction was confirmed by LR analysis, which indicated that possession of one minor *CYP2C8-NAT1* allele was associated with a 1.3-fold increase in risk [OR (95%CI) = 1.28 (1.04-1.57); p = 0.019; *Table 24*].

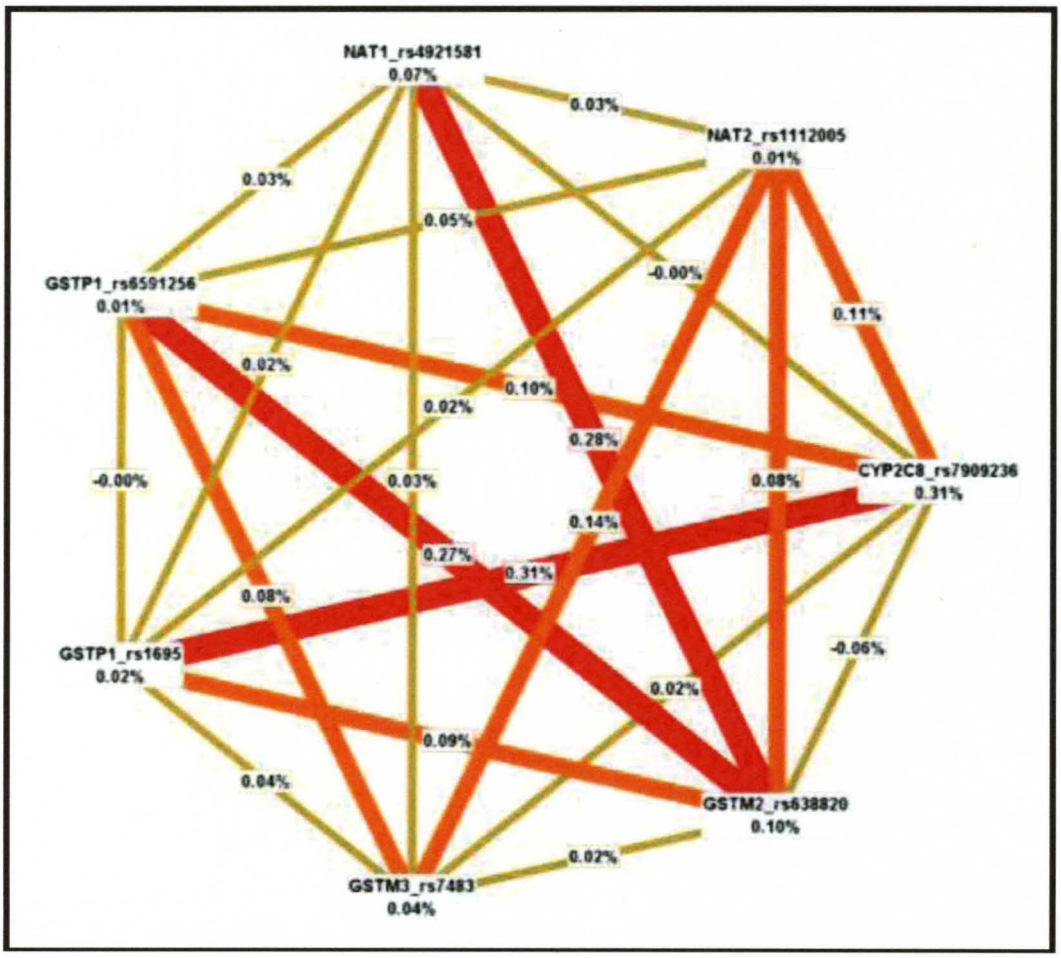
Table 23. Unfiltered MDR models for antioxidative-related OSR polymorphisms and prostate cancer risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor *CYP2C8_rs7909236*	34	10/10	0.527	0.085
Two Factor *CYP2C8_rs7909236* *NAT1_rs4921581*	1156	10/10	0.545	0.011
Three Factor *CYP2C8_rs7909236* *GSTP1_rs1695* *NAT1_rs4921581*	39304	3/10	0.502	0.409

hIG showed only a moderately synergistic effect from the *CYP2C8-NAT1* combination (IG = 0.11%) [*See Figure 12*]. However, the entropy graph revealed strong interactions between *CYP2C8_rs7909236-GSTP1_rs1695* (IG = 0.31%), *NAT1_rs4921581-GSTM2_rs638820* (IG = 0.28%), and *GSTP1_rs6591256-GSTM2_rs638820* (IG = 0.27%). LR two-way analysis of these interactions validated *CYP2C8-GSTP1* and *NAT1-GSTM2* [*Table 24*]. Men possessing ≥2 variant *CYP2C8-GSTP1* alleles was associated with a 1.4-

fold increase in risk [OR (95%CI) = 1.38 (1.10-1.74; p = 0.006]. Also, carriers of at least two minor *NAT1-GSTM1* alleles were linked to increased PCA risk [OR (95%CI) = 1.39 (1.06-1.82); p = 0.016].

Figure 4. Interaction entropy graph for antioxidative-related OSR polymorphisms and PCA risk among MED subjects



This graphical model describes the percent entropy that is explained by each OSR SNP or a combination of two loci within our MED study population. The joint effects of the *GSTM2_rs1638820-NAT1_rs4921581* interaction yields an information gain of 0.28%, in comparison to either *GSTM2 or NAT1* loci alone (IG = 0.10% and 0.07%, respectively).

Table 24. Association between gene-gene interactions & PCA risk among MED

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
TNFRSF1A_rs4149576	AA	0	1.00 (reference)	1.00 (reference)		
PRKCE_rs281508	TT	1	1.02 (0.75-1.38)	1.02 (0.75-1.38)	0.815	
		2	0.76 (0.56-1.03)	0.76 (0.56-1.03)	0.093	0.972
		≥3	0.82 (0.59-1.14)	0.82 (0.59-1.14)	0.239	
PRKCE_rs281508	TT	0	1.00 (reference)	1.00 (reference)		
BCL2L11_rs616130	AA	1	1.25 (0.97-1.60)	1.22 (0.95-1.56)	0.123	
		2	1.17 (0.91-1.51)	1.15 (0.90-1.49)	0.268	0.135
		≥3	1.00 (0.74-1.36)	0.98 (0.72-1.32)	0.879	
XRCC1_rs3213255	CC	0	1.00 (reference)	1.00 (reference)		
POLI_rs8305	GG	1	0.75 (0.54-1.05)	0.76 (0.55-1.06)	0.103	
		2	0.81 (0.59-1.12)	0.83 (0.60-1.14)	0.249	0.112
		≥3	0.83 (0.59-1.15)	0.84 (0.60-1.17)	0.290	
UNG_rs3219243	CC	0	1.00 (reference)	1.00 (reference)		
OGG1_rs125701	GG	1	1.16 (0.97-1.39)	1.17 (0.98-1.40)	0.089	
		2	1.02 (0.79-1.32)	1.04 (0.80-1.35)	0.776	0.329
		≥3	1.71 (0.89-3.29)	1.74 (0.91-3.35)	0.097	
CYP2C8_rs7909236	TT	0	1.00 (reference)	1.00 (reference)		
GSTP1_rs1695	GG	1	1.12 (0.91-1.38)	1.10 (0.89-1.35)	0.384	
		2	1.40 (1.11-1.76)	1.38 (1.10-1.74)	0.006	0.100
		≥3	0.98 (0.70-1.38)	0.97 (0.69-1.37)	0.851	
NAT1_rs4921581	AA	0	1.00 (reference)	1.00 (reference)		
GSTM2_rs638820	TT	1	1.29 (0.98-1.69)	1.28 (0.98-1.68)	0.074	
		2	1.39 (1.06-1.81)	1.39 (1.06-1.82)	0.016	0.001
		≥3	1.03 (0.77-1.39)	1.03 (0.76-1.38)	0.860	
CYP2C8_rs7909236	TT	0	1.00 (reference)	1.00 (reference)		
NAT1_rs4921581	AA	1	1.29 (1.05-1.58)	1.28 (1.04-1.57)	0.019	
		2	1.07 (0.86-1.35)	1.06 (0.85-1.34)	0.598	0.389
		≥3	1.06 (0.74-1.51)	1.02 (0.71-1.46)	0.912	
GSTP1_rs6591256	GG	0	1.00 (reference)	1.00 (reference)		
GSTM2_rs638820	TT	1	0.94 (0.69-1.28)	0.93 (0.68-1.26)	0.623	
		2	0.79 (0.59-1.07)	0.78 (0.58-1.06)	0.111	0.034
		≥3	1.19 (0.87-1.64)	1.19 (0.87-1.64)	0.274	

*Adjusted OR are adjusted for age & family history

SPECIFIC AIM 1 FINDINGS - MAD SUBJECTS

For MAD, we examined the single effects of 25 OSR SNPs in relation to PCA risk among 224 PCA cases and 699 controls. From this analysis, we possession of one or more minor *BAX_rs4645878* T allele was linked to a 1.8-fold increase in PCA risk [OR (95%CI) = 1.80 (1.11-2.92); p = 0.017); *See Table 27*]. We also detected a significant association between men having one least variant *BCL2L11_rs3789068* C allele and disease risk [OR (95%CI) = 1.93 (1.15-3.24); p = 0.013). We did not find any single risk effects among antioxidative or BER SNPs among MAD subjects [*See Tables 25 & 26*].

Table 25. Association between Antioxidative-related polymorphisms and Prostate Cancer Risk among MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs1695	*GSTP1*	AA	195 (31.8)	55 (29.4)	1.00 (reference)	1.00 (reference)			
		AG	294 (47.8)	84 (44.9)	1.01 (0.69-1.49)	1.03 (0.66-1.61)	0.888		
		GG	125 (20.4)	48 (25.7)	1.36 (0.87-2.13)	1.55 (0.93-2.58)	0.095	0.204	0.212
		AG+GG	419 (68.2)	132 (70.6)	1.12 (0.78-1.60)	1.19 (0.79-1.79)	0.414		
	GSTM1	*1/*1	37 (26.1)	55 (30.7)	1.00 (reference)	1.00 (reference)			
		*1/*0	58 (40.8)	76 (42.5)	0.88 (0.51-1.51)	0.92 (0.51-1.63)	0.765		
		*0/*0	47 (33.1)	48 (26.8)	0.69 (0.39-1.23)	0.71 (0.38-1.33)	0.287	0.202	0.313
		≥ *0	105 (73.9)	124 (69.3)	0.79 (0.49-1.30)	0.83 (0.49-1.40)	0.477		
	GSTT1	*1/*1	30 (21.3)	53 (29.4)	1.00 (reference)	1.00 (reference)			
		*1/*0	71 (50.3)	81 (45.0)	0.65 (0.37-1.12)	0.62 (0.34-1.14)	0.125		
		*0/*0	40 (28.4)	46 (25.6)	0.65 (0.35-1.21)	0.59 (0.30-1.17)	0.130	0.179	0.144
		≥ *0	111 (78.7)	127 (70.6)	0.65 (0.39-1.08)	0.61 (0.35-1.08)	0.090		
rs2069514	*CYP1A2*	GG	356 (55.0)	106 (57.6)	1.00 (reference)	1.00 (reference)			
		GA	224 (34.6)	62 (33.7)	0.93 (0.65-1.33)	0.87 (0.57-1.31)	0.498		
		AA	67 (10.4)	16 (8.7)	0.80 (0.45-1.44)	0.54 (0.27-1.09)	0.083	0.448	0.186
		GA+AA	291 (45.0)	78 (42.4)	0.90 (0.65-1.25)	0.78 (0.53-1.15)	0.213		
rs4646903	*CYP1A1*	AA	253 (39.2)	73 (37.8)	1.00 (reference)	1.00 (reference)			
		AC	289 (44.7)	92 (47.7)	1.10 (0.78-1.57)	1.22 (0.81-1.83)	0.350		
		CC	104 (16.1)	278 (14.5)	0.93 (0.57-1.53)	1.22 (0.69-2.15)	0.496	0.965	0.143
		AC+CC	393 (60.8)	120 (62.2)	1.06 (0.76-1.47)	1.22 (0.83-1.79)	0.321		

*Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 26. Association between Base Excision Repair polymorphisms and Prostate Cancer Risk among MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs1130409	*APEX1*	TT	260 (40.3)	82 (43.6)	1.00 (reference)	1.00 (reference)			
		TG	294 (45.5)	87 (46.3)	0.94 (0.67-1.32)	1.02 (0.68-1.52)	0.928		
		GG	92 (14.2)	19 (10.1)	0.66 (0.38-1.14)	0.92 (0.49-1.72)	0.797	0.185	0.346
		TG+GG	386 (59.8)	106 (56.4)	0.87 (0.63-1.21)	1.00 (0.68-1.46)	0.993		
rs1052133	*OGG1*	CC	465 (69.6)	135 (68.5)	1.00 (reference)	1.00 (reference)			
		CG	182 (27.3)	58 (29.5)	1.10 (0.77-1.56)	1.05 (0.70-1.57)	0.832		
		CG+GG	203 (30.4)	62 (31.5)	1.05 (0.75-1.48)	1.00 (0.67-1.48)	0.991	0.772	0.290
rs25487	*XRCC1*	GG	476 (73.0)	138 (73.4)	1.00 (reference)	1.00 (reference)			
		GA	159 (24.4)	46 (24.5)	1.00 (0.68-1.46)	0.98 (0.63-1.51)	0.921		
		GA+AA	176 (27.0)	50 (26.6)	0.98 (0.68-1.41)	0.95 (0.62-1.45)	0.814	0.836	0.245

*Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 27. Association between Apoptotic polymorphisms and Prostate Cancer Risk among MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs4645878	*BAX*	CC	86 (60.1)	83 (46.9)	1.00 (reference)	1.00 (reference)			
		CT	42 (29.4)	70 (39.6)	1.73 (1.06-2.81)	1.80 (1.06-3.06)	0.029		
		TT	15 (10.5)	24 (13.6)	1.66 (0.81-3.38)	1.80 (0.85-3.84)	0.128	0.038	0.090
		CT+TT	57 (39.9)	94 (53.1)	1.71 (1.09-2.67)	1.80 (1.11-2.92)	0.017		
rs3789068	*BCL2L11*	TT	68 (47.5)	67 (38.3)	1.00 (reference)	1.00 (reference)			
		TC	53 (37.1)	92 (52.6)	1.76 (1.09-2.84)	1.93 (1.15-3.24)	0.013		
		CC	22 (15.4)	16 (9.1)	0.74 (0.36-1.53)	0.82 (0.37-1.84)	0.632	0.690	0.125
		TC+CC	75 (52.5)	108 (61.7)	1.46 (0.93-2.29)	1.62 (1.00-2.64)	0.051		
rs4488761	*BCL2L13*	AA	52 (36.1)	60 (33.3)	1.00 (reference)	1.00 (reference)			
		AG	63 (43.8)	83 (46.1)	1.14 (0.70-1.87)	0.87 (0.51-1.48)	0.597		
		GG	29 (20.1)	37 (20.6)	1.11 (0.60-2.04)	0.95 (0.49-1.84)	0.875	0.695	0.259
		AG+GG	92 (63.9)	120 (66.7)	1.13 (0.71-1.79)	0.89 (0.54-1.47)	0.648		
rs6488494	*BCL2L14*	TT	45 (31.5)	51 (27.7)	1.00 (reference)	1.00 (reference)			
		TC	70 (49.0)	89 (48.4)	1.12 (0.68-1.87)	1.15 (0.67-1.99)	0.614		
		CC	28 (19.5)	44 (23.9)	1.39 (0.75-2.58)	1.38 (0.71-2.69)	0.343	0.310	0.259
		TC+CC	98 (68.5)	133 (72.3)	1.20 (0.74-1.93)	1.22 (0.73-2.03)	0.450		
rs1883263	*BIK*	AA	115 (79.9)	148 (81.8)	1.00 (reference)	1.00 (reference)			
		AC+CC	29 (21.1)	33 (18.2)	0.88 (0.51-1.54)	0.69 (0.37-1.27)	0.227	0.664	0.390
rs738276	*BIK*	GG	48 (39.3)	73 (46.5)	1.00 (reference)	1.00 (reference)			
		GA	61 (50.0)	68 (43.3)	0.73 (0.44-1.21)	0.74 (0.43-1.28)	0.278		
		AA	13 (10.7)	16 (10.2)	0.81 (0.36-1.83)	0.85 (0.36-2.03)	0.714	0.336	0.333
		GA+AA	74 (60.7)	84 (53.5)	0.75 (0.46-1.21)	0.76 (0.45-1.28)	0.299		
rs6509364	*CARD8*	CC	88 (61.5)	114 (64.4)	1.00 (reference)	1.00 (reference)			
		CT	39 (27.3)	54 (30.5)	1.07 (0.65-1.76)	1.06 (0.62-1.81)	0.838		
		TT	16 (11.2)	9 (5.1)	0.43 (0.18-1.03)	0.51 (0.20-1.29)	0.158	0.210	0.221
		CT+TT	55 (38.5)	63 (35.6)	0.88 (0.56-1.40)	0.91 (0.56-1.49)	0.708		

*Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 27. Association between Apoptotic polymorphisms and Prostate Cancer Risk among MAD, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs6509366	*CARD8*	GG	91 (63.6)	105 (60.0)	1.00 (reference)	1.00 (reference)			
		GA	44 (30.8)	65 (35.5)	1.28 (0.80-2.06)	1.32 (0.79-2.20)	0.290		
		AA	8 (5.6)	8 (4.5)	0.87 (0.31-2.40)	0.76 (0.26-2.27)	0.627	0.591	0.343
		GA+AA	52 (36.4)	73 (41.0)	1.22 (0.77-1.91)	1.23 (0.75-2.00)	0.413		
rs1049216	*CASP3*	TT	88 (69.3)	113 (66.9)	1.00 (reference)	1.00 (reference)			
		TC+CC	39 (30.7)	56 (33.1)	1.12 (0.68-1.83)	1.34 (0.79-2.28)	0.282	0.658	0.355
rs507879	*CASP5*	AA	25 (17.7)	31 (17.0)	1.00 (reference)	1.00 (reference)			
		AG	67 (47.5)	91 (49.7)	1.10 (0.59-2.02)	1.38 (0.72-2.68)	0.336		
		GG	49 (34.8)	61 (33.3)	1.00 (0.53-1.92)	1.28 (0.64-2.57)	0.491	0.936	0.272
		AG+GG	116 (82.3)	152 (83.1)	1.06 (0.59-1.89)	1.34 (0.72-2.50)	0.359		
rs537093	*CASP5*	GG	78 (54.2)	91 (50.0)	1.00 (reference)	1.00 (reference)			
		GA	58 (40.3)	74 (40.7)	1.09 (0.69-1.73)	1.16 (0.71-1.90)	0.555		
		AA	8 (5.6)	17 (9.3)	1.82 (0.75-4.45)	1.69 (0.65-4.40)	0.279	0.260	0.212
		GA+AA	66 (45.8)	91 (50.0)	1.18 (0.76-1.83)	1.23 (0.77-1.97)	0.393		
rs6747918	*CASP8*	AA	30 (30.0)	43 (38.0)	1.00 (reference)	1.00 (reference)			
		AG	12 (12.0)	9 (8.0)	0.52 (0.20-1.40)	0.56 (0.19-1.61)	0.280		
		GG	58 (58.0)	61 (54.0)	0.73 (0.41-1.32)	0.98 (0.52-1.88)	0.962	0.342	0.356
		AG+GG	70 (70.0)	70 (62.0)	0.70 (0.39-1.24)	0.90 (0.48-1.69)	0.743		
rs1052576	*CASP9*	GG	69 (48.6)	81 (44.5)	1.00 (reference)	1.00 (reference)			
		GA	56 (39.4)	82 (45.1)	1.25 (0.78-1.99)	1.43 (0.86-2.38)	0.165		
		AA	17 (12.0)	19 (10.4)	0.95 (0.46-1.97)	1.04 (0.48-2.26)	0.929	0.734	0.268
		GA+AA	73 (51.4)	101 (55.5)	1.18 (0.76-1.83)	1.34 (0.83-2.15)	0.232		
rs12817549	*CRADD*	TT	79 (55.6)	96 (53.6)	1.00 (reference)	1.00 (reference)			
		TC	50 (35.2)	65 (36.3)	1.07 (0.67-1.72)	1.23 (0.74-2.05)	0.430		
		CC	13 (9.2)	18 (10.1)	1.14 (0.53-2.47)	1.17 (0.51-2.69)	0.705	0.698	0.308
		TC+CC	63 (44.4)	83 (46.4)	1.08 (0.70-1.69)	1.22 (0.76-1.96)	0.420		

*Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 27. Association between Apoptotic polymorphisms and Prostate Cancer Risk among MAD, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value	p trend	MDRpt p value
rs3858606	*CRADD*	GG	43 (30.3)	39 (22.2)	1.00 (reference)	1.00 (reference)			
		GA	72 (50.7)	99 (56.3)	1.52 (0.89-2.57)	1.23 (0.70-2.17)	0.476		
		AA	27 (19.0)	38 (21.5)	1.55 (0.81-2.99)	1.55 (0.76-3.16)	0.224	0.163	0.357
		GA+AA	99 (69.7)	137 (77.8)	1.53 (0.92-2.53)	1.31 (0.76-2.25)	0.325		

*Adjusted Odds Ratios are adjusted for age, family history, & WAA

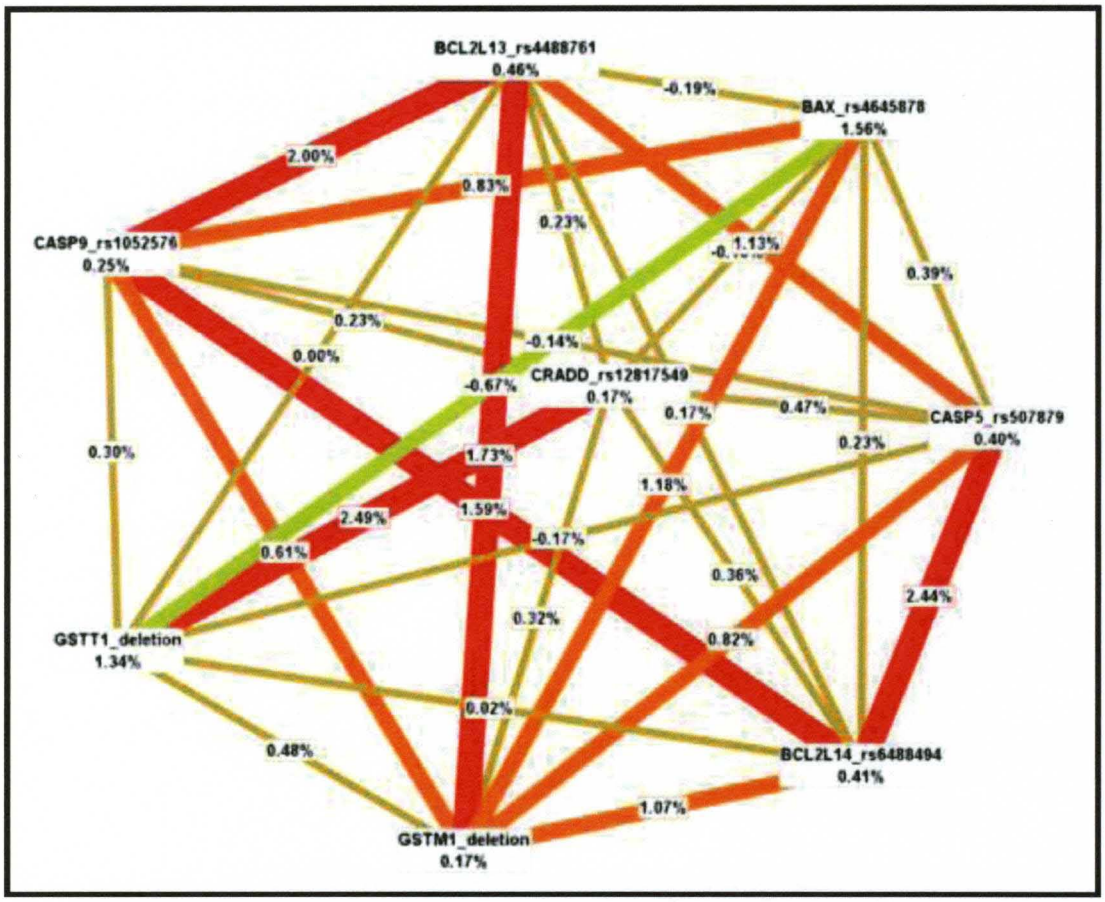
Consistent with LR, MDR found the *BAX_rs4645878* polymorphism was the best single factor predictor of disease risk (CVC = 6/10; p = 0.350); however this model was not statistically significant [*See Table 28*]. Permutation testing indicated the three factor model containing *BCL2L13_rs4488761-CASP5_rs507879-BCL2L14_rs6488494* was significant (p = 0.048) and although this model had a high testing accuracy (ATA = 0.585) the CVC value was only 3/10.

Table 28. Unfiltered MDR models for OSR polymorphisms and prostate cancer risk among MAD (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor *BAX_rs4645878*	25	6/10	0.517	0.350
Two Factor *CRADD_rs12817549 GSTT1_deletion*	625	8/10	0.571	0.073
Three Factor *BCL2L13_rs4488761 CASP5_rs507879 BCL2L14_rs6488494*	15625	3/10	0.585	0.048

The entropy graph also showed the largest independent IG was attributed to the *BAX_rs4645878* variant (IG = 1.56%) in addition to revealing several strongly synergistic interactions occurred between polymorphic *CASPs* and *BCL2*-related genes [*See Figure 13*]. We also observed strong interactions between the *GST* gene deletions and apoptotic markers; however the *BCL2L14_rs6488464-CASP_rs507879* was the only interaction that could be confirmed by LR two-way analysis (p interaction = 0.013) [*See Table 29*].

Figure 1. Interaction entropy model for OSR polymorphisms and prostate cancer risk among MAD



This graphical model describes the percent entropy that is explained by each OSR SNP or a combination of two loci within our MAD study population. Note that the gene combination effect yields an information gain of 2.49% comparing the *GSTT1_deletion-CRADD_rs12817549* axis to either *GSTT1* or *CRADD* loci alone (IG = 1.34% and 0.17%, respectively).

Table 29. Association between gene-gene interactions & PCA risk among MAD

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
GSTT1_deletion	*0/*0	0-2	1.00 (reference)	1.00 (reference)		
CRADD_rs12817549	CC	2-3	0.90 (0.54-1.48)	0.87 (0.50-1.48)	0.598	0.392
		4	0.62 (0.20-1.90)	0.61 (0.18-2.07)	0.430	
BCL2L14_rs6488494	CC	0-2	1.00 (reference)	1.00 (reference)		
CASP5_rs507879	GG	2-3	0.70 (0.44-1.09)	0.70 (0.43-1.14)	0.152	0.013
		4	2.32 (0.89-6.05)	2.51 (0.91-6.92)	0.075	
BCL2L13_rs4488761	GG	0-2	1.00 (reference)	1.00 (reference)		
CASP9_rs1052576	AA	2-3	0.68 (0.41-1.12)	0.73 (0.43-1.25)	0.249	0.106
		4	2.09 (0.41-10.58)	1.58 (0.29-8.51)	0.593	
GSTM1_deletion	*0/*0	0-2	1.00 (reference)	1.00 (reference)		
BCL2L13_rs4488761	GG	2-3	0.62 (0.39-0.98)	0.65 (0.39-1.07)	0.088	0.229
		4	0.92 (0.38-2.25)	0.94 (0.36-2.45)	0.902	
BCL2L14_rs6488494	CC	0-2	1.00 (reference)	1.00 (reference)		
CASP9_rs1052576	AA	2-3	0.93 (0.58-1.51)	0.91 (0.54-1.53)	0.710	0.337
		4	1.87 (0.36-9.85)	1.88 (0.34-10.45)	0.469	

*Adjusted OR are adjusted for age & WAA

SPECIFIC AIM 2 FINDINGS - MED SUBJECTS

We evaluated the individual- and combined impact of 173 apoptotic-related polymorphisms in relation to PCA aggressiveness for 1,176 MED subjects (688 aggressive and 488 non-aggressive cases). LR analysis found that possession of at least one minor *AKT3_rs12031994* C allele was associated with increased disease aggressiveness [OR (95%CI) = 1.50 (0.15-1.96); p = 0.003; *See Table 30*].

Table 30. Association between Apoptotic polymorphisms and disease aggressiveness among MED

dbSNP ID	Genes	Allele	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs12031994	*AKT3*	TT	483 (70.2)	380 (77.9)	1.00 (reference)	1.00 (reference)			
		TC	192 (27.9)	94 (19.2)	1.61 (1.21-2.13)	1.61 (1.22-2.14)	0.001		
		CC	13 (1.9)	14 (2.9)	0.73 (0.34-1.57)	0.73 (0.34-1.57)	0.421	0.025	0.052
		TC+CC	205 (29.8)	108 (22.1)	1.49 (1.14-1.95)	1.50 (0.15-1.96)	0.003		
rs10860361	*APAF1*	AA	200 (29.1)	136 (27.9)	1.00 (reference)	1.00 (reference)			
		AG	349 (50.8)	252 (51.6)	0.94 (0.72-1.24)	0.94 (0.72-1.23)	0.650		
		GG	138 (20.1)	100 (20.5)	0.94 (0.67-1.32)	0.93 (0.67-1.31)	0.688	0.688	0.356
		AG+GG	487 (70.9)	352 (72.1)	0.94 (0.73-1.22)	0.94 (0.72-1.21)	0.623		
rs905238	*BAX*	AA	189 (27.5)	130 (26.6)	1.00 (reference)	1.00 (reference)			
		AG	330 (48.0)	228 (46.8)	1.00 (0.75-1.32)	0.99 (0.75-1.31)	0.928		
		GG	169 (24.5)	130 (26.6)	0.89 (0.65-1.23)	0.88 (0.64-1.21)	0.425	0.498	0.280
		AG+GG	499 (72.5)	358 (73.4)	0.96 (0.74-1.25)	0.95 (0.73-1.23)	0.686		
rs616130	*BCL2L11*	CC	193 (28.1)	123 (25.2)	1.00 (reference)	1.00 (reference)			
		AC	353 (51.3)	252 (51.6)	0.89 (0.68-1.18)	0.88 (0.66-1.16)	0.353		
		AA	142 (20.6)	113 (23.2)	0.80 (0.57-1.12)	0.80 (0.57-1.11)	0.182	0.192	0.168
		AC+AA	495 (71.9)	365 (74.8)	0.86 (0.66-1.13)	0.85 (0.65-1.11)	0.232		
rs10845479	*BCL2L14*	AA	379 (55.1)	265 (54.3)	1.00 (reference)	1.00 (reference)			
		AG	256 (37.2)	192 (39.3)	0.93 (0.73-1.19)	0.93 (0.73-1.19)	0.565		
		GG	53 (7.7)	31 (6.4)	1.20 (0.75-1.91)	1.23 (0.77-1.97)	0.388	0.879	0.223
		AG+GG	309 (44.9)	223 (45.7)	0.97 (0.77-1.22)	0.97 (0.77-1.23)	0.811		
rs366542	*BID*	CC	158 (23.0)	120 (24.5)	1.00 (reference)	1.00 (reference)			
		TC	351 (51.0)	253 (51.8)	1.05 (0.79-1.40)	1.06 (0.79-1.41)	0.705		
		TT	179 (26.0)	115 (23.6)	1.18 (0.85-1.65)	1.20 (0.86-1.67)	0.296	0.323	0.216
		TC+TT	530 (77.0)	368 (75.4)	1.09 (0.83-1.44)	1.10 (0.84-1.45)	0.493		

*Adjusted OR are adjusted for age & WAA

Table 30. Association between Apoptotic polymorphisms and disease aggressiveness among MED, *continued*

dbSNP ID	Genes	Allele	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs4988366	*BIK*	AA	550 (79.9)	403 (82.6)	1.00 (reference)	1.00 (reference)			
		AG	130 (18.9)	81 (16.6)	1.18 (0.87-1.60)	1.19 (0.87-1.62)	0.270		
		GG	8 (1.2)	4 (0.8)	1.47 (0.44-4.90)	1.50 (0.45-5.04)	0.509	0.236	0.207
		AG+GG	138 (20.1)	85 (17.4)	1.19 (0.88-1.61)	1.20 (0.89-1.62)	0.227		
rs10503786	*BNIP3L*	CC	328 (48.8)	235 (49.2)	1.00 (reference)	1.00 (reference)			
		TC	294 (43.8)	189 (39.5)	1.11 (0.87-1.43)	1.11 (0.86-1.42)	0.424		
		TT	50 (7.4)	54 (11.3)	0.66 (0.44-1.01)	0.66 (0.44-1.01)	0.055	0.367	0.208
		TC+TT	344 (51.2)	243 (50.8)	1.01 (0.80-1.28)	1.01 (0.80-1.28)	0.946		
rs12870	*DIABLO*	GG	242 (35.2)	146 (29.9)	1.00 (reference)	1.00 (reference)			
		AG	328 (47.7)	250 (51.2)	0.79 (0.61-1.03)	0.80 (0.61-1.04)	0.091		
		AA	118 (17.1)	92 (18.9)	0.77 (0.55-1.09)	0.78 (0.55-1.10)	0.151	0.092	0.171
		AG+AA	446 (64.8)	342 (70.1)	0.79 (0.61-1.01)	0.79 (0.62-1.02)	0.067		
rs1539243	*IKBKE*	CC	502 (73.0)	341 (69.9)	1.00 (reference)	1.00 (reference)			
		TC	172 (25.0)	125 (25.6)	0.94 (0.72-1.22)	0.95 (0.73-1.24)	0.712		
		TT	14 (2.0)	22 (4.5)	0.43 (0.22-0.86)	0.44 (0.22-0.88)	0.200	0.075	0.248
		TC+TT	186 (27.0)	147 (30.1)	0.86 (0.67-1.11)	0.88 (0.68-1.13)	0.310		
rs11688	*JUN*	GG	608 (88.4)	446 (91.2)	1.00 (reference)	1.00 (reference)			
		AG	79 (11.5)	42 (8.6)	1.38 (0.93-2.05)	1.38 (0.93-2.04)	0.112	0.084	0.243
		AG+AA	80 (11.6)	42 (8.6)	1.40 (0.94-2.07)	1.40 (0.94-2.07)	0.097		
rs4727666	*PIK3CG*	AA	447 (65.5)	301 (62.3)	1.00 (reference)	1.00 (reference)			
		AG	207 (30.3)	162 (33.6)	0.86 (0.67-1.11)	0.86 (0.66-1.10)	0.225		
		GG	29 (4.2)	20 (4.1)	0.98 (0.54-1.76)	0.98 (0.54-1.76)	0.934	0.372	0.200
		AG+GG	236 (35.5)	182 (37.7)	0.87 (0.69-1.11)	0.87 (0.68-1.11)	0.255		

*Adjusted OR are adjusted for age & WAA

Table 30. Association between Apoptotic polymorphisms and disease aggressiveness among MED, *continued*

dbSNP ID	Genes	Allele	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adjusted OR (95%CI)*	p value*	p trend	MDRpt p value
rs281508	*PRKCE*	GG	368 (53.5)	279 (57.2)	1.00 (reference)	1.00 (reference)			
		TG	279 (40.5)	170 (34.8)	1.24 (0.97-1.59)	1.24 (0.97-1.59)	0.089		
		TT	41 (6.0)	39 (8.0)	0.80 (0.50-1.27)	0.80 (0.50-1.27)	0.334	0.654	0.102
		TG+TT	320 (46.5)	209 (42.8)	1.16 (0.92-1.47)	1.16 (0.91-1.46)	0.226		
rs571715	*PRKCQ*	TT	432 (62.9)	329 (67.7)	1.00 (reference)	1.00 (reference)			
		TC	221 (32.2)	138 (28.4)	1.22 (0.94-1.58)	1.23 (0.95-1.59)	0.119		
		CC	34 (4.9)	19 (3.9)	1.36 (0.76-2.43)	1.37 (0.76-2.44)	0.293	0.086	0.178
		TC+CC	255 (37.1)	157 (32.3)	1.24 (0.97-1.58)	1.24 (0.97-1.59)	0.082		
rs585881	*PRKCQ*	TT	439 (63.8)	332 (68.0)	1.00 (reference)	1.00 (reference)			
		TC	217 (31.5)	138 (28.3)	1.19 (0.92-1.54)	1.20 (0.93-1.55)	0.173		
		CC	32 (4.7)	18 (3.7)	1.34 (0.74-2.44)	1.35 (0.74-2.45)	0.328	0.123	0.206
		TC+CC	249 (36.2)	156 (32.0)	1.21 (0.94-1.54)	1.21 (0.95-1.55)	0.124		
rs6442322	*RAF1*	AA	203 (29.6)	141 (29.2)	1.00 (reference)	1.00 (reference)			
		AG	350 (51.1)	223 (46.2)	1.09 (0.83-1.43)	1.08 (0.82-1.42)	0.580		
		GG	132 (19.3)	119 (24.6)	0.77 (0.56-1.07)	0.76 (0.55-1.06)	0.105	0.168	0.142
		AG+GG	482 (70.4)	342 (70.8)	0.98 (0.76-1.26)	0.97 (0.75-1.25)	0.811		
rs11135693	*TNFRSF10B*	CC	330 (48.0)	251 (51.5)	1.00 (reference)	1.00 (reference)			
		AC	293 (42.6)	196 (40.3)	1.14 (0.89-1.45)	1.14 (0.89-1.46)	0.296		
		AA	65 (9.4)	40 (8.2)	1.24 (0.81-1.89)	1.25 (0.82-1.92)	0.307	0.210	0.182
		AC+AA	358 (52.0)	236 (48.5)	1.15 (0.92-1.46)	1.16 (0.92-1.46)	0.217		
rs4149576	*TNFRSF1A*	AA	138 (20.2)	97 (20.1)	1.00 (reference)	1.00 (reference)			
		AG	320 (46.9)	232 (48.0)	0.97 (0.71-1.32)	0.99 (0.72-1.34)	0.923		
		GG	224 (32.5)	154 (31.9)	1.02 (0.73-1.42)	1.04 (0.75-1.45)	0.814	0.849	0.343
		AG+GG	554 (79.4)	386 (79.9)	0.99 (0.74-1.33)	1.01 (0.75-1.35)	0.962		

*Adjusted OR are adjusted for age & WAA

Since the apoptotic SNP panel contained 173 targets, we had to use the SURF & TuRF filter in order to conduct the analysis. To analysis the entire panel would require MDR to evaluate more than 5 million one-, two-, and three-way combinations. Since it is not computationally possible to exhaustively analyze all 173 SNPs, we used the SURF & TuRF filter for the top 50 percentile. This feature allows MDR to rank and select apoptotic polymorphisms most likely to be associated with disease aggressiveness and reduces the number of pair-wise and three-way combinations to amount that is possible to analyze (i.e., approximately 643,500).

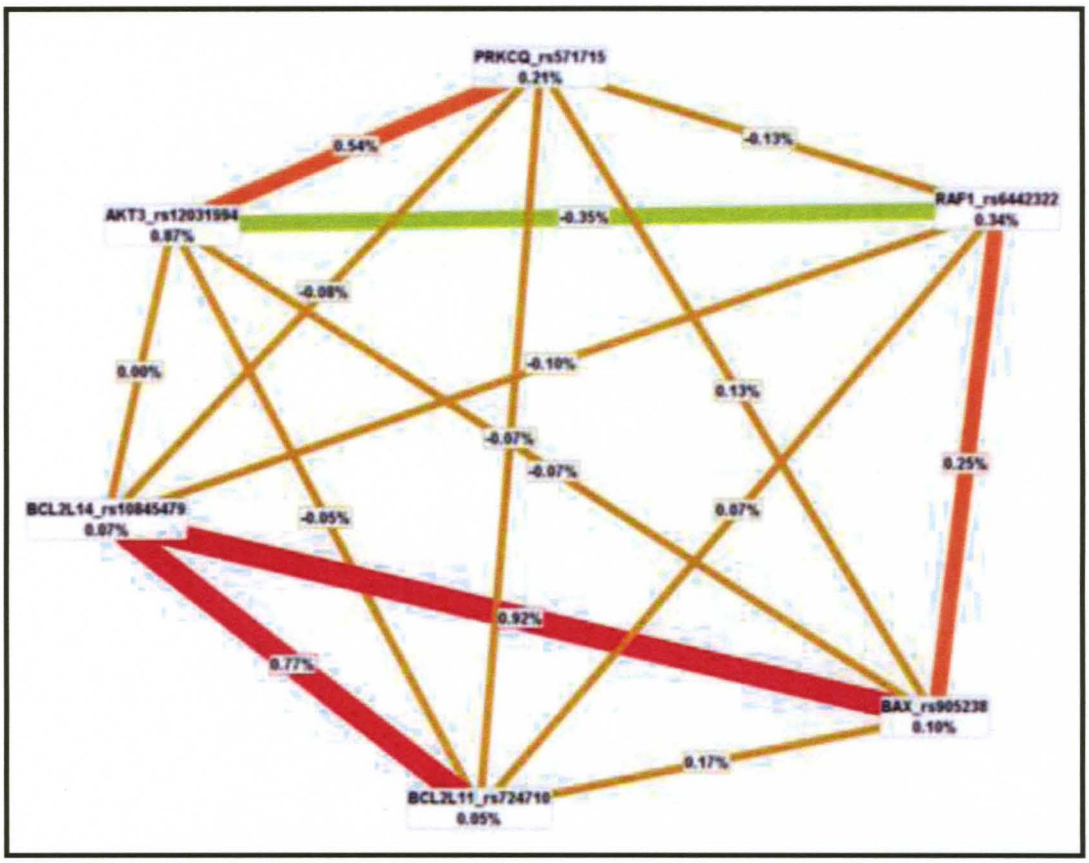
For the filtered apoptotic SNP datafile MDR identified *AKT3_rs12031994* as the best single factor model, but permutation testing indicated this finding was not statistically significant [*See Table 31*]. However, MDR modeling and permutation testing found this SNP combined with *PRKCQ_rs571715* was the best predictor of PCA aggressiveness (CVC = 8/10; p = 0.024).

Table 31. Top 50th Percentile MDR models for apoptotic SNPs and prostate cancer aggressiveness among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***AKT3_rs12031994***	**86**	**6/10**	**0.533**	**0.095**
Two Factor ***AKT3_rs12031994*** ***PRKCQ_rs571715***	**7396**	**8/10**	**0.542**	**0.024**
Three Factor ***BAX_rs905238*** ***BCL2L14_rs10845479*** ***RAF1_rs6442322***	**636056**	**5/10**	**0.538**	**0.072**

When the apoptotic SNPs were visualized using hIG, we also observed two synergistic interactions: *BCL2L14_rs10845479-BAX_rs905238* (IG = 0.92%) and *BCL2L14_rs10845479-BCL2L11_rs724710* (IG = 0.77%) [*See Figure 14*]. Although LR two-analysis did not find the *AKT3-PRKCQ* significant (p ≥ 0.102), the *BCL2L14-BAX* and *BCL2L14-BCL2L11* combinations were each associated with increased PCA aggressiveness [OR (95%CI) = 1.72 (1.20-2.45); p = 0.003 and OR (95%CI) = 1.44 (1.07-1.95); p = 0.017, respectively]; *See Table 32*].

Figure 1. Interaction entropy model for apoptotic SNPs in relation to prostate cancer aggressiveness among MED



The combined effects of *BCL214_rs10845479-BAX_rs905238* and *BCL214_rs10845479 -BCL2L11_rs724710* yield an information gain of 0.92% and 0.77%, respectively; compared to considering any on these loci individually *BCL2L14* (IG = 0.07%), *BAX* (IG = 0.10%), or *BCL2L11* (IG = 0.05%).

Table 32. Association between apoptotic gene-gene interactions & PCA aggressiveness among MED

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value	interaction p value
AKT3_rs12031994	CC	0	1.00 (reference)	1.00 (reference)		
PRKCQ_rs571715	CC	1	1.84 (1.43-2.38)	1.86 (1.40-2.40)	0.102	
		2	1.37 (0.93-2.03)	1.39 (0.94-2.06)	0.915	0.013
		≥3	1.04 (0.51-2.13)	1.04 (0.51-2.13)	0.484	
BCL2L14_rs10845479	GG	0	1.00 (reference)	1.00 (reference)		
BAX_rs905238	TT	1	1.74 (1.22-2.48)	1.72 (1.20-2.45)	0.003	
		2	1.11 (0.78-1.57)	1.10 (0.77-1.56)	0.599	0.055
		≥3	1.26 (0.83-1.91)	1.23 (0.81-1.88)	0.326	
BCL2L14_rs10845479	GG	0	1.00 (reference)	1.00 (reference)		
BCL2L11_rs724710	TT	1	1.45 (1.07-1.95)	1.44 (1.07-1.95)	0.017	
		2	0.97 (0.70-1.34)	0.97 (0.70-1.34)	0.838	0.042
		≥3	0.95 (0.57-1.59)	0.95 (0.57-1.60)	0.867	

*Adjusted OR are adjusted for age & family history

SPECIFIC AIM 2 FINDINGS - MAD SUBJECTS

Among MAD subjects, we examined 15 apoptotic polymorphisms within our OSR panel as predictors of PCA progression as measured by Tumor Stage (i.e., Gleason score). The study population consisted of 137 case subjects, (68 aggressive and 69 non-aggressive). LR analysis of independent SNP effects did not reveal any significant associations in disease aggressiveness ($p \geq 0.062$) [*See Table 33*].

Table 33. Association between Apoptotic polymorphisms and Tumor Grade among MAD

dbSNP ID	Genes	Allele	Low N (%)*	High N (%)*	OR (95%CI)	Adjusted OR (95%CI)**	p value**	p trend	MDRpt p value
rs4645878	*BAX*	CC	18 (33.3)	28 (50.0)	1.00 (reference)	1.00 (reference)			
		CT	29 (53.7)	21 (37.5)	0.47 (0.21-1.05)	0.43 (0.19-1.00)	0.049		
		TT	7 (13.0)	7 (12.5)	0.64 (0.19-2.14)	0.64 (0.19-2.20)	0.482	0.188	0.272
		CT+TT	36 (66.7)	28 (50.0)	0.50 (0.23-1.08)	0.47 (0.21-1.04)	0.062		
rs3789068	*BCL2L11*	TT	21 (38.9)	16 (30.2)	1.00 (reference)	1.00 (reference)			
		TC	29 (53.7)	30 (56.6)	1.36 (0.59-3.10)	1.61 (0.66-3.89)	0.291		
		CC	4 (7.4)	7 (13.2)	2.30 (0.57-9.22)	2.64 (0.64-10.95)	0.182	0.232	0.263
		TC+CC	33 (61.1)	37 (69.8)	1.47 (0.66-3.28)	1.75 (0.74-4.11)	0.200		
rs4488761	*BCL2L13*	AA	19 (33.9)	18 (32.7)	1.00 (reference)	1.00 (reference)			
		AG	21 (37.5)	27 (49.1)	1.36 (0.57-3.21)	1.39 (0.58-3.34)	0.461		
		GG	16 (28.6)	10 (18.2)	0.66 (0.24-1.83)	0.66 (0.24-1.87)	0.437	0.517	0.159
		AG+GG	37 (66.1)	37 (67.3)	1.06 (0.48-2.33)	1.07 (0.48-2.40)	0.862		
rs6488494	*BCL2L14*	TT	16 (28.1)	16 (28.6)	1.00 (reference)	1.00 (reference)			
		TC	26 (45.6)	27 (48.2)	1.04 (0.43-2.50)	0.96 (0.39-2.40)	0.931		
		CC	15 (26.3)	13 (23.2)	0.87 (0.31-2.39)	0.79 (0.28-2.25)	0.660	0.793	0.262
		TC+CC	41 (71.9)	40 (71.4)	0.98 (0.43-2.21)	0.90 (0.38-2.11)	0.805		
rs1883263	*BIK*	AA	41 (74.6)	48 (87.3)	1.00 (reference)	1.00 (reference)			
		AC+CC	14 (25.5)	7 (12.7)	0.43 (0.16-1.16)	0.45 (0.16-1.23)	0.120	0.095	0.326
rs738276	*BIK*	GG	22 (48.9)	23 (41.8)	1.00 (reference)	1.00 (reference)			
		GA+AA	23 (51.1)	32 (58.2)	1.33 (0.60-2.94)	1.30 (0.59-2.91)	0.517	0.222	0.224
rs6509364	*CARD8*	CC	35 (63.6)	35 (68.6)	1.00 (reference)	1.00 (reference)			
		CT+TT	20 (36.4)	13 (25.5)	0.80 (0.36-1.79)	0.83 (0.37-1.88)	0.656	0.932	0.272
rs6509366	*CARD8*	GG	35 (62.5)	30 (57.7)	1.00 (reference)	1.00 (reference)			
		GA	18 (32.1)	18 (34.6)	1.17 (0.52-2.64)	1.17 (0.52-2.67)	0.705		
		AA	3 (5.4)	4 (7.7)	1.56 (0.32-7.51)	1.46 (0.30-7.10)	0.643	0.547	0.336
		GA+AA	21 (37.5)	22 (42.3)	1.22 (0.57-2.64)	1.21 (0.56-2.64)	0.625		

*Low Tumor Grade: Gleason score: >7; High Tumor Grade: Gleason score: ≤7; **Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

Table 33. Association between Apoptotic polymorphisms and Tumor Grade among MAD, *continued*

dbSNP ID	Genes	Allele	Low N (%)*	High N (%)*	OR (95%CI)	Adjusted OR (95%CI)**	p value**	p trend	MDRpt p value
rs1049216	*CASP3*	TT	37 (69.8)	35 (67.3)	1.00 (reference)	1.00 (reference)			
		TC	13 (24.5)	15 (28.9)	1.22 (0.51-2.93)	1.21 (0.50-2.95)	0.670		
		CC	3 (5.7)	2 (3.9)	0.71 (0.11-4.47)	0.68 (0.11-4.38)	0.688	0.951	0.371
		TC+CC	16 (30.2)	17 (32.7)	1.12 (0.49-2.56)	1.11 (0.48-2.57)	0.803		
rs507879	*CASP5*	AA	11 (19.6)	6 (10.7)	1.00 (reference)	1.00 (reference)			
		AG	27 (48.2)	29 (51.8)	1.97 (0.64-6.06)	2.50 (0.70-8.94)	0.159		
		GG	18 (32.1)	21 (37.5)	2.14 (0.66-6.94)	2.14 (0.56-8.11)	0.265	0.268	0.235
		AG+GG	45 (80.4)	50 (89.3)	2.04 (0.70-5.96)	2.34 (0.69-7.93)	0.171		
rs537093	*CASP5*	GG	30 (53.6)	28 (50.9)	1.00 (reference)	1.00 (reference)			
		GA+AA	26 (46.4)	27 (49.1)	1.11 (0.53-2.34)	1.12 (0.53-2.39)	0.764	0.779	0.431
rs6747918	*CASP8*	AA	15 (39.5)	14 (41.2)	1.00 (reference)	1.00 (reference)			
		AG	3 (7.9)	3 (8.8)	1.07 (0.19-6.22)	0.97 (0.16-5.77)	0.971		
		GG	20 (52.6)	17 (50.0)	0.91 (0.34-2.41)	0.85 (0.32-2.31)	0.755	0.847	0.433
		AG+GG	23 (60.5)	20 (58.8)	0.93 (0.36-2.39)	0.87 (0.33-2.28)	0.774		
rs1052576	*CASP9*	GG	19 (34.6)	27 (48.2)	1.00 (reference)	1.00 (reference)			
		GA	29 (52.7)	24 (42.9)	0.58 (0.26-1.29)	0.59 (0.27-1.32)	0.203		
		AA	7 (12.7)	5 (8.9)	0.50 (0.14-1.82)	0.51 (0.14-1.86)	0.306	0.163	0.163
		GA+AA	36 (65.5)	29 (51.8)	0.57 (0.26-1.22)	0.58 (0.27-1.24)	0.160		
rs12817549	*CRADD*	TT	32 (57.1)	26 (48.2)	1.00 (reference)	1.00 (reference)			
		TC	19 (33.9)	19 (35.2)	1.23 (0.54-2.79)	1.27 (0.56-2.93)	0.568		
		CC	5 (8.9)	9 (16.7)	2.22 (0.66-7.43)	2.29 (0.68-7.76)	0.182	0.215	0.295
		TC+CC	24 (42.9)	28 (51.9)	1.44 (0.68-3.05)	1.49 (0.70-3.19)	0.305		
rs3858606	*CRADD*	GG	13 (24.5)	11 (20.0)	1.00 (reference)	1.00 (reference)			
		GA	32 (60.4)	30 (54.6)	1.11 (0.43-2.85)	1.12 (0.43-2.92)	0.815		
		AA	8 (15.1)	14 (25.5)	2.07 (0.63-6.75)	2.17 (0.65-7.19)	0.205	0.238	0.261
		GA+AA	40 (75.5)	44 (80.0)	1.30 (0.52-3.23)	1.32 (0.53-3.33)	0.551		

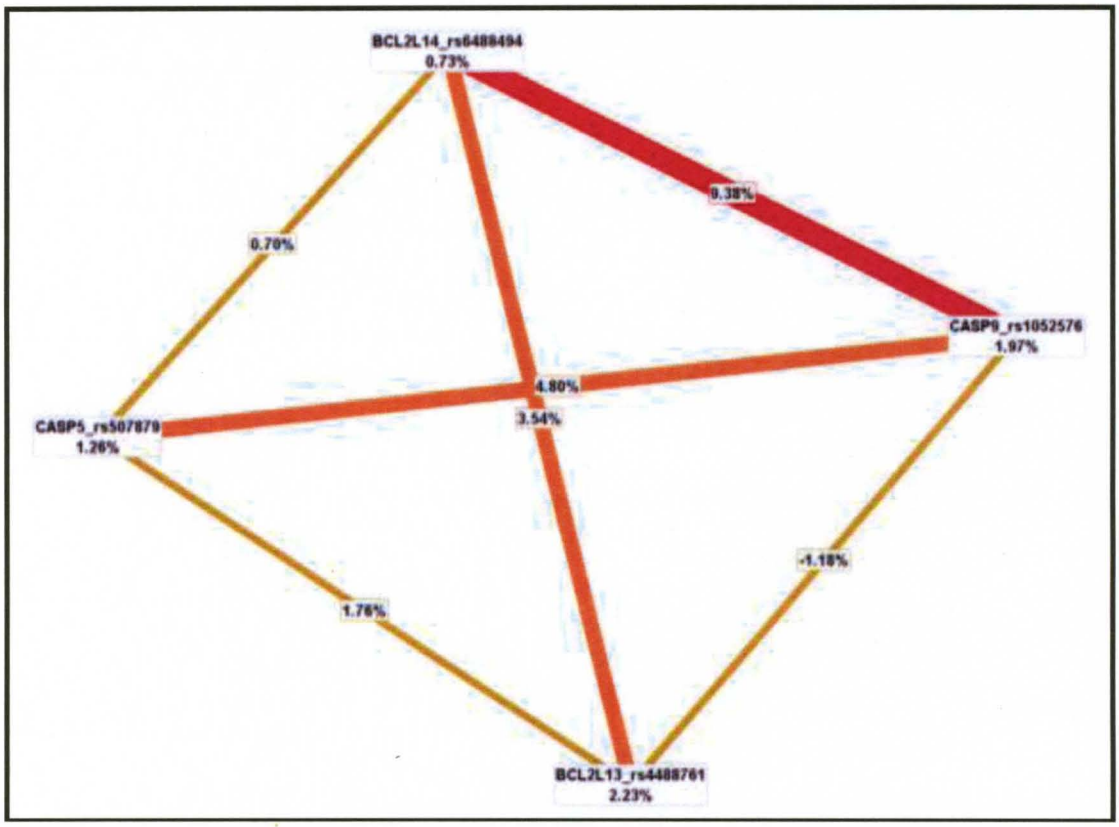
*Low Tumor Grade: Gleason score: >7; High Tumor Grade: Gleason score: ≤7; **Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

MDR revealed the two factor model containing *CASP9_rs1052576-BCL2L14_rs6488494* as the best predictor of aggressiveness (CVC = 10/10; p=0.011) [*See Table 34*]. Due to limited sample size this interaction was confirmed visually by the entropy graph which showed a 9.38% IG attributable to this gene combination [*See Figure 15*]. Moderately synergistic interactions were also detected between *CASP9-CASP5* (IG = 4.80%) and *BCL2L13-BCL2L14* (IG = 3.54%), however LR analysis was not able validate any of these combinations as statistically significant ($p \geq 0.114$) [*See Table 35*].

Table 34. Unfiltered MDR models for apoptotic gene variations and PCA aggressiveness among MAD (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***BCL2L13_rs4488761***	**15**	**5/10**	**0.498**	**0.501**
Two Factor ***CASP9_rs1052576*** ***BCL2L14_rs6488494***	**225**	**10/10**	**0.681**	**0.011**
Three Factor ***CASP9_rs1052576*** ***CASP5_rs507879*** ***BCL2L14_rs6488494***	**3375**	**5/10**	**0.596**	**0.097**

Figure 1. Interaction entropy graph for apoptotic gene variants and PCA aggressiveness among MAD subjects



This graphical model describes the percent entropy that is explained by each apoptotic SNP or a combination of two loci. The *BCL2L14-CASP9* interaction provides an IG=9.38%, compared to either *BCL2L14* or *CASP5* considered individually (0.73% & 1.97%, respectively).

Table 35. Association between apoptotic gene-gene interactions & PCA aggressiveness among MAD

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
BCL2L14_rs6488494	CC	0-2	1.00 (reference)	1.00 (reference)		
CASP9_rs1052576	AA	2-3	0.77 (0.34-1.73)	0.73 (0.32-1.65)	0.440	0.961
		4	0.44 (0.04-4.99)	0.43 (0.04-5.15)	0.502	
CASP9_rs1052576	AA	0-2	1.00 (reference)	1.00 (reference)		
CASP5_rs507879	GG	2-3	1.44 (0.65-3.17)	1.41 (0.63-3.14)	0.403	0.545
		4	0.51 (0.09-2.96)	0.59 (0.10-3.46)	0.555	
BCL2L14_rs6488494	CC	0-2	1.00 (reference)	1.00 (reference)		
BCL2L13_rs4488761	GG	2-3	1.02 (0.47-2.22)	0.96 (0.43-2.11)	0.909	0.114
		4	0.15 (0.02-1.27)	0.15 (0.02-1.31)	0.086	

***Adjusted OR are adjusted for age & WAA**

SPECIFIC AIM 3 FINDINGS – MED SUBJECTS

We assessed the effects 27 environmental OSR factors along with our panel of 219 gene variants in relation to PCA development. We evaluated 27 variables related to dietary habits, vitamin/ supplement intake and exposure to meat- and cigarette-derived carcinogens using data collected from 2,277 CGEMS project participants (1176 cases, 1101 controls). Risk categories for dietary intakes and vitamin/supplement use were based on values established in the 2005 USDA Dietary Guidelines Report & NIH Office of Dietary Supplements.[120-121] However, variables related to meat consumption, meat cooking methods, and meat-derived carcinogens, were divided into quartiles using data for the control subjects. Statistical analyses were conducted using the 1st quartile as the low risk category.

LR analysis found men in the 4nd quartile of MeIQx exposure (i.e., ≥ 46.64 ng/day) were associated with a 23% reduction in PCA risk [OR (95%CI) = 0.77 (0.61-0.97); p = 0.025; *See Table 36*]. We also observed a decrease in disease risk among current smokers in contrast to never smokers [OR (95%CI) = 0.69 (0.51-0.94); p = 0.018].

Table 36. Single effects of Environmental OSR Factors and risk among MED

Dietary Factor	N (%)	Cases N (%)	Controls N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Fruit (servings/day)	≥ 4	188 (16.2)	159 (14.3)	1.00 (reference)	1.00 (reference)			
	< 4	975 (83.8)	952 (85.7)	0.87 (0.69-1.09)	0.88 (0.70-1.10)	0.260	0.220	0.238
Vegetables (servings/day)	≥ 5	256 (22.0)	280 (25.2)	1.00 (reference)	1.00 (reference)			
	< 5	907 (78.0)	831 (74.8)	1.19 (0.98-1.45)	1.20 (0.99-1.46)	0.067	0.073	0.237
Total Meat (g/day)	≤ 129.33	330 (28.4)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	129.33-174.54	294 (25.3)	303 (27.3)	0.82 (0.65-1.03)	0.82 (0.66-1.04)	0.096		
	174.54-252.89	268 (23.0)	252 (22.7)	0.90 (0.71-1.14)	0.92 (0.73-1.16)	0.474	0.173	0.131
	≥ 252.89	271 (23.3)	278 (25.0)	0.82 (0.65-1.04)	0.83 (0.65-1.05)	0.111		
	> 129.33	833 (71.6)	833 (75.0)	0.84 (0.70-1.02)	0.85 (0.71-1.03)	0.100		
White Meat (g/day)	≤ 26.21	288 (24.8)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	26.21-44.63	357 (30.7)	319 (28.8)	1.08 (0.86-1.35)	1.11 (0.88-1.39)	0.378		
	44.63-71.83	249 (21.4)	236 (21.2)	1.02 (0.80-1.30)	1.04 (0.81-1.33)	0.754	0.470	0.187
	≥ 71.83	269 (23.1)	278 (25.0)	0.93 (0.74-1.18)	0.96 (0.76-1.22)	0.747		
	> 26.21	875 (75.2)	833 (75.0)	1.01 (0.84-1.23)	1.04 (0.86-1.26)	0.689		
Red Meat (g/day)	≤ 53.90	317 (27.3)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	53.90-82.72	320 (27.5)	313 (28.2)	0.90 (0.72-1.12)	0.91 (0.73-1.15)	0.433		
	82.72-124.19	249 (21.4)	242 (21.8)	0.90 (0.71-1.15)	0.91 (0.71-1.15)	0.418	0.287	0.181
	≥ 124.19	277 (23.8)	278 (25.0)	0.87 (0.69-1.10)	0.88 (0.70-1.12)	0.301		
	> 53.90	846 (72.7)	833 (75.0)	0.89 (0.74-1.07)	0.90 (0.75-1.09)	0.282		
Processed Meat (g/day)	≤ 6.08	322 (27.7)	279 (25.1)	1.00 (reference)	1.00 (reference)			
	6.08-11.42	315 (27.1)	317 (28.6)	0.86 (0.69-1.08)	0.87 (0.70-1.10)	0.252		
	11.42-20.96	210 (18.0)	237 (21.3)	0.77 (0.60-0.98)	0.79 (0.61-1.01)	0.056	0.745	0.146
	≥ 20.96	316 (27.2)	278 (25.0)	0.99 (0.79-1.24)	1.00 (0.80-1.26)	0.995		
	> 6.08	841 (72.3)	832 (74.9)	0.88 (0.73-1.06)	0.89 (0.74-1.08)	0.232		

*Adjusted Odds Ratios (OR) are adjusted for age and family history

Table 36. Single effects of Environmental OSR Factors and risk among MED, *continued*

Dietary Factor	N (%)	Cases N (%)	Controls N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Red Meat not processed (g/day)	≤ 38.65	314 (27.0)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	38.65-62.14	324 (27.9)	326 (29.3)	0.88 (0.70-1.10)	0.88 (0.71-1.10)	0.272		
	62.14-95.72	251 (21.6)	229 (20.7)	0.97 (0.76-1.24)	0.98 (0.77-1.25)	0.887	0.402	0.203
	≥ 95.72	274 (23.5)	278 (25.0)	0.87 (0.69-1.10)	0.88 (0.70-1.11)	0.281		
	> 38.65	849 (73.0)	833 (75.0)	0.90 (0.75-1.09)	0.91 (0.75-1.10)	0.321		
Red Meat rare/med done (g/day)	≤ 3.86	278 (23.9)	273 (24.6)	1.00 (reference)	1.00 (reference)			
	3.86-15.98	348 (29.9)	298 (26.8)	1.15 (0.91-1.44)	1.17 (0.93-1.47)	0.185		
	15.98-32.41	257 (22.1)	262 (23.6)	0.96 (0.76-1.22)	0.99 (0.78-1.26)	0.913	0.560	0.155
	≥ 32.41	280 (24.1)	278 (25.0)	0.99 (0.78-1.25)	1.00 (0.79-1.28)	0.971		
	> 3.86	885 (76.1)	838 (75.4)	1.04 (0.86-1.26)	1.06 (0.87-1.28)	0.570		
Red Meat well/very well done (g/day)	≤ 4.95	319 (27.4)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	4.95-9.84	320 (27.5)	299 (27.0)	0.93 (0.75-1.17)	0.94 (0.75-1.18)	0.605		
	9.84-19.82	250 (21.5)	256 (23.0)	0.85 (0.67-1.08)	0.86 (0.68-1.09)	0.215	0.144	0.156
	≥ 19.82	274 (23.6)	278 (25.0)	0.86 (0.67-1.08)	0.86 (0.68-1.09)	0.213		
	> 4.95	844 (72.6)	833 (75.0)	0.88 (0.73-1.07)	0.89 (0.74-1.07)	0.226		

*Adjusted Odds Ratios (OR) are adjusted for age and family history

Table 36. Single effects of Environmental OSR Factors and risk among MED, *continued*

Dietary Factor	N (%)	Cases N (%)	Controls N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Kcal from diet (g/day)	2000-3000	559 (48.1)	522 (47.0)	1.00 (reference)	1.00 (reference)			
	< 2000	395 (33.9)	391 (35.2)	0.94 (0.79-1.13)	0.94 (0.78-1.13)	0.480	0.768	0.276
	> 3000	209 (18.0)	198 (17.8)	0.97 (0.79-1.24)	0.98 (0.78-1.24)	0.884		
Fat from diet (g/day)	≤ 73.11	626 (53.8)	590 (53.1)	1.00 (reference)	1.00 (reference)			
	> 73.11	537 (46.2)	521 (46.9)	0.97 (0.82-1.15)	0.96 (0.82-1.14)	0.663	0.730	0.348
Saturated Fat from diet	≤ 24.95	628 (54.0)	602 (54.2)	1.00 (reference)	1.00 (reference)			
(g/day)	> 24.95	535 (46.0)	509 (45.8)	1.01 (0.85-1.19)	1.00 (0.85-1.18)	0.976	0.929	0.407
Body Mass Index (BMI)	Under/normal weight	305 (26.2)	271 (24.4)	1.00 (reference)	1.00 (reference)			
	Overweight	612 (52.6)	574 (51.7)	0.95 (0.78-1.16)	0.97 (0.79-1.19)	0.758	0.111	0.192
	Obese	246 (21.2)	266 (23.9)	0.82 (0.65-1.04)	0.84 (0.66-1.06)	0.143		
Physically Active (≥30 min	Yes	556 (47.8)	494 (44.5)	1.00 (reference)	1.00 (reference)			
/day)	No	607 (52.2)	617 (53.5)	0.87 (0.74-1.03)	0.88 (0.74-1.04)	0.125	0.110	0.234
Vitamin A (µg/day)	≥ 900	1054 (90.6)	1008 (90.6)	1.00 (reference)	1.00 (reference)			
	< 900	110 (9.4)	105 (9.4)	1.00 (0.76-1.33)	1.03 (0.77-1.36)	0.867	0.990	0.421
Vitamin C (mg/day)	≥ 90	1103 (94.8)	1042 (93.6)	1.00 (reference)	1.00 (reference)			
	< 90	61 (5.2)	71 (6.4)	0.81 (0.57-1.16)	0.84 (0.59-1.19)	0.317	0.246	0.383
Vitamin E (IU/day)	≥ 22.4	1014 (87.1)	952 (85.5)	1.00 (reference)	1.00 (reference)			
	< 22.4	150 (12.9)	161 (14.5)	0.88 (0.69-1.11)	0.89 (0.70-1.13)	0.325	0.273	0.332
Zinc (mg/day)	≥ 11	838 (72.0)	775 (69.6)	1.00 (reference)	1.00 (reference)			
	< 11	326 (28.0)	338 (30.4)	0.89 (0.74-1.07)	0.88 (0.74-1.06)	0.179	0.215	0.215
Selenium (µg/day)	≥ 55	1128 (97.0)	1085 (97.7)	1.00 (reference)	1.00 (reference)			
	< 55	35 (3.0)	26 (2.3)	1.30 (0.77-2.17)	1.30 (0.77-2.17)	0.324	0.325	0.390
Alcohol Consumption	≥ 2	960 (82.6)	923 (83.1)	1.00 (reference)	1.00 (reference)			
(drinks /day)	< 2	203 (17.4)	188 (16.9)	1.04 (0.84-1.29)	1.04 (0.83-1.29)	0.747	0.736	0.427

*Adjusted Odds Ratios (OR) are adjusted for age and family history

Table 36. Single effects of Environmental OSR Factors and risk among MED, *continued*

Dietary Factor	N (%)	Cases N (%)	Controls N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
MeIQx (ng/day)	≤ 13.10	335 (28.8)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	13.10-23.93	310 (26.7)	278 (25.0)	0.93 (0.74-1.16)	0.94 (0.75-1.00)	0.601		
	23.93-46.64	263 (22.6)	277 (25.0)	0.79 (0.63-0.99)	0.79 (0.63-1.00)	0.051	0.009	
	≥ 46.64	255 (21.9)	278 (25.0)	0.76 (0.60-0.96)	0.77 (0.61-0.97)	0.025	0.042	0.055
	> 13.10	828 (71.2)	833 (75.0)	0.83 (0.69-0.99)	0.83 (0.69-1.01)	0.057		
PhIP (ng/day)	≤ 36.74	297 (25.5)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	36.74-73.98	328 (28.2)	300 (27.0)	1.02 (0.82-1.28)	1.04 (0.83-1.31)	0.722		
	73.98-156.86	283 (24.3)	255 (23.0)	1.04 (0.82-1.31)	1.06 (0.84-1.35)	0.620	0.251	
	≥ 156.86	255 (21.9)	278 (25.0)	0.86 (0.68-1.09)	0.89 (0.70-1.13)	0.323	0.778	0.166
	> 36.75	866 (74.5)	833 (75.0)	0.97 (0.81-1.18)	1.00 (0.82-1.21)	0.983		
DiMeIQx (ng/day)	≤ 0.39	308 (26.5)	279 (25.1)	1.00 (reference)	1.00 (reference)			
	0.39-1.22	365 (31.4)	297 (26.8)	1.11 (0.89-1.39)	1.12 (0.89-1.40)	0.340		
	1.22-2.58	246 (21.1)	257 (23.1)	0.87 (0.68-1.10)	0.88 (0.69-1.12)	0.297	0.014	
	≥ 2.58	244 (21.0)	278 (25.0)	0.80 (0.63-1.01)	0.81 (0.64-1.02)	0.074	0.456	0.067
	> 0.39	855 (73.5)	832 (75.0)	0.93 (0.77-1.12)	0.94 (0-78-1.14)	0.522		
BaP (mcg/day)	≤ 1.705	303 (26.0)	278 (25.0)	1.00 (reference)	1.00 (reference)			
	1.705-9.14	330 (28.4)	294 (26.5)	1.03 (0.82-1.29)	1.03 (0.82-1.29)	0.792		
	9.14-44.585	288 (24.8)	261 (23.5)	1.01 (0.80-1.28)	1.02 (0.81-1.29)	0.873	0.077	
	≥ 44.585	242 (20.8)	278 (25.0)	0.80 (0.63-1.01)	0.81 (0.63-1.02)	0.076	0.573	0.107
	> 1.705	860 (74.0)	833 (75.0)	0.95 (0.78-1.14)	0.95 (0.79-1.15)	0.621		
Tobacco Use	Never	477 (41.0)	421 (37.9)	1.00 (reference)	1.00 (reference)			
	Former	593 (51.0)	570 (51.3)	0.92 (0.77-1.09)	0.92 (0.77-1.09)	0.337	0.026	
	Current	93 (8.0)	120 (10.8)	0.68 (0.51-0.92)	0.69 (0.51-0.94)	0.018	0.128	0.178
	Ever[†]	686 (59.0)	690 (62.1)	0.88 (0.74-1.04)	0.88 (0.74-1.04)	0.135		

*Adjusted Odds Ratios (OR) are adjusted for age and family history

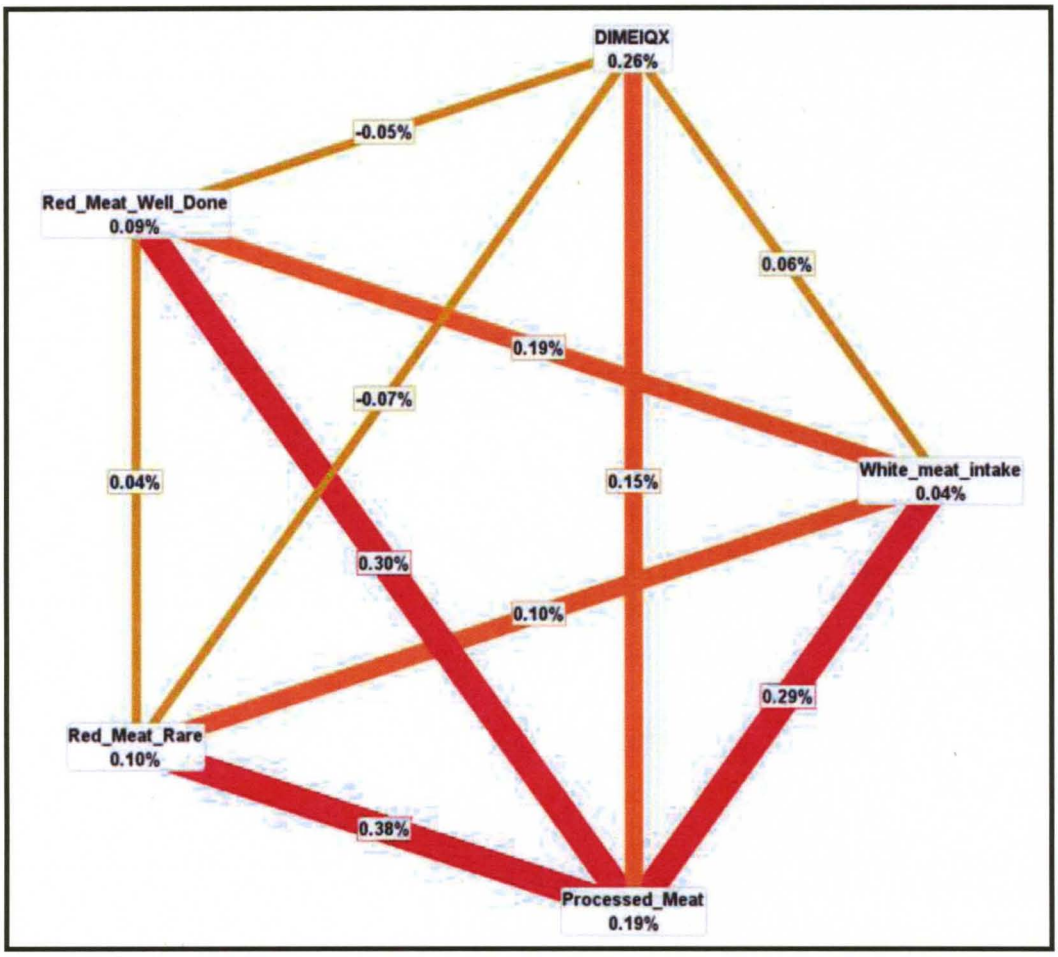
Although MDR modeling did not confirm any single effects observed by LR, a significant association was found between consumption of *White_meat-Processed_meat- Well_done_red_meat* (CVC = 7/10; p = 0.038) [*See Table 37*].

Table 37. Unfiltered MDR models for environmental OSR factors and prostate cancer risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor *DiMelQx*	27	6/10	0.497	0.544
Two Factor *Processed_Meat Red_Meat_Well_Done*	729	2/10	0.497	0.563
Three Factor *White_meat_intake Processed_Meat Red_Meat_Well_Done*	19683	7/10	0.534	0.038

hIG illustrated that the strongest risk effects were attributed to variables related to meat intake in our panel. Taken individually IG values were considerably less (i.e., IG ≤ 0.19%), compared to those obtained from the combined effects of *Processed_meat-Rare_red_*meat (0.38%); *Processed_meat-Well_done_*red_meat (0.30%); and *Processed_meat-White_meat* (0.29%) [*See Figure 16*]. LR modeling was used to validate these interactions, however only *Processed_meat-White_meat* was statistically significant [*See Table 38*]. This combination was associated with a decrease in risk comparing the highest quartiles of meat intake to the lowest quartiles [OR (95%CI) = 0.77 (0.60-0.98); p = 0.032].

Figure 1. Interaction entropy model for unfiltered environmental OSR panel and prostate cancer risk among MED



The combined effect of *Processed meat-Rare red meat* consumption yield an information gain of 0.38% in comparison to considering either *Processed_meat* or *Rare_red_meat* alone (IG = 0.19% and 0.10%, respectively).

Table 38. Association between environment - environment interactions & PCA risk among MED

Genes	Minor Category (g/day)	# Minor Category	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
Processed Meat	≥ 20.96	0	1.00 (reference)	1.00 (reference)		
Red meat rare	≥ 124.19	1	1.11 (0.87-1.43)	1.09 (0.85-1.40)	0.506	
		2	0.96 (0.77-1.19)	0.97 (0.78-1.20)	0.780	0.181
		≥3	1.11 (0.88-1.41)	1.12 (0.89-1.43)	0.325	
Processed Meat	≥ 20.96	0	1.00 (reference)	1.00 (reference)		
Red meat well-done	≥ 19.82	1	0.89 (0.67-1.18)	0.88 (0.66-1.17)	0.368	
		2	0.95 (0.77-1.18)	0.97 (0.79-1.20)	0.791	0.256
		≥3	0.78 (0.61-0.99)	0.79 (0.62-1.01)	0.057	
Processed Meat	≥ 20.96	0	1.00 (reference)	1.00 (reference)		
White meat	≥ 71.83	1	0.98 (0.76-1.27)	0.96 (0.74-1.24)	0.744	
		2	0.96 (0.78-1.19)	0.97 (0.79-1.20)	0.806	0.942
		≥3	0.76 (0.60-0.97)	0.77 (0.60-0.98)	0.032	

*Adjusted OR are adjusted for age & family history

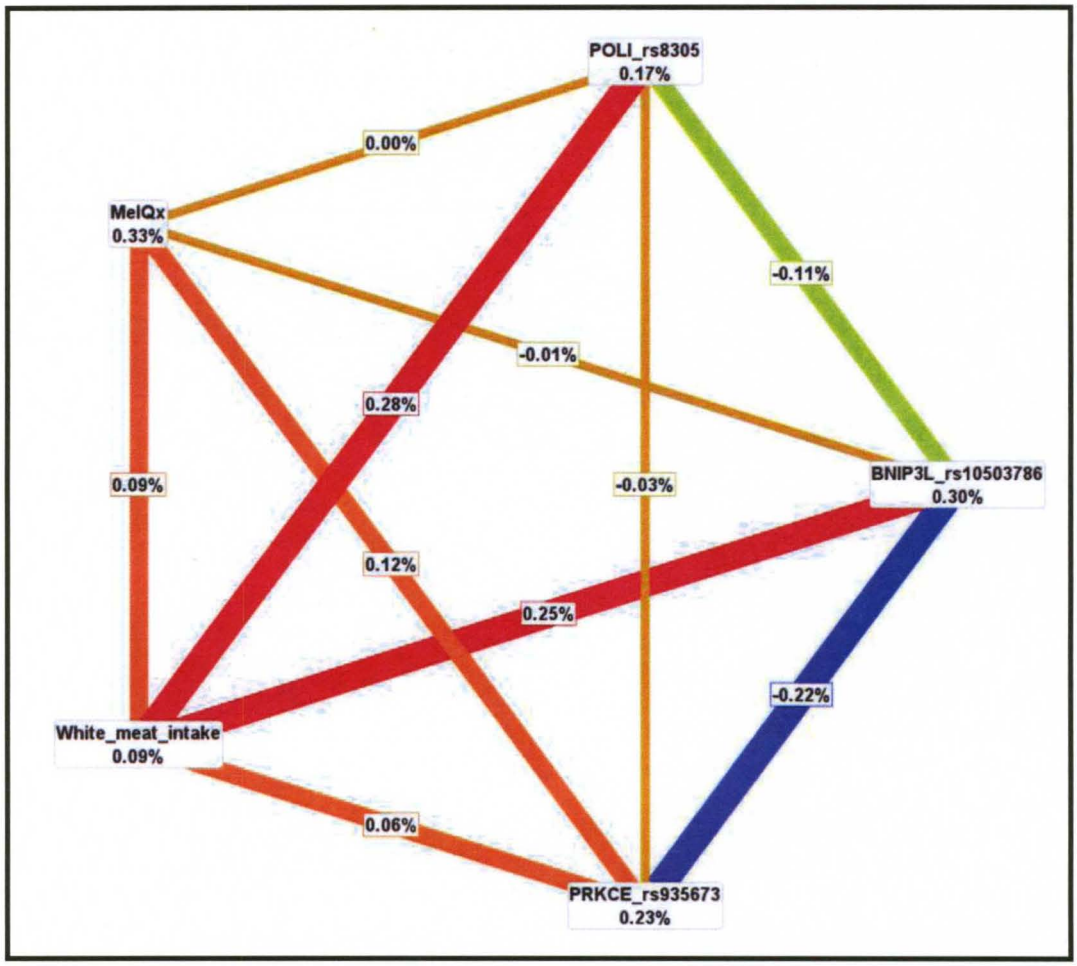
To conduct MDR modeling for the entire genetic and environmental OSR panel in relation to disease risk, we again subjected the datafile to the SURF & TuRF filter. With MDR ranking and selecting factors most likely to be associated with PCA risk the number of possible one-, two-, and three-way combinations was reduced from over 14 million to about 1.3 million. Although this was still computationally challenging, MDR was able to carry out this analysis in roughly one week. Unfortunately, this analysis did not did not detect any models significantly associated with disease risk ($p \geq 0.289$) [*See Table 39*].

Table 39. Top 25th Percentile MDR models for OSR panel and PCA risk among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor *MeIQx*	61	5/10	0.494	0.603
Two Factor *PRKCE_rs935673* *MeIQx*	3721	6/10	0.503	0.420
Three Factor *BNIP3L_rs10503786* *White_meat_intake* *MeIQx*	226981	4/10	0.510	0.289

hIG revealed synergistic interactions between *White meat intake-POLI_rs8305* and *White meat intake-BNIP3L_rs10503786* [*See Figure 17*]. However, neither combination was significant in LR analysis ($p \geq 0.129$) [*See Table 40*].

Figure 2. Entropy graph for OSR panel and PCA risk among MED



The combined effect of *White meat intake-POLI_rs8305* yield an information gain of 0.28% in comparison to consumption of either *White meat* intake or *POLI_rs8305* individually (IG = 0.09% and 0.17%, respectively).

Table 40. Association between OSR gene-environment interactions & PCA risk among MED

Genes	Minor Factors	# Minor Factors	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
White_meat (g/day)	≥ 71.83	0	1.00 (reference)	1.00 (reference)		
POLI_rs8305	GG	1	1.17 (0.95-1.45)	1.18 (0.95-1.46)	0.129	
		2	0.98 (0.79-1.21)	0.98 (0.79-1.21)	0.816	0.073
		≥3	1.18 (0.90-1.54)	1.18 (0.90-1.54)	0.227	
White_meat (g/day)	≥ 71.83	0	1.00 (reference)	1.00 (reference)		
BNIP3L_rs10503786	TT	1	0.86 (0.69-1.07)	0.86 (0.69-1.07)	0.174	
		2	1.09 (0.88-1.35)	1.10 (0.88-1.36)	0.402	0.477
		≥3	0.82 (0.63-1.07)	0.83 (0.64-1.08)	0.161	

*Adjusted OR are adjusted for age & family history

When we evaluated our candidate OSR panel as predictors of disease aggressiveness LR identified several environmental factors that independently modified PCA progression. Subjects that had more than 2 alcoholic drinks per day were associated with a decrease in disease aggressiveness compared to those having less than 2 drinks daily [OR (95%CI) = 0.73 (0.54-0.99); p = 0.044; *See Table 41*]. We also observed a decrease in PCA aggressiveness among men in 3rd quartile of daily PhIP exposure (i.e., 73.98-156.86 ng/day) compared the men exposed to less than 36.74 ng each day [OR (95%CI) = 0.71 (0.51-0.99); p = 0.045].

Men in the 2nd quartile of processed meat consumption (i.e., 6.08-11.42 g/day) were associated with a 1.5-fold increase in disease aggressiveness in contrast to men who consume less than 6.08 g per day. In addition, men in the 2nd quartile for daily consumption of well-done or very well-done red meat (i.e., 4.95-9.84 g/day) were linked to increased disease aggressiveness compared to men in the 1st quartile (consuming less than 4.95 g per day) [OR (95%CI) = 1.38 (1.00-1.89); p = 0.049].

Table 41. Single effects of Environmental OSR Factors and PCA aggressiveness among MED

Dietary Factor	N (%)	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Fruit (servings/day)	≥ 4	584 (85.0)	403 (82.6)	1.00 (reference)	1.00 (reference)			
	< 4	103 (15.0)	85 (17.4)	1.20 (0.87-1.64)	1.16 (0.85-1.59)	0.352	0.264	0.288
Vegetables (servings/day)	≥ 5	547 (79.6)	370 (75.8)	1.00 (reference)	1.00 (reference)			
	< 5	140 (20.4)	118 (24.2)	1.25 (0.94-1.65)	1.22 (0.92-1.61)	0.169	0.121	0.206
Total Meat (g/day)	≤ 129.33	189 (27.5)	147 (30.1)	1.00 (reference)	1.00 (reference)			
	129.33-174.54	187 (27.2)	108 (22.1)	1.35 (0.98-1.86)	1.30 (0.94-1.80)	0.107		
	174.54-252.89	150 (21.9)	120 (24.6)	0.97 (0.70-1.34)	0.97 (0.70-1.33)	0.831	0.951	0.153
	≥ 252.89	161 (23.4)	113 (23.2)	1.11 (0.80-1.53)	1.06 (0.77-1.48)	0.712		
	> 129.33	498 (72.5)	341 (69.9)	1.14 (0.88-1.47)	1.10 (0.85-1.43)	0.453		
White Meat (g/day)	≤ 26.21	179 (26.1)	112 (23.0)	1.00 (reference)	1.00 (reference)			
	26.21-44.63	213 (31.0)	148 (30.3)	0.90 (0.66-1.24)	0.89 (0.65-1.22)	0.454		
	44.63-71.83	146 (21.2)	106 (21.7)	0.86 (0.61-1.22)	0.83 (0.59-1.18)	0.295	0.116	0.175
	≥ 71.83	149 (21.7)	122 (25.0)	0.76 (0.55-1.07)	0.74 (0.53-1.04)	0.078		
	> 26.21	508 (73.9)	376 (77.0)	0.85 (0.65-1.11)	0.82 (0.63-1.08)	0.162		
Red Meat (g/day)	≤ 53.90	185 (26.9)	137 (28.1)	1.00 (reference)	1.00 (reference)			
	53.90-82.72	198 (28.8)	123 (25.2)	1.19 (0.87-1.63)	1.18 (0.86-1.62)	0.302		
	82.72-124.19	137 (20.0)	116 (23.8)	0.88 (0.63-1.22)	0.87 (0.62-1.21)	0.392	0.996	0.146
	≥ 124.19	167 (24.3)	112 (22.9)	1.10 (0.80-1.53)	1.07 (0.77-1.48)	0.700		
	> 53.90	502 (73.1)	351 (71.9)	1.06 (0.82-1.37)	1.04 (0.80-1.35)	0.774		
Processed Meat (g/day)	≤ 6.08	179 (26.1)	148 (30.3)	1.00 (reference)	1.00 (reference)			
	6.08-11.42	206 (29.8)	113 (23.2)	1.50 (1.09-2.06)	1.49 (1.08-2.05)	0.014		
	11.42-20.96	124 (18.0)	89 (18.2)	1.15 (0.81-1.63)	1.13 (0.80-1.61)	0.486	0.958	0.059
	≥ 20.96	179 (26.1)	138 (28.3)	1.07 (0.79-1.46)	1.06 (0.78-1.45)	0.707		
	> 6.08	508 (73.9)	340 (69.7)	1.24 (0.96-1.60)	1.22 (0.94-1.58)	0.127		

*Adjusted Odds Ratios (OR) are adjusted for age & family history

Table 41. Single effects of Environmental OSR Factors and PCA aggressiveness among MED, *continued*

Dietary Factor	N (%)	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Red Meat not processed (g/day)	≤ 38.65	188 (27.4)	132 (27.0)	1.00 (reference)	1.00 (reference)			
	38.65-62.14	195 (28.4)	130 (26.6)	1.05 (0.77-1.44)	1.04 (0.76-1.42)	0.852		
	62.14-95.72	139 (20.2)	114 (23.4)	0.86 (0.61-1.19)	0.85 (0.61-1.18)	0.326	0.844	0.197
	≥ 95.72	165 (24.0)	112 (23.0)	1.03 (0.75-1.44)	1.00 (0.72-1.39)	0.999		
	> 38.65	499 (72.6)	356 (73.0)	0.98 (0.76-1.28)	0.96 (0.74-1.25)	0.781		
Red Meat rare/med done (g/day)	≤ 3.86	161 (23.4)	123 (25.2)	1.00 (reference)	1.00 (reference)			
	3.86-15.98	225 (32.8)	125 (25.7)	1.38 (1.00-1.90)	1.36 (0.99-1.88)	0.060		
	15.98-32.41	129 (18.8)	130 (26.6)	0.76-0.54-1.06)	0.75 (0.54-1.06)	0.101	0.866	0.049
	≥ 32.41	172 (25.0)	110 (22.5)	1.20 (0.85-1.67)	1.17 (0.83-1.63)	0.375		
	> 3.86	526 (76.6)	365 (74.8)	1.10 (0.84-1.44)	1.09 (0.83-1.42)	0.555		
Red Meat well/very well done (g/day)	≤ 4.95	177 (25.8)	143 (29.3)	1.00 (reference)	1.00 (reference)			
	4.95-9.84	203 (29.5)	119 (24.4)	1.38 (1.01-1.89)	1.38 (1.00-1.89)	0.049		
	9.84-19.82	138 (20.1)	118 (24.2)	0.95 (0.68-1.31)	0.95 (0.68-1.32)	0.756	0.510	0.088
	≥ 19.82	169 (24.6)	108 (22.1)	1.26 (0.91-1.75)	1.26 (0.91-1.75)	0.170		
	> 4.95	510 (74.2)	345 (70.7)	1.19 (0.92-1.55)	1.19 (0.92-1.55)	0.183		

*Adjusted Odds Ratios (OR) are adjusted for age & family history

Table 41. Single effects of Environmental OSR Factors and PCA aggressiveness among MED, *continued*

Dietary Factor	N (%)	Aggressive Cases N (%)	Non-aggressive Cases N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
Kcal from diet (g/day)	2000-3000	237 (34.5)	161 (33.0)	1.00 (reference)	1.00 (reference)			
	< 2000	336 (48.9)	230 (47.1)	1.01 (0.78-1.31)	1.02 (0.78-1.32)	0.894	0.258	0.176
	> 3000	114 (16.6)	97 (19.9)	0.80 (0.59-1.11)	0.80 (0.58-1.10)	0.169		
Fat from diet (g/day)	≤ 73.11	381 (55.5)	252 (51.6)	1.00 (reference)	1.00 (reference)			
	> 73.11	306 (44.5)	236 (48.4)	0.86 (0.68-1.08)	0.85 (0.68-1.08)	0.179	0.196	0.186
Saturated Fat from diet	≤ 24.95	384 (55.9)	250 (51.2)	1.00 (reference)	1.00 (reference)			
(g/day)	> 24.95	303 (44.1)	238 (48.8)	0.83 (0.66-1.05)	0.83 (0.66-1.04)	0.110	0.114	0.140
Body Mass Index (BMI)	Under/normal weight	180 (26.2)	127 (26.0)	1.00 (reference)	1.00 (reference)			
	Overweight	350 (51.0)	272 (55.8)	0.91 (0.69-1.20)	0.90 (0.68-1.19)	0.452	0.273	0.156
	Obese	157 (22.8)	89 (18.2)	1.25 (0.88-1.76)	1.21 (0.85-1.71)	0.294		
Physically Active (≥30 min	Yes	333 (48.5)	229 (46.9)	1.00 (reference)	1.00 (reference)			
/day)	No	354 (51.5)	259 (53.1)	0.94 (0.75-1.19)	0.93 (0.74-1.18)	0.557	0.601	0.225
Vitamin A (µg/day)	≥ 900	620 (90.1)	444 (91.0)	1.00 (reference)	1.00 (reference)			
	< 900	68 (9.9)	44 (9.0)	1.11 (0.74-1.65)	1.08 (0.72-1.60)	0.723	0.618	0.403
Vitamin C (mg/day)	≥ 90	40 (5.8)	22 (4.5)	1.00 (reference)	1.00 (reference)			
	< 90	648 (94.2)	466 (95.5)	1.31 (0.77-2.23)	1.31 (0.77-2.24)	0.316	0.325	0.364
Vitamin E (IU/day)	≥ 22.4	93 (13.5)	59 (12.1)	1.00 (reference)	1.00 (reference)			
	< 22.4	595 (13.6)	429 (87.9)	1.14 (0.80-1.61)	1.15 (0.81-1.63)	0.438	0.472	0.319
Zinc (mg/day)	≥ 11	491 (71.5)	351 (71.9)	1.00 (reference)	1.00 (reference)			
	< 11	196 (28.5)	137 (28.1)	1.02 (0.79-1.32)	1.03 (0.79-1.33)	0.840	0.877	0.365
Selenium (µg/day)	≥ 55	24 (3.5)	11 (2.3)	1.00 (reference)	1.00 (reference)			
	< 55	663 (96.5)	477 (97.7)	1.57 (0.76-3.24)	1.60 (0.77-3.29)	0.206	0.222	0.359
Alcohol Consumption	≥ 2	579 (84.3)	390 (79.9)	1.00 (reference)	1.00 (reference)			
(drinks /day)	< 2	108 (15.7)	98 (20.1)	0.74 (0.55-1.00)	0.73 (0.54-0.99)	0.044	0.053	0.197

*Adjusted Odds Ratios (OR) are adjusted for age & family history

Table 41. Single effects of Environmental OSR Factors and PCA aggressiveness among MED, *continued*

Dietary Factor	N (%)	Aggressive Cases N (%)	Non-Aggressive Controls N (%)	OR (95%CI)	Adj OR (95%CI)*	p value*	p trend	MDRpt p value
MeIQx (ng/day)	≤ 13.10	190 (27.7)	148 (30.3)	1.00 (reference)	1.00 (reference)			
	13.10-23.93	178 (25.9)	133 (27.3)	1.04 (0.76-1.42)	1.03 (0.75-1.40)	0.875		
	23.93-46.64	159 (23.1)	107 (21.9)	1.16 (0.84-1.60)	1.14 (0.82-1.59)	0.423	0.153	0.193
	≥ 46.64	160 (23.3)	100 (20.5)	1.25 (0.90-1.73)	1.23 (0.89-1.72)	0.215		
	> 13.10	497 (72.3)	340 (69.7)	1.14 (0.88-1.47)	1.12 (0.87-1.45)	0.373		
PhIP (ng/day)	≤ 36.74	178 (25.9)	119 (24.4)	1.00 (reference)	1.00 (reference)			
	36.74-73.98	212 (30.9)	119 (24.4)	1.19 (0.86-1.65)	1.16 (0.84-1.61)	0.366		
	73.98-156.86	149 (21.7)	137 (28.0)	0.73 (0.52-1.01)	0.71 (0.51-0.99)	0.045	0.086	0.059
	≥ 156.86	148 (21.5)	113 (23.2)	0.88 (0.63-1.23)	0.84 (0.60-1.19)	0.329		
	> 36.75	509 (74.1)	369 (75.6)	0.92 (0.71-1.21)	0.90 (0.67-1.18)	0.435		
DiMeIQx (ng/day)	≤ 0.39	175 (25.5)	134 (27.5)	1.00 (reference)	1.00 (reference)			
	0.39-1.22	215 (31.3)	153 (31.3)	1.08 (0.79-1.46)	1.07 (0.79-1.46)	0.661		
	1.22-2.58	150 (21.8)	99 (20.3)	1.16 (0.83-1.63)	1.15 (0.82-1.62)	0.418	0.483	0.237
	≥ 2.58	147 (21.4)	102 (20.9)	1.10 (0.79-1.55)	1.09 (0.77-1.52)	0.635		
	> 0.39	512 (74.5)	354 (72.5)	1.11 (0.85-1.44)	1.10 (0.84-1.43)	0.488		
BaP (mcg/day)	≤ 1.705	172 (25.0)	132 (27.1)	1.00 (reference)	1.00 (reference)			
	1.705-9.14	203 (29.5)	130 (26.6)	1.20 (0.87-1.64)	1.19 (0.87-1.63)	0.289		
	9.14-44.585	170 (24.8)	120 (24.6)	1.09 (0.79-1.51)	1.06 (0.76-1.47)	0.739	0.992	0.260
	≥ 44.585	142 (20.7)	106 (21.7)	1.03 (0.73-1.44)	1.01 (0.72-1.42)	0.941		
	> 1.705	515 (75.0)	356 (72.9)	1.11 (0.85-1.45)	1.09 (0.84-1.42)	0.517		
Tobacco Use	Never	296 (43.1)	186 (38.1)	1.00 (reference)	1.00 (reference)			
	Former	335 (48.8)	265 (54.3)	0.79 (0.62-1.01)	0.80 (0.63-1.03)	0.079		
	Current	56 (8.1)	37 (7.6)	0.95 (0.60-1.50)	0.92 (0.59-1.46)	0.732	0.228	0.160
	Ever[†]	391 (56.9)	302 (61.9)	0.81 (0.64-1.03)	0.82-0.65-1.04)	0.098		

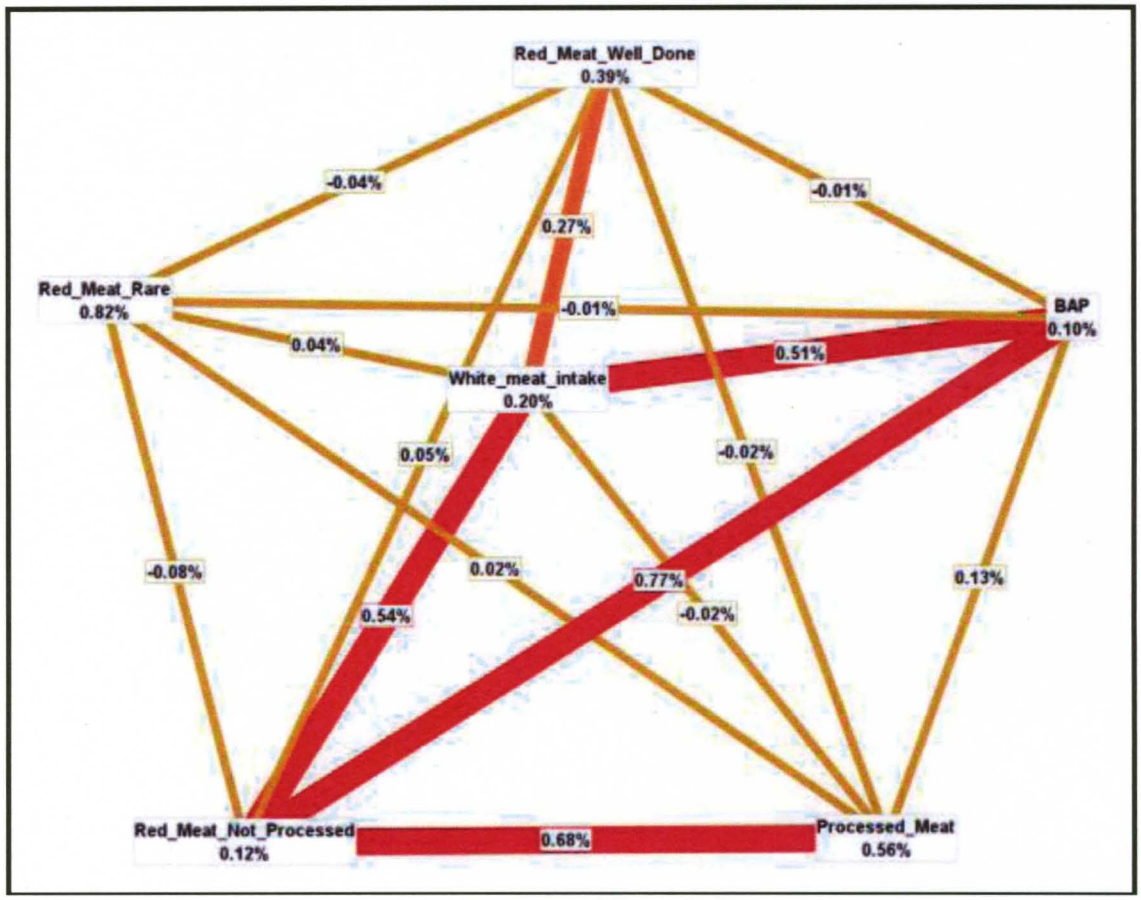
*Adjusted Odds Ratios (OR) are adjusted for age & family history

MDR identified the three factor model with consumption of *Processed_meat-Rare_red_meat- BaP* as a modestly significant predictor of PCA aggressiveness (CVC = 10/10; p = 0.053) [*See Table 42*]. Visualization by hIG revealed additional synergistic effects due to the meat-related variables [*See Figure 18*]. The strongest combined effects were seen for *Red_meat_not_processed-BaP* (IG = 0.77%); *Red_meat_not_processed-Processed_meat* (IG = 0.68%); *Red_meat_not_processed-White_meat* (IG = 0.54%); and *White_meat-BaP* (IG = 0.51%). LR confirmed the *Red_meat_not_processed-Processed_meat* interaction was linked with increased disease aggressiveness [OR (95%CI) = 1.45 (1.08-2.04); p = 0.016) [*See Table 43*].

Table 42. Unfiltered MDR models for environmental OSR factors and disease aggressiveness among men of European descent (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***Red_Meat_Rare***	27	9/10	0.5344	0.093
Two Factor ***Processed_Meat Red_Meat_Rare***	729	3/10	0.4961	0.536
Three Factor ***Processed_Meat Red_Meat_Rare BAP***	19683	10/10	0.5459	0.053

Figure 1. Interaction entropy model for unfiltered environmental OSR factors and disease aggressiveness in men of European descent



The strongest synergistic interaction was attributed to the interaction between *BaP_meat-Non-processed red meat* (IG = 0.77%). Note that additional IG attributed to this combination compared to the single effects of or *BaP* (IG = 0.10%) or *Non-processed red meat* (IG = 0.12%).

Table 43. Association between environment-environment OSR interactions & PCA aggressiveness among MED

Genes	Minor Category	# Minor Category	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
Red_meat_not processed (g/day)	≥ 95.72	0	1.00 (reference)	1.00 (reference)		
BaP (mcg/day)	≥ 44.585	1	0.74 (0.51-1.06)	0.76 (0.53-1.09)	0.133	
		2	1.31 (0.98-1.76)	1.30 (0.97-1.75)	0.078	0.456
		≥3	0.90 (0.64-1.27)	0.89 (0.63-1.25)	0.506	
Red_meat_not processed (g/day)	≥ 95.72	0	1.00 (reference)	1.00 (reference)		
Processed_Meat (g/day)	≥ 20.96	1	1.03 (0.71-1.50)	1.05 (0.72-1.53)	0.802	
		2	1.48 (1.07-2.03)	1.45 (1.08-2.04)	0.016	0.002
		≥3	0.94 (0.67-1.32)	0.94 (0.67-1.32)	0.740	
Red_meat_not processed (g/day)	≥ 95.72	0	1.00 (reference)	1.00 (reference)		
White_meat (g/day)	≥ 71.83	1	0.83 (0.58-1.18)	0.84 (0.59-1.20)	0.342	
		2	1.26 (0.93-1.72)	1.25 (0.92-1.70)	0.161	0.657
		≥3	0.75 (0.54-1.04)	0.75 (0.54-1.05)	0.093	
White_meat (g/day)	≥ 71.83	0	1.00 (reference)	1.00 (reference)		
BaP (mcg/day)	≥ 44.585	1	1.11 (0.77-1.60)	1.14 (0.79-1.64)	0.497	
		2	1.12 (0.84-1.51)	1.12 (0.83-1.50)	0.469	0.459
		≥3	0.95 (0.69-1.31)	0.94 (0.68-1.30)	0.704	

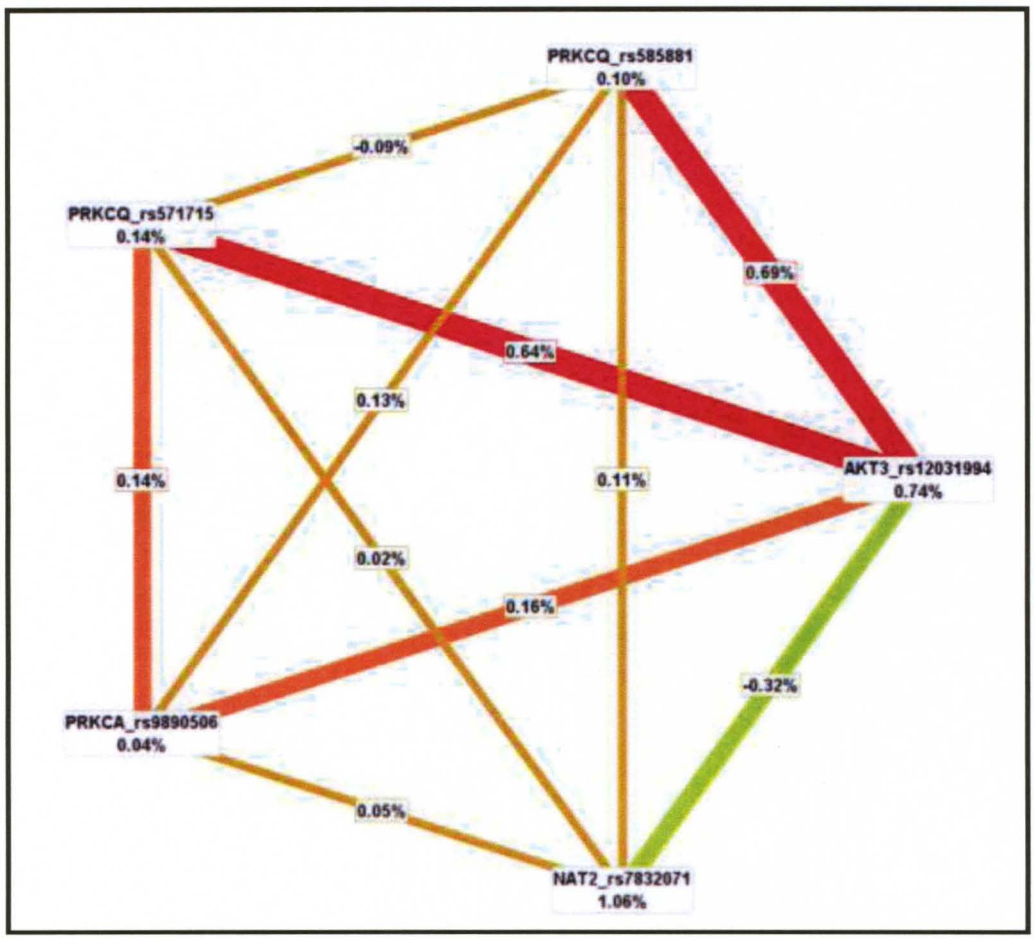
*Adjusted OR are adjusted for age & family history

Similar to our MDR modeling of OSR risk effects, we filtered the OSR panel using SURF & TuRF in order to evaluate genetic and environmental OSR factor in relation to disease aggressiveness. MDR analysis of the top 25th percentile of OSR factors revealed the three factor model *AKT3_rs12031994-NAT2_rs7832071-PRKCQ_rs571715* as the best predictor of disease aggressiveness among all genetic and environmental OSR factors (CVC = 7/10; p = 0.006) [*See Table 44*]. hIG detected synergistic effects from *PRKCQ_rs571715-AKT3_rs12031994* and *PRKCQ_rs585881-AKT3_rs12031994* interactions [*See Figure 19*]. LR confirmed the *PRKCQ_rs585881-AKT3_rs12031994* combination was associated with increased PCA aggressiveness [OR (95%CI) = 1.86 (1.44-2.64); p = <0.001]. LR models for the *PRKCQ_rs571715-AKT3_rs12031994* interaction were not associated with disease aggressiveness (p = ≥ 0.102), but the interaction p value was significant (interaction p value = 0.001) [*See Table 45*].

Table 44. Top 25th percentile MDR models OSR panel and PCA aggressiveness among MED (adjusted for age and family history)

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***NAT2_rs7832071***	**61**	**7/10**	**0.529**	**0.118**
Two Factor ***AKT3_rs12031994*** ***PRKCQ_rs571715***	**3721**	**5/10**	**0.539**	**0.069**
Three Factor ***AKT3_rs12031994*** ***NAT2_rs7832071*** ***PRKCQ_rs571715***	**226981**	**10/10**	**0.587**	**0.001**

Figure 2. Interaction entropy model for top 25th percentile genetic environmental OSR factors in relation to PCA aggressiveness among men of European descent



This graphical model describes the percent entropy that is explained by each OSR factor or a combination of two factors. The strongest synergistic effect of exists in the interaction between *PRKCQ_rs571715-AKT3_rs12031994* (IG = 0.64%). However, this interaction is mainly driven by *AKT3* (IG = 0.74%) due to lack of additional IG obtained by considering *PRKCQ_rs571715* (IG = 0.14%).

Table 45. Association between OSR interactions & PCA aggressiveness among MED

Genes	Minor Factors	# Minor Factors	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
AKT3_rs12031994	CC	0	1.00 (reference)	1.00 (reference)		
PRKCQ_rs585881	CC	1	1.88 (1.43-2.38)	1.86 (1.44-2.40)	< 0.001	
		2	1.34 (0.91-1.98)	1.36 (0.92-2.00)	0.127	0.001
		≥3	0.99 (0.47-2.08)	0.98 (0.46-2.07)	0.957	
AKT3_rs12031994	CC	0	1.00 (reference)	1.00 (reference)		
PRKCQ_rs571715	CC	1	1.84 (1.43-2.38)	1.86 (1.40-2.40)	0.102	
		2	1.37 (0.93-2.03)	1.39 (0.94-2.06)	0.915	0.001
		≥3	1.04 (0.51-2.13)	1.04 (0.51-2.13)	0.484	

*Adjusted OR are adjusted for age & family history

SPECIFIC AIM 3 FINDINGS – MAD SUBJECTS

We used LR along with MDR to assess the role of 25 OSR SNPs combined with a history of tobacco use in relation to PCA risk among 137 MAD case subjects (68 aggressive, 69 non-aggressive). LR revealed that current or former smokers missing at least one copy of the *GSTT1* gene were associated with a 2.3-fold increase in disease risk [OR (95%CI) = 2.27 (1.20-4.30); p = 0.012; *See Table 46*]. In addition, 11 out of the 15 apoptotic markers we examined were associated with a 2.1- to 3.3-fold increase in risk among subjects exposed to cigarette smoke ($p \leq 0.020$) [*See Table 48*]. LR models for *GSTP1_rs1695, CYP1A1_rs4646903,* and the three BER polymorphisms had extremely small p- values (<0.0001) [*Tables 46 & 47*], suggesting that their accuracy needs to be validated in additional MAD populations.

Table 46. Association between variant Antioxidative genes - Tobacco Use Interaction and disease risk among men of MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	Non- smokers Adj OR (95%CI)*	Current/Former smokers Adj OR (95%CI)*	p value*	p trend	MDRpt p value
rs1695	*GSTP1*	AA	37 (31.1)	39 (31.2)	1.00 (reference)	13.56 (5.52-33.31)	<0.0001		
		AG+GG	82 (68.9)	86 (68.8)	11.38 (6.10-21.23)	11.85 (6.36-22.07)	<0.0001	0.278	0.114
	GSTM1	*1/*1	37 (31.1)	43 (32.6)	1.00 (reference)	4.42 (1.80-10.88)	0.001		
		*1/*0 + *1/*0	82 (68.9)	89 (67.4)	2.39 (1.23-4.62)	1.89 (1.00-3.58)	0.051	0.265	0.162
	GSTT1	*1/*1	30 (24.4)	38 (29.2)	1.00 (reference)	2.69 (1.05-6.90)	0.039		
		*1/*0 + *1/*0	93 (75.6)	92 (70.8)	2.05 (1.08-3.88)	2.27 (1.20-4.30)	0.012	0.571	0.068
rs2069514	*CYP1A2*	GG	67 (50.8)	91 (62.3)	1.00 (reference)	12.93 (6.69-24.99)	<0.0001		
		GA+AA	65 (49.2)	55 (37.7)	13.73 (6.65-28.34)	9.55 (4.48-20.39)	<0.0001	0.014	0.113
rs4646903	*CYP1A1*	AA	60 (44.8)	52 (35.9)	1.00 (reference)	10.19 (4.76-21.84)	<0.0001		
		AC+CC	74 (55.2)	93 (64.1)	11.45 (5.82-22.51)	11.94 (6.19-23.02)	<0.0001	0.810	0.062

*Adjusted Odds Ratios are adjusted for age &WAA

Table 47. Association between variant Base Excision Repair genes - Tobacco Use Interaction and disease risk among MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	Non- smokers Adj OR (95%CI)*	Current/Former smokers Adj OR (95%CI)*	p value*	p trend	MDRpt p value
rs1130409	*APEX1*	TT	59 (45.4)	67 (46.9)	1.00 (reference)	17.06 (8.09-35.98)	<0.0001		
		TG+GG	71 (54.6)	76 (53.1)	9.40 (4.78-18.50)	7.43 (3.75-14.72)	<0.0001	0.261	0.077
rs1052133	*OGG1*	CC	102 (77.3)	96 (63.6)	1.00 (reference)	9.30 (5.12-16.90)	<0.0001		
		CG+GG	30 (22.7)	55 (36.4)	10.72 (3.92-29.34)	10.00 (4.35-22.99)	<0.0001	0.846	0.133
rs25487	*XRCC1*	GG	93 (72.1)	97 (64.2)	1.00 (reference)	11.18 (5.86-21.33)	<0.0001		
		GA+AA	36 (27.9)	54 (35.8)	6.22 (2.45-15.83)	7.16 (3.44-14.90)	<0.0001	0.654	0.175

*Adjusted Odds Ratios are adjusted for age &WAA

Table 48. Association between variant Apoptotic genes - Tobacco Use Interaction and disease risk among MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	Non- smokers Adj OR (95%CI)*	Current/Former smokers Adj OR (95%CI)*	p value*	p trend	MDRpt p value
rs4645878	*BAX*	CC	62 (50.8)	67 (49.6)	1.00 (reference)	1.54 (0.77-3.07)	0.224		
		CT+TT	60 (49.2)	68 (50.4)	2.90 (1.39-6.02)	4.23 (2.02-8.87)	0.0001	0.966	0.075
rs3789068	*BCL2L11*	TT	56 (46.3)	50 (37.9)	1.00 (reference)	3.85 (1.67-8.88)	0.002		
		TC+CC	65 (53.7)	82 (62.1)	2.55 (1.28-5.08)	2.06 (1.08-3.92)	0.029	0.111	0.003
rs4488761	*BCL2L13*	AA	47 (37.9)	45 (33.6)	1.00 (reference)	2.26 (0.99-5.15)	0.052		
		AG+GG	77 (62.1)	89 (66.4)	2.20 (1.14-4.23)	2.40 (1.28-4.52)	0.007	0.857	0.118
rs6488494	*BCL2L14*	TT	29 (23.6)	36 (26.7)	1.00 (reference)	1.84 (0.81-4.19)	0.148		
		TC+CC	94 (76.4)	99 (73.3)	2.47 (1.31-4.67)	3.47 (1.78-6.78)	0.0003	0.416	0.150
rs1883263	*BIK*	AA	99 (80.5)	113 (84.3)	1.00 (reference)	2.41 (1.37-4.27)	0.002		
		AC+CC	24 (19.5)	21 (15.7)	2.58 (0.92-7.26)	0.92 (0.30-2.80)	0.881	0.147	0.150
rs738276	*BIK*	GG	49 (48.0)	45 (38.8)	1.00 (reference)	2.58 (1.14-5.83)	0.023		
		GA+AA	53 (52.0)	71 (61.2)	2.83 (1.31-6.12)	2.08 (1.03-4.22)	0.042	0.428	0.165
rs6509364	*CARD8*	CC	69 (57.0)	80 (61.5)	1.00 (reference)	2.06 (1.10-3.88)	0.025		
		CT+TT	52 (43.0)	50 (38.5)	1.76 (0.82-3.80)	1.96 (0.89-4.34)	0.097	0.626	0.113
rs6509366	*CARD8*	GG	69 (56.6)	85 (63.9)	1.00 (reference)	2.36 (1.23-4.53)	0.010		
		GA+AA	53 (43.4)	48 (36.1)	2.49 (1.16-5.35)	2.09 (0.97-4.52)	0.060	0.738	0.131
rs1049216	*CASP3*	TT	76 (66.1)	93 (74.4)	1.00 (reference)	1.87 (1.00-3.49)	0.050		
		TC+CC	39 (33.9)	32 (25.6)	1.27 (0.57-2.83)	3.38 (1.24-9.19)	0.017	0.150	0.176
rs507879	*CASP5*	AA	15 (12.3)	27 (20.2)	1.00 (reference)	3.62 (1.22-10.74)	0.023		
		AG+GG	107 (87.7)	107 (79.8)	2.80 (1.50-5.22)	2.81 (1.50-5.25)	0.001	0.126	0.063
rs537093	*CASP5*	GG	68 (54.8)	59 (44.0)	1.00 (reference)	2.26 (1.10-4.64)	0.026		
		GA+AA	56 (45.2)	75 (56.0)	1.88 (0.90-3.93)	2.05 (1.04-4.02)	0.038	0.584	0.094
rs6747918	*CASP8*	AA	25 (30.1)	28 (30.1)	1.00 (reference)	6.03 (1.79-20.38)	0.004		
		AG+GG	58 (69.9)	65 (69.9)	2.07 (0.93-4.59)	1.96 (0.91-4.23)	0.088	0.500	0.178
rs1052576	*CASP9*	GG	42 (34.1)	68 (51.9)	1.00 (reference)	2.15 (1.09-4.26)	0.028		
		GA+AA	81 (65.9)	63 (48.1)	2.81 (1.44-5.48)	2.57 (1.22-5.39)	0.013	0.599	0.114

* Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

Table 48. Association between variant Apoptotic genes - Tobacco Use Interaction and disease risk among MAD, *continued*

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	Non- smokers Adj OR (95%CI)*	Current/Former smokers Adj OR (95%CI)*	p value*	p trend	MDRpt p value
rs12817549	*CRADD*	TT	67 (54.5)	75 (56.0)	1.00 (reference)	2.50 (1.30-4.80)	0.006		
		TC+CC	56 (45.5)	59 (44.0)	2.74 (1.23-6.12)	1.90 (0.89-4.05)	0.099	0.744	0.051
rs3858606	*CRADD*	GG	27 (22.3)	40 (30.3)	1.00 (reference)	1.90 (0.76-4.74)	0.170		
		GA+AA	94 (77.7)	92 (69.7)	2.86 (1.51-5.42)	3.24 (1.71-6.15)	0.0003	0.845	0.188

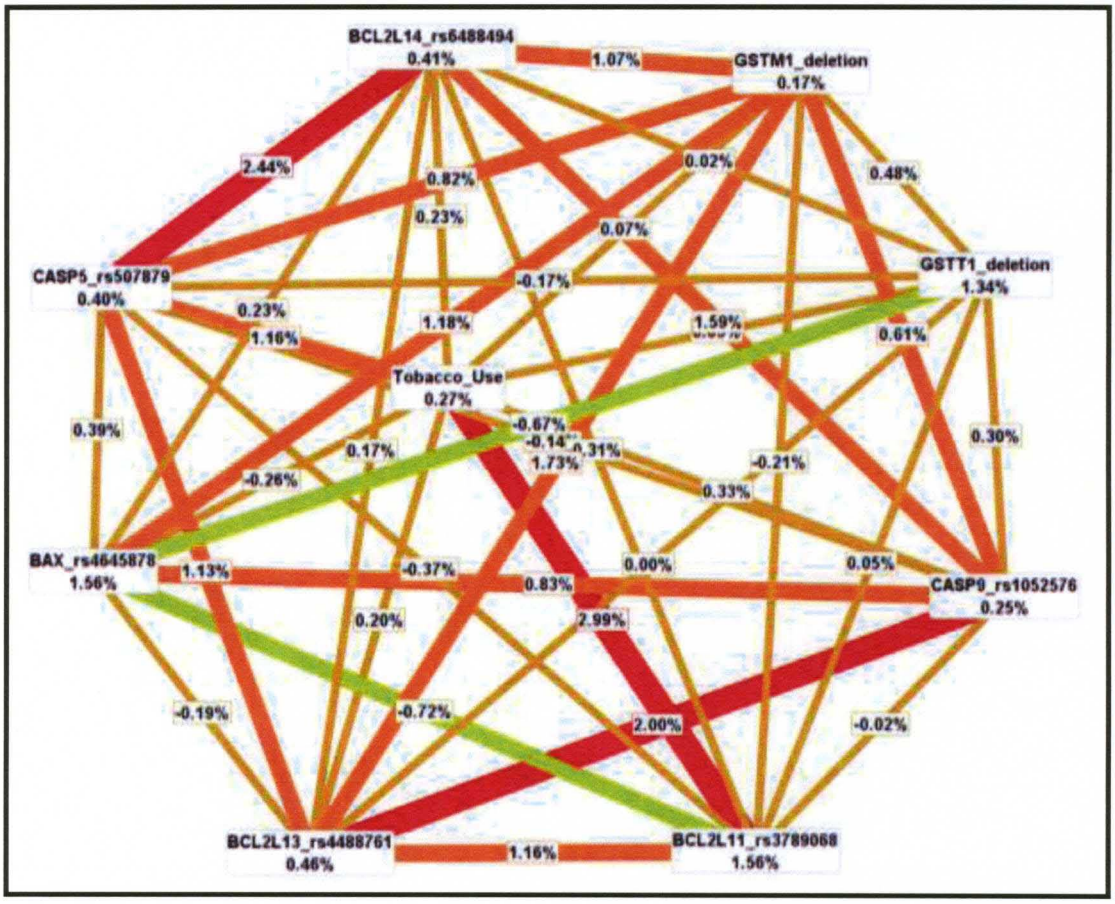
*Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

MDR revealed the two factor model containing *BCL2L11_rs3789068-Tobacco Use* as the best predictor of risk (CVC = 10/10; p = 0.025) [*See Table 49*]. MDR findings may be limited by the small sample size (n = 216) since this method is recommended for populations which have at least 200 cases and 200 controls. However, *BCL2L11-Tobacco_Use* was also significantly linked with a 2.1-fold increase in PCA risk by LR analysis [*See Table 48*]. Furthermore, hIG showed a synergistic effect attributed to the *BCL2L11-Tobacco_Use* interaction as well (IG = 2.99%) [*See Figure 20*].

Table 49. Unfiltered MDR models for OSR polymorphisms and Tobacco Use in relation to PCA risk among MAD

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***BAX_rs4645878***	**26**	**6/10**	**0.5169**	**0.352**
Two Factor ***Tobacco_Use*** ***BCL2L11_rs3789068***	**676**	**10/10**	**0.6071**	**0.020**
Three Factor ***Tobacco_Use*** ***CASP5_rs507879*** ***BCL2L14_rs6488494***	**17576**	**9/10**	**0.6581**	**0.001**

Figure 1. Interaction graph for OSR polymorphisms and Tobacco Use in relation to PCA risk among MAD



This graphical model describes the percent entropy that is explained by each OSR factor or a combination of two factors. The combined effect of *Tobacco_Use-BCL2L11_rs3789068* provides an (IG = 2.99%), in comparison to considering either *Tobacco_Use* or *BCL2L11_rs3789068* loci individually (IG = 0.27% and 1.56%, respectively).

When we examined the combined effects of OSR sequence variants and tobacco use in relation to disease aggressiveness among MAD, we found significant single effects linked to both *GST* gene deletions [*See Table 50*]. Former/current smokers lacking one or more copies of *GSTM1* were associated with a 3.1-fold increase in PCA aggressiveness [OR (95%CI) = 3.10 (1.12-8.57); p = 0.030]. Also, missing at least one copy of *GSTT1* among former/current smokers resulted in increased association with disease aggressiveness [OR (95%CI) = 3.39 (1.27-9.06); p = 0.015]. In addition, we observed a 3.1- to 6.0-fold increase in disease aggressiveness associated with six apoptotic SNPs (*BCL2L11_rs3789068*, *BIK_ rs738276*, *CARD8_rs6509366*, *CASP3_rs1049213*, *CRADD_rs12817549*, and *CRADD_rs3858606*) when combined with a history of tobacco use [*See Table 50*].

Table 50. Association between variant Antioxidation genes - Tobacco Use Interaction and Tumor Grade among men of MAD

dbSNP ID	Genes	Allele	Cases N (%)	Controls N (%)	Non- smokers Adj OR (95%CI)*	Current/Former smokers Adj OR (95%CI)*	p value*	p trend	MDRpt p value
rs1695	*GSTP1*	AA	37 (31.1)	39 (31.2)	1.00 (reference)	2.43 (0.80-7.39)	0.119		
		AG+GG	82 (68.9)	86 (68.8)	1.33 (0.49-3.66)	1.82 (0.68-4.85)	0.232	0.362	0.048
	GSTM1	*1/*1	37 (31.1)	43 (32.6)	1.00 (reference)	2.13 (0.70-6.46)	0.182		
		*1/*0 + *1/*0	82 (68.9)	89 (67.4)	1.51 (0.54-4.27)	3.10 (1.12-8.57)	0.030	0.844	0.048
	GSTT1	*1/*1	30 (24.4)	38 (29.2)	1.00 (reference)	3.68 (1.00-13.54)	0.050		
		*1/*0 + *1/*0	93 (75.6)	92 (70.8)	2.17 (0.77-6.12)	3.39 (1.27-9.06)	0.015	0.151	0.042
rs2069514	*CYP1A2*	GG	67 (50.8)	91 (62.3)	1.00 (reference)	2.19 (0.84-5.75)	0.111		
		GA+AA	65 (49.2)	55 (37.7)	0.97 (0.34-2.77)	1.67 (0.56-4.98)	0.354	0.925	0.027
rs4646903	*CYP1A1*	AA	60 (44.8)	52 (35.9)	1.00 (reference)	3.61 (1.18-11.08)	0.025		
		AC+CC	74 (55.2)	93 (64.1)	0.98 (0.34-2.78)	1.23 (0.48-3.17)	0.669	0.231	0.052

*Low Gleason score: >7; High Gleason score: ≤7; **Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 51. Association between variant Base Excision Repair genes - Tobacco Use Interaction and Tumor Grade among MAD

dbSNP ID	Genes	Allele	High N (%)*	Low N (%)*	Non-smokers Adj OR (95%CI)**	Current/former smokers Adj OR (95%CI)**	p value**	p trend	MDRpt p value
rs1130409	*APEX1*	TT	59 (45.4)	67 (46.9)	1.00 (reference)	0.94 (0.34-2.58)	0.906		
		TG+GG	71 (54.6)	76 (53.2)	0.66 (0.23-1.89)	1.92 (0.65-5.63)	0.238	0.171	0.018
rs1052133	*OGG1*	CC	102 (77.3)	96 (63.6)	1.00 (reference)	1.66 (0.69-4.02)	0.258		
		CG+GG	30 (22.7)	55 (36.4)	0.73 (0.19-2.79)	2.02 (0.71-5.77)	0.187	0.516	0.046
rs25487	*XRCC1*	GG	93 (72.1)	97 (64.2)	1.00 (reference)	1.26 (0.55-2.88)	0.587		
		GA+AA	36 (27.9)	54 (35.8)	0.16 (0.02-1.44)	3.11 (0.88-11.01)	0.078	0.029	0.052

*Low Gleason score: >7; High Gleason score: ≤7; **Adjusted Odds Ratios are adjusted for age, family history, & WAA

Table 52. Association between variant Apoptotic genes - Tobacco Use Interaction and Tumor Grade among men of MAD

dbSNP ID	Genes	Allele	High N (%)*	Low N (%)*	Non-smokers Adj OR (95%CI)**	Current/former smokers Adj OR (95%CI)**	p value**	p trend	MDRpt p value
rs4645878	*BAX*	CC	62 (50.8)	67 (49.6)	1.00 (reference)	3.83 (1.07-13.74)	0.040		
		CT+TT	60 (49.2)	68 (50.4)	0.50 (0.15-1.60)	1.22 (0.48-3.14)	0.676	0.806	0.048
rs3789068	*BCL2L11*	TT	56 (46.3)	50 (37.9)	1.00 (reference)	1.34 (0.42-4.32)	0.621		
		TC+CC	65 (53.7)	82 (62.1)	0.99 (0.33-2.95)	3.68 (1.29-10.46)	0.015	0.282	0.048
rs4488761	*BCL2L13*	AA	47 (37.9)	45 (33.6)	1.00 (reference)	3.91 (1.11-13.69)	0.033		
		AG+GG	77 (62.1)	89 (66.4)	1.40 (0.50-3.94)	2.15 (0.81-5.74)	0.127	0.171	0.033
rs6488494	*BCL2L14*	TT	29 (23.6)	36 (26.7)	1.00 (reference)	2.60 (0.65-10.36)	0.177		
		TC+CC	94 (76.4)	99 (73.3)	0.71 (0.25-2.04)	1.74 (0.67-4.50)	0.257	0.800	0.048
rs1883263	*BIK*	AA	99 (80.5)	113 (64.3)	1.00 (reference)	2.08 (0.91-4.78)	0.084		
		AC+CC	24 (19.5)	21 (15.7)	0.48 (0.09-2.66)	1.75 (0.35-8.69)	0.496	0.570	0.048
rs738276	*BIK*	GG	49 (48.0)	45 (38.8)	1.00 (reference)	1.88 (0.61-5.80)	0.274		
		GA+AA	53 (52.0)	71 (61.2)	1.02 (0.33-3.14)	3.32 (1.10-10.04)	0.034	0.593	0.034
rs6509364	*CARD8*	CC	69 (57.0)	80 (61.5)	1.00 (reference)	3.33 (1.25-8.87)	0.016		
		CT+TT	52 (43.0)	50 (38,5)	0.78 (0.20-3.03)	1.35 (0.44-4.12)	0.597	0.565	0.026
rs6509366	*CARD8*	GG	69 (56.6)	85 (63.9)	1.00 (reference)	2.13 (0.82-5.54)	0.122		
		GA+AA	53 (43.4)	48 (36.1)	1.80 (0.59-5.50)	5.49 (1.47-20.42)	0.011	0.688	0.032
rs1049216	*CASP3*	TT	76 (66.1)	93 (74.4)	1.00 (reference)	1.38 (0.57-3.34)	0.475		
		TC+CC	39 (33.9)	32 (25.6)	0.41 (0.10-1.73)	6.01 (1.16-30.99)	0.032	0.030	0.027
rs507879	*CASP5*	AA	15 (12.3)	27 (20.2)	1.00 (reference)	2.14 (0.46-9.91)	0.331		
		AG+GG	107 (87.7)	107 (79.8)	1.39 (0.49-3.95)	2.73 (0.99-7.52)	0.052	0.946	0.039
rs537093	*CASP5*	GG	68 (54.8)	59 (44.0)	1.00 (reference)	2.82 (0.94-8.46)	0.064		
		GA+AA	56 (45.2)	75 (56.0)	0.88 (0.27-2.87)	1.81 (0.69-4.73)	0.225	0.771	0.048
rs6747918	*CASP8*	AA	25 (30.1)	28 (30.1)	1.00 (reference)	8.73 (1.75-43.56)	0.008		
		AG+GG	58 (69.9)	65 (69.9)	1.52 (0.38-6.14)	3.34 (0.92-12.12)	0.067	0.120	0.050
rs1052576	*CASP9*	GG	42 (34.2)	68 (51.9)	1.00 (reference)	2.85 (0.96-8.47)	0.060		
		GA+AA	81 (65.9)	63 (48.1)	0.89 (0.33-2.44)	1.90 (0.63-5.71)	0.253	0.942	0.040

*Low Gleason score: >7; High Gleason score: ≤7; **Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

Table 52. Association between variant Apoptotic genes - Tobacco Use Interaction and Tumor Grade among men of MAD, *continued*

dbSNP ID	Genes	Allele	High N (%)*	Low N (%)*	Non-smokers Adj OR (95%CI)**	Current/former smokers Adj OR (95%CI)**	p value**	p trend	MDRpt p value
rs12817549	*CRADD*	TT	67 (54.5)	75 (56.0)	1.00 (reference)	2.37 (0.92-6.13)	0.074		
		TC+CC	56 (45.5)	59 (44.0)	2.38 (0.71-7.93)	4.06 (1.28-12.84)	0.017	0.622	0.017
rs3858606	*CRADD*	GG	27 (22.3)	40 (30.3)	1.00 (reference)	2.35 (0.58-9.59)	0.232		
		GA+AA	94 (77.7)	92 (69.7)	1.58 (0.56-4.49)	3.10 (1.10-8.71)	0.032	0.953	0.013

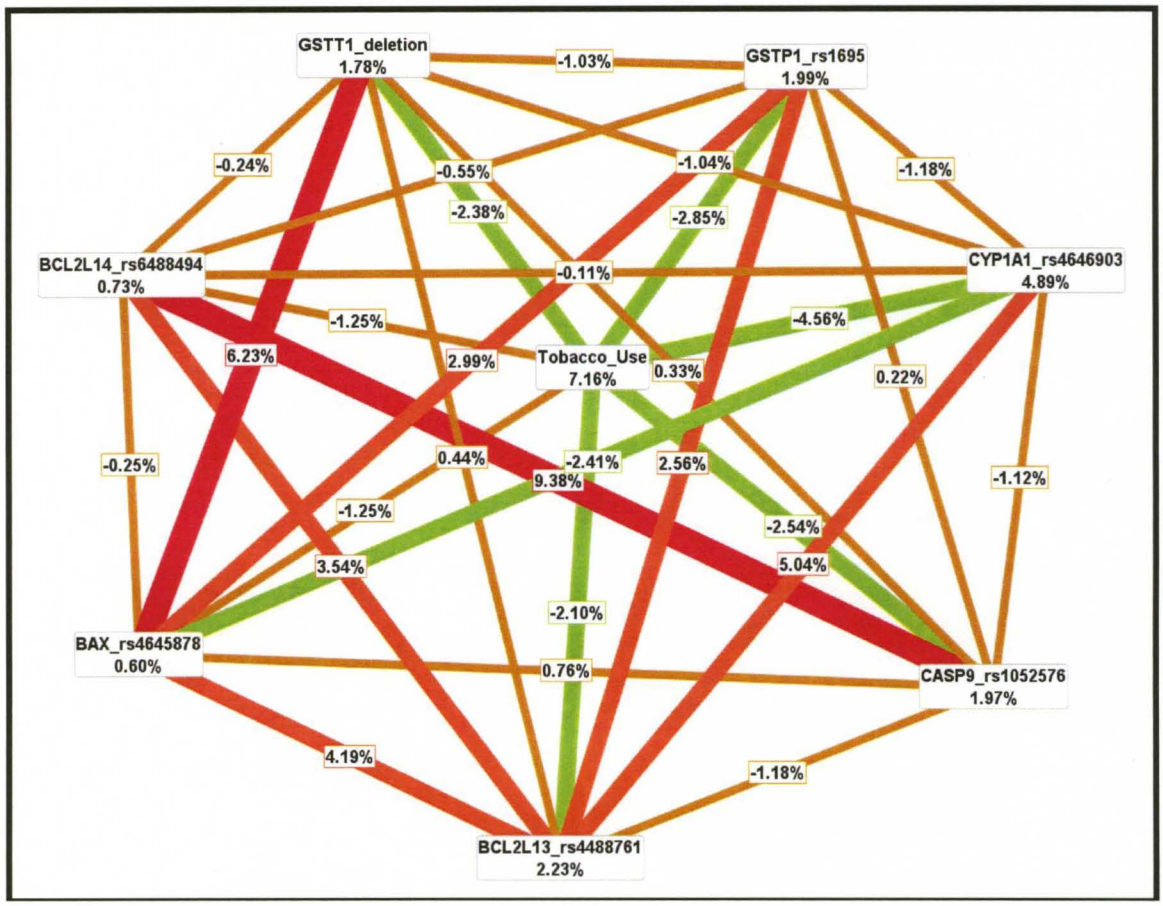
*Low Gleason score: >7; High Gleason score: ≤7; **Adjusted Odds Ratios (ORs) are adjusted for age, family history, & WAA

MDR modeling identified Tobacco Use alone as the best predictor of disease aggressiveness (CVC = 10/10, p = 0.034) [*See Table 53*]. This finding was confirmed by hIG which revealed Tobacco Use as the strongest independent effect (IG = 7.16%) [*See Figure 21*]. Synergistic interactions between *CASP9_rs1052576-BCL2L14_rs6488494* and *BAX_rs4645878-GSTT1_deletion* were also observed in the entropy graph. However, neither combination was statistically significant in LR two-way analysis (p ≥ 0.961) [*Table 53*].

Table 53. Unfiltered MDR models for OSR polymorphisms and Tobacco Use in relation to PCA aggressiveness among MAD

Best Model	Number of Combinations	Cross Validation Consistency (CVC)	Average Testing Accuracy (ATA)	Permutation Testing p value
One Factor ***Tobacco_Use***	26	10/10	0.637	0.034
Two Factor ***CASP9_rs1052576*** ***BCL2L14_rs6488494***	676	7/10	0.629	0.056
Three Factor ***BCL2L13_rs4488761*** ***GSTP1_rs1695*** ***CYP1A1_rs4646903***	17576	5/10	0.639	0.058

Figure 21. Interaction graph for OSR polymorphisms and Tobacco Use in relation to PCA aggressiveness among MAD



This graphical model describes the percent entropy that is explained by each OSR factor or a combination of two factors. The combined effect of *BCL2L14_rs6488464-CASP9_rs1052576* provides an (IG = 9.38%), in comparison to considering either *BCL2L14*_rs6488464 or CASP9_*rs1052576* loci individually (IG = 0.73% and 1.97%, respectively).

Table 54. Association between apoptotic gene-gene interactions & PCA aggressiveness among MAD

Genes	Minor Alleles	# Minor Alleles	OR (95% CI)	Adj OR (95% CI)*	p value*	interaction p value
BCL2L14_rs6488494	CC	0-2	1.00 (reference)	1.00 (reference)		
CASP9_rs1052576	AA	2-3	0.77 (0.34-1.73)	0.73 (0.32-1.65)	0.440	0.961
		4	0.44 (0.04-4.99)	0.43 (0.04-5.15)	0.502	
BAX_rs46465878	TT	0-2	1.00 (reference)	1.00 (reference)		
GSTT1_deletion	*0/*0	>2	1.65 (0.77-3.56)	1.60 (0.74-3.46)	0.236	0.985

*Adjusted OR are adjusted for age & WAA

SUMMARY AND CONCLUSIONS

Specific Aim 1 Summary. We evaluated a panel of 242 oxidative stress response (OSR)-related polymorphisms to determine their single- and joint-modifying effects on PCA risk. LR analysis revealed seven genetic variants capable of individually modifying risk among MED. We found one antioxidative (*CYP2C8_rs7909236*) and one BER (*OGG1_rs125701*) SNP independently associated with a 1.2-fold increase in PCA risk. In addition, the *EPHX1_rs1051741* polymorphism was linked with 2.5-fold increase in disease risk. We also observed an 18-25% decrease in PCA risk associated with one antioxidative-related (*NAT1_rs4921581*), one BER (*POLI_rs8305*), and four apoptotic (*BIK_rs4988366, BNIP3L_rs10503786, IKBKE_rs1539243, TNFRSF1A_rs4149576*) polymorphisms.

MDR indentified *CYP2C8_rs7909236-NAT1_rs4921581* as the best two factor model in predicting disease risk. LR two-way analysis indicated this combination was linked with 1.3-fold increase in PCA risk [OR (95%CI) = 1.28 (1.04-1.57); p = 0.019]. hIG did reveal any synergistic effects due to *NAT1-CYP2C8*, but several additional interactions were seen that remained significant in LR analysis. In particular, men with 3 or more minor *TNFRSF1A_rs4149576-PRKCE*_rs935673 alleles were associated with a 42% decrease in PCA risk [OR (95%CI) = 0.58 (0.42-0.81); p = 0.001]. Also, possessing at

least 2 variant *CYP2C8_rs7909236-GSTP1_rs1695* or *NAT1_rs4921581-GSTM2_rs638820* alleles resulted in a 1.4-fold increase in PCA susceptibility.

Among the MAD subjects, we detected two apoptotic polymorphisms associated with increased PCA risk (*BAX_rs4645878* & *BCL2L11_rs3789068*). However, there were no significant single effects were observed for antioxidative or BER targets. MDR did not confirm the B*AX* SNP, but MDR and hIG revealed five interactions containing apoptotic targets and both *GST* gene deletions. Only one of these interactions remained significant in LR (*BCL2L14_rs6488494_CASP5_rs507879)*.

Specific Aim 1 Conclusions. Among both populations we observed single risk effects in antioxidative, BER, and apoptotic gene variants. For MED, these SNPs were either a decrease or increase in risk, however, in MAD subjects significant effects were limited to apoptotic markers associated with increased risk. These SNP associations in relation to PCA susceptibility may be attributable to altered gene/protein function caused by the variation [*See Table 53*]. For instance, *CYP2C8_rs7909236* was associated with increased risk. This particular SNP is located in the promoter region of *CYP2C8* and predicted to interfere with transcription factor binding sites (TFBS), resulting in increased transcription.[129] As a cyp450 enzyme, 2C8 can that can detoxify or bioactivate a wide range of xenobiotics via oxidation or reduction.[52] However, one of cyp2c8's substrates is the suspected carcinogen B[a]P which is able to form DNA adducts during is metabolism.[140] Therefore, increased *CYP2C8* transcription leading to higher gene expression or protein activity could ultimately result in elevated BaP bioactivation.

Table 55. Possible function consequences of genetic variants associated with PCA outcomes based on previous publication or SNP prediction database tools

Gene	Function	dbSNP ID	Location	Amino Acid Change	Predicted/Observed effects*
AKT	Inhibits pro-apoptotic BAD	rs12031994	Intron 1		Increase apoptosis
BAX	Pro-apoptotic; increases mitochondria channel opening	rs4645878	Promoter (-248)		TFBS interference may decrease function
BAX	Pro-apoptotic; increases mitochondria channel opening	rs905238	Promoter (-85)		TFBS interference may decrease function
BCL2L11	Pro-apoptotic	rs724710	Exon 1	Ile95Ile	Altered splicing may decrease expression
BCL2L13	Pro-apoptotic	rs4488761	Exon 7	Ser257Ser	Altered splicing may decrease expression
BCL2L14	(aka BIM); Pro-apoptotic	rs10845479	Intron 1		Decrease apoptosis
BCL2L14	(aka BIM); Pro-apoptotic	rs6488494	Promoter		Decrease apoptosis
BIK	Pro-apoptotic, but may be a target for anti-apoptotic proteins	rs4988366	Promoter (-2288)		Disruption apoptosis- suppressing interactions
BNIP3L	(aka NIX); Anti-apoptotic	rs10503786	3'UTR		Decreased ability to block apoptosis
CASP5	Initiator caspase; mediates apoptosis	rs507879	Exon 2	Thr106Ala	Decreased apoptotic signaling
CASP9	Initiator caspase; mediates apoptosis	rs1052576	Exon 9	Arg221Gln	Decreased apoptotic signaling
CYP2C8	Oxidize / reduce xenobiotics (benzo[a]pyrene)	rs7909236	Promoter (-271)		TFBS: increased transcription
EPHX1	Detoxify or bioactivate aromatic compound	rs1051741	Exon 2	Asn357Asn	Altered splicing may decrease expression/detoxification
GSTM1	Detoxifies xenobiotics through glutathione conjugation				Loss of gene; decreased detoxification
GSTM2	Detoxifies xenobiotics through glutathione conjugation	rs638820	Promoter (+765)		TFBS may decrease detoxification
GSTP1	Detoxifies xenobiotics through glutathione conjugation	rs1695	Exon 5	Ile105Val	Decreased detoxification; reduced efficiency for diol epoxides or PAHs
GSTT1	Detoxifies xenobiotics through glutathione conjugation				Loss of gene; decreased detoxification
IKBKE	Inhibits NFkB	rs1539243	Exon 4	Ile67Ile	Interference with splicing may lead to decreased ability to block apoptosis
NAT1	Detoxify / bioactivate via transfer of acetyl group from acetyl-CoA	rs4921581	Intron 1		Increased detoxification/ decreased bioactivation
OGG1	Excises 8-oxoguanine	rs125701	5'UTR		Decreased function may increase risk

*Predicted or observed effects of genetic variants are based on previous publications and SNP prediction database tools[52, 129]

Table 55. Possible function consequences of genetic variants associated with PCA outcomes based on previous publication or SNP prediction database tools, *continued*

Gene	Function	dbSNP ID	Location	Amino Acid Change	Predicted/Observed effects*
POLI	Proceeds when normal polymerases stall	rs8305	Exon 1	Thr731Ala	Decreased function may lower risk due to error-prone activity
PRKCE	Activates pro-survival NFkB gene	rs935673	Intron 1		Increase apoptosis
PRKCQ	Activates pro-survival NFkB gene	rs571715	Intron 1		Increase apoptosis
PRKCQ	Activates pro-survival NFkB gene	rs585881	Intron 1		Increase apoptosis
TNFRSF1A	Major TNFα receptor; activates NFkB	rs4149576	Intron 1		Decreased ability to block apoptosis

*Predicted or observed effects of genetic variants are based on previous publications and SNP prediction database tools[52, 129]

Similarly, nat1 enzyme activity can either detoxify or bioactivate many xenobiotics and these effects are largely substrate dependent. Unfortunately, no published data or functional predictions are available regarding the intronic rs4921581 SNP. Therefore, we can only speculate the protective association we observed is due to decreased bioactivation or increased detoxification. Interestingly, when *NAT1_rs4921581* was combined *CYP2C8_rs7909236* or *GSTM2_rs638820*, the interaction was associated an increase in PCA risk. Unlike *CYP2C8*, the *GSTM2* variant was not individually linked to risk, however both are promoter region SNPs so altered TF binding may be the reason their effects. Taken together, these findings warrant further investigation of the functional consequences caused by *CYP2C8*, *NAT1*, and *GSTM2* polymorphisms.

Decreased protein function may explain the risk effects observed in two BER SNPs: *OGG1_rs125701* and *POLI_rs8305*. Ogg1 is a DNA glycosylase involved in the repair of the 8-oxoguanine. Therefore, the rs125701 may compromise ogg1's capacity to remove these mutagenic adducts and subsequently increase PCA susceptibility. Poli is polymerase that proceeds during DNA synthesis when normal polymerases may fail. Since this protein is error prone, particularly opposite a thymidine template, a SNP linked to decrease poli activity may decrease risk by reducing the protein's ability to insert in correct bases.

The decreased PCA risk observed in the four apoptotic SNPs may be attributed to a reduction in their ability to promote cell survival. For example, *BIK* is a pro-apoptotic gene, but is believed to be a target for anti-apoptotic proteins. Consequently, the

rs4988366 variant is located in the promoter region of and may result in disruption of transcription or apoptotic suppressors interacting with BIK, and would therefore be associated with decreased PCA risk. *BNIP3L* is pro-survival, *IKBKE* inhibits the pro-survival *NFkB* gene, and *TNFRSF1A* is a major cell death receptor in apoptosis. Therefore, the SNPs we found linked to risk may be due a reduced the ability of these markers to block apoptosis.

BAX_rs4645878 was linked to increased PCA risk in MAD subjects and is also located in the promoter region of this gene. Since bax is induces apoptosis, transcription factor interference could reduce protein expression, and ultimately decrease apoptosis. Similarly, the increase risk associated with *BCL2L11_rs3789068*, *BCL2L14_rs6488494*, and *CASP5_rs507879* among the subjects may result from a comprised ability for the targets to induce or signal apoptosis.

Gene-gene interactions identified by MDR and hIG modeling validated as significant by LR only contained antioxidative or apoptotic markers. These findings suggest a possible jointly modifying effect among variant antioxidative and apoptotic genes may contribute to risk. However, BER polymorphisms appear to play a less important role in PCA risk, particularly among men of African descent.

Specific Aim 2 Summary. In a case-only analysis, we examined the role of 173 apoptotic variants on disease aggressiveness in a population of 1,176 MED (688 aggressive and 488 non-aggressive cases). We found the *AKT3_rs12031994* alone and in the two-factor

MDR model with *PRKCQ_rs571715* was significantly associated PCA aggressiveness. hIG and two-way LR analysis revealed the *BCL2L14_rs10845479-BAX_rs905238* and *BCL2L14_rs10845479-BCL2L11_rs724710* interactions were significantly linked to increase aggressiveness in LR two-analysis.

Evaluation of 15 apoptotic sequence variants among 137 MAD (68 aggressive and 69 non-aggressive cases) did not show any single effects. We observed several interactions using MDR and hIG modeling between *CASP9_rs1052576-BCL2L14_rs6488494, CASP9_rs1052576-CASP5_rs507879*, and *BCL2L13_rs4488761-BCL2L14_rs6488494*. However, two-way LR analysis was not able validate any of these combinations as statistically significant ($p \geq 0.114$).

Specific Aim 2 Conclusions. We detected several gene-gene interactions linked to PCA aggressiveness among both populations involving *BCL2*-related genes. Since *BCL2L11, BCL2L13, BCL2L14, BAX,* as well as *CASP5/9* all function in cell death signaling and induction. Combined polymorphisms that reduce their ability to signal apoptosis would like promote cellular transformation or tumor formation (i.e., more aggressive phenotypes). In fact, a previous study found the amino acid change of glutamine to arginine in *CASP9_rs1052576* has also been shown to have functional significance.[129, 141] *CASP9* activation is an important step that occurs early in apoptosis and our data suggest this polymorphism along with other apoptotic SNPs increase PCA risk possibly due to compromised cell death mechanisms.[141]

Although we found *AKT3* individually modified risk, we would anticipate that most single effects would not strongly contribute to risk since apoptotic regulation involves many complex interacting mechanisms. Akt3 and prkcq are important upstream signaling proteins in apoptotic regulation and the intronic SNPs we examined in these may interfere with splicing or miRNA binding; thereby possibly lead to deformed or non functional proteins due to skipped or inhibited exon sites.[99]

Specific Aim 3 Summary. We assessed the effects 27 environmental OSR factors along with our panel of 219 gene variants in relation to PCA development. We evaluated 27 variables related to dietary habits, vitamin/ supplement intake and exposure to meat- and cigarette-derived carcinogens using data collected from 2,277 CGEMS project participants (1176 cases, 1101 controls). LR analysis revealed that MeIQx exposure and current smokers were independently associated with a decrease in disease risk. MDR and hIG also identified interactions involving meat consumption linked with PCA risk. LR modeling validated *Processed_meat-White_meat* was associated with a decrease in risk.

We also found subjects that had more than 2 alcoholic drinks per day and PhIP exposure were associated with a decrease in disease aggressiveness. However, consumption of processed meat and well-done or very well-done red meat were independently linked to increased disease aggressiveness. Interaction analyses revealed the combinations effects of *Red_meat_not_processed-Processed_meat* and

PRKCQ_rs585881-AKT3_rs12031994 were associated with increased disease aggressiveness.

Among MAD subjects, LR revealed that current or former smokers missing at least one copy of the *GSTT1* gene were associated with a 2.3-fold increase in PCA risk. Also, 11 apoptotic polymorphisms were associated with a 2.1- to 3.3-fold increase in risk among subjects exposed to cigarette smoke ($p \leq 0.020$). However, we found several LR models had extremely small p values (<0.0001), suggesting that the targets may need to be validated in larger MAD populations.

When we examined the combined effects of OSR sequence variants and tobacco use in relation to disease aggressiveness among MAD, we found significant single effects linked to both *GST* gene deletions and six apoptotic SNPs.

Specific Aim 3 Conclusions. We were surprised to find MeIQx and PhIP exposure, smoking, alcohol use independently associated with a decreased PCA development among MED. MeIQx and PhIP are both possible carcinogens capable of producing damaging DNA adduct during their metabolism. These compounds are derived from cooking meats at high temperature or for long durations, but we found consumption of well-done or very well-done red meat was linked to increased disease aggressiveness. This inconsistency may be caused by the PLCO project deriving these exposures from meat consumption data, so the measurements may not accurately reflect actual levels of these compounds. Therefore, further analysis of measured adducts or plasma metabolites would be needed to validate this finding.

Also the association between men who had more than 2 alcoholic drinks per day and decreased PCA risk may require future analyses examining the type of alcohol and further stratification of the number of drinks per day. This finding may have been limited by only considering men consuming either more or less than 2 drinks based on the USDA recommendation that these beverages should be limited to no more than two.

That fact that smoking was associated with a decreased risk in MED but increased risk and aggressiveness when combined with OSR variants among MAD subjects suggests that its possible protective effect in the former population likely involves a mechanism that was not examined in this study. For instance, smoking may activate additional detoxification targets that we either did not investigate or weren't due to genetic variation. Nevertheless, when we analyzed higher order interactions in the MED subjects, smoking was not involved with any significant models.

In fact, the combined effects we observed were related to meat consumption. We found *Processed_meat-White_meat* associated with a decrease in risk, but consumption of *Red_meat_not_processed-Processed_meat* was linked to increased disease aggressiveness. This finding warrants further investigation into the biological mechanisms involved in the metabolism of these meats to examine how processed meat was associated with a decrease in risk with white meat but increased aggressiveness with non-processed red meat.

DISCUSSION

Despite high incidence and mortality rates of PCA, especially among African-American men in particular, its etiology is poorly characterized. Identifying and validating new genomic profiles in biological pathways to serve as effective predictors of PCA susceptibility and aggressiveness are critical to overcoming this limitation.[3, 9]

Oxidative stress response (OSR) is one such biological pathway that appears to play an important role in prostate carcinogenesis.[3, 7] Oxidative stress is a condition in which the amount of reactive oxygen species (ROS) produced exceeds the amount removed.[13-16] Cells are constantly exposed to reactive oxygen species (ROS) generated from multiple endogenous and exogenous sources.[13-16] Although they are required for cellular functioning, ROS are highly reactive electrophiles that can interact with biomolecules, interfere with cell signaling, and promote cellular malignant transformation.[11, 14-17] ROS can directly damage nucleic acids and proteins, as well as alter protein function or activation.[9, 14-15, 17-18] These effects can be manifested as altered gene and protein expression, cell proliferation or apoptosis.[15] Left unrepaired, accumulating ROS damage can lead to cellular transformation and ultimately progress into to cancer.[12, 15, 18-19]

Genetic variation resulting in decreased function of OSR related mechanisms, such as antioxidation (e.g., carcinogen metabolism/ detoxification), DNA repair, and

apoptotic regulation may contribute to PCA progression.[2-3, 87] Previous studies have investigated the relationship between single variant OSR alleles and PCA, but many are either limited in scope, null, or conflicting.[2-3, 5, 87] Such inconsistencies may be attributed to inadequate statistical rigor or failure to consider gene-gene and gene-environment interactions. Consequently, this study evaluated the single- and joint- modifying effects of OSR factors on PCA using a combination of traditional and advanced statistical methods. This comprehensive analytical strategy utilized LR combined with MDR and hIG to examine the role of a unique OSR panel in relation to the PCA risk and disease aggressiveness.

Our unique candidate panel included 242 genetic and 27 environmental OSR factors related to diet and lifestyle habits. The OSR panel was generated using factors involved in antioxidation (e.g., carcinogen detoxification and metabolism), repair of oxidative DNA damage, and apoptotic regulation. We identified targets based on published PCA epidemiology studies as well as functional/pathway databases and tools. The latter provided important molecular interactions and genes that may not be readily found by literature search or traditional candidate SNP search methods. In addition, prediction tools aid in selecting markers likely to have a functional consequence resulting in compromised OSR capacity that may modify PCA disease outcomes. From an initial list of 118 OSR genes, more than 1500 had genotype available in through the CGEMS project. We finalized this list by first confirming sequence variants were related to our pathway of interest using NCBI Entrez SNP/Gene databases. Then we focused on polymorphisms that were (1) detected within all exons, 2.5kb upstream of the gene,

2.5kb downstream of intron 1, 2.5kb downstream of the gene; (2) had a minor allele frequency >1%; and (3) the genotype frequency among controls passed the Hardy-Weinberg Equilibrium test (HWE $p > 0.005$).

We evaluated our OSR panel using genetic profiles from 2277 men of European descent (MED) [488 non-aggressive and 688 aggressive cases, 1101 controls] and 923 men of African descent (MAD) [224 PCA cases and 699 controls]. Tumor grade (measured by Gleason Score) was available for 137 (68 aggressive, 69 non-aggressive) to examine disease aggressiveness in the population. Statistical analyses were conducted adjusting for age and family history of PCA, as well as population admixture (WAA) for MAD subjects. Our single risk findings associated several OSR sequence variants to PCA risk among MED. In contrast, only antioxidative- and apoptotic-related SNPs were linked to increased disease risk in MAD. Higher order interaction analyses for across both populations detected gene-gene combinations associated with increased risk.

Several of the targets we found that modify risk are intronic or have unknown functional consequence. However, based on data available from previous publications and prediction tools, as well as considering gene function, we presume that these variants result in compromised OSR. More specifically, our findings suggest that reduced detoxification and apoptotic induction are linked to increased PCA susceptibility.

When we investigated the role of apoptotic polymorphisms in relation to disease progression, *BCL2*-related and *CASPs* markers were jointly associated with increased PCA aggressiveness. This effect was found across both populations. These genes are

critical to apoptotic regulation and can activate downstream targets that commit cells to undergo this process.[97, 107] Failure to undergo apoptosis may enable survival of transformed cells that are prone to undergo further genetic alteration and show genomic instability, leading to more invasive phenotypes.[100]

Unfortunately we were not able to characterize the role of environmental factors in PCA among our study populations. The MAD analysis findings suggest smoking and apoptotic targets jointly increased risk. However, the apoptotic variants independently increased disease risk and aggressiveness so they may be driving this association. Also, these findings are limited by the small MAD sample size so these effects require validation in larger study populations. We were able to evaluate 27 environmental factors within the larger MED population. Our results indicate that meat consumption and cooking methods may contribute to PCA development. However, these factors most likely involve additional targets or mechanisms that were not examined in this study. To address this issue, future studies would need to focus on improved exposure analyses as well as biological mechanisms involved in meat metabolism.

Our study findings may be limited by filtering some of the OSR analyses for MED subjects. MDR filtering allows users to analyze large numbers of SNPs (e.g., GWAS) by ranking and selecting factors most likely to be associated with the disease outcome.[130-131] The filter essentially reduces "background noise" by removing SNPs that have the lowest predictive value.[130-131] The resulting filtered dataset improves the chance of detecting relevant interactions in MDR analysis. [130-131] However, it is possible that

filtering the largest datasets in this study removed some relevant targets. To overcome this limitation, future analyses will secure additional computational support to order to analyze unfiltered OSR and apoptotic targets in relation to PCA.

In addition, MAD findings are limited due to small sample size. However, future analyses using consortia and GWAS data will allow us to confirm results from this study.

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CURRICULUM VITAE

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A. EDUCATION

University of Louisville Louisville, KY

Ph.D. Pharmacology and Toxicology
December 2010
Dissertation Title: The Role of Genetic and Environmental Oxidative Stress Factors in Prostate Cancer

M.S. Pharmacology and Toxicology
December 2008
Thesis title: Joint Modifying Effects of Variant Oxidative Stress Factors in Relation to Prostate Cancer

B.S. Chemistry with a concentration in biochemistry
Minor: Philosophy.
May 2005
Honors: Woodford R. Porter Scholar, Golden Key International Honour Society

B. PROFESSIONAL EXPERIENCE

2004-2005 *Undergraduate Research Fellow*, Hormone Receptor Laboratory, Biochemistry and Molecular Biology, University of Louisville, School of Medicine, Louisville KY

2006- *Graduate Student Researcher*, Pharmacology and Toxicology, University of Louisville, School of Medicine, Louisville KY

C. PROFESSIONAL MEMBERSHIPS AND ACTIVITIES

2006- American Society for Pharmacology and Toxicology and Experimental Therapeutics (ASPET), Student member
2007- Black Biomedical Graduate Student Organization (BBGSO), *Vice-President 2008-2009*
2007- Ohio Valley Chapter of Society of Toxicology (OVSOT), Student member
2007- American Association for Cancer Research (AACR), Associate member
2009- American Society of Human Genetics (ASHG), Trainee Student Member
2009-2010 University of Louisville School of Medicine Academic Grievance Committee, graduate student member

D. HONORS AND AWARDS

2007 University of Louisville Graduate Bridge Fellowship (May 1 – July 31)
2007-2008 Integrated Programs in the Biomedical Sciences Fellowship, Department of Pharmacology and Toxicology
2008 American Association for Cancer Research Minorities in Cancer Travel Award, 2008 Annual Meeting
2008- Environmental Health Sciences Training Program, Department of Pharmacology and Toxicology
2009-2010 CODRE/Graduate School Diversity Grant for Graduate Students Research Award
2010 2009-2010 K.C. Huang Outstanding Graduate Student Award, Department of Pharmacology and Toxicology

E. ABSTRACTS AND PRESENTATIONS

E1. ORAL PRESENTATIONS: LOCAL/REGIONAL MEETINGS

Lavender, N.A., Kruer, T.L., Kerr II, D.A., Smolenkova, I.A., Wittliff, J.L. Fractionation of Botanicals Exhibiting Estrogen Mimicry. Undergraduate Research Symposium, UofL, Louisville, KY, April 18, 2005.

Lavender, N.A. Impact of Xeroderma Pigmentosum Group D (XPD) Polymorphisms on Prostate Cancer Risk. Pharmacology and Toxicology 1st year graduate departmental seminar, University of Louisville, Louisville, KY, March 9, 2007.

Lavender, N.A. Influence of Polymorphic Genes Involved in Oxidative Stress and Apoptosis on Prostate Cancer Risk, Scientific Writing Course lecture. Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, September 25, 2007.

Lavender, N.A. Insulin Therapy. Endocrinology and Metabolism Course lecture. Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, October 31, 2007.

Lavender, N.A. Joint Modifying Effects Variant Oxidative Stress in Relation to Prostate Cancer. Master's Thesis Defense. Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, November 6, 2008.

Lavender, N.A. Joint Modifying Effects of Variant Oxidative Stress and Apoptosis Markers and Smoking in Relation to Prostate Cancer Risk in African-American Men. University of Louisville CODRE Monthly meeting, University of Louisville, KY, June 11, 2010.

E2. POSTER PRESENTATIONS: NATIONAL/INTERNATIONAL MEETINGS

Kerr II, D.A., Smolenkova, I.A., Andres, S.A., Russell, A.J., Nicholson, E.S., Smolenkov, A.S., **Lavender, N.A.**, Kruer, T.L., Spatola, A.S., Zabel, S., Gangemi, J.D., Wittliff, J.L. Elucidating Medicinal Properties of Botanicals: Activities Altering Ligand & DNA Recognition by Estrogen Receptors. Annual International Clinical Ligand Assay Society Meeting, San Diego, CA, May 11, 2005.

Lavender, N.A., Komolafe, O.O., VanCleave, T.T., Srivastava, D.S., Thacker, B., States, J.C., Brock, G.N., Kidd, L.R. Interplay Between Xeroderma Pigmentosum Complementation Group D and Multi-drug Resistant 1 Genes (*XPD and MDR1*) and Prostate Cancer Risk. Annual American Society for Pharmacology and Toxicology and Experimental Therapeutics, Washington DC, April 27-30, 2007.

Lavender, N.A., Komolafe, O.O., Brock, G.N., Moore, J.H., Vancleave, T.T., Srivastava, D.S., Benford, M.L., States, J.C., Kittles, R.A., Kidd, L.R. Influence of high order interactions between variant DNA repair genes on prostate cancer risk in African-American Men. 99th Annual American Association for Cancer Research Conference, San Diego, CA, April 12-16, 2008.

Zhu, Y., Benford, M., **Lavender, N.A.**, Vancleave, T.T., Kittles, R., Wittliff, J., Kidd, L.R. TaqMan Allelic Discrimination Validation of Angiogenesis-associated Biomarkers. 99th Annual American Association for Cancer Research Conference, San Diego, CA, April 12-16, 2008.

Lavender, N.A., Zhu, Y., Benford, M.L., Vancleave, T.T., Kidd, L.R. Role of Glutathione S-Transferases (GSTs) Polymorphisms in Predicting Prostate Cancer Risk Among African-American Men. 100th Annual American Association for Cancer Research Conference, Denver, CO, April 18-22, 2009.

Benford, M.L., VanCleave, T.T., **Lavender, N.A.**, Kittles, R.A., Kidd, L.R. 8q24 Sequence Variation in Relation to Prostate Cancer Risk among African-American Men. 100th Annual American Association for Cancer Research Conference, Denver, CO, April 18-22, 2009.

Lavender, N.A., Kimbro, K.S., Tang, W., Vancleave, T.T., Bouzyk, M., Kidd, L.R. Oxidative Stress Response Sequence Variants as Predictors of Prostate Cancer Risk and Aggressive Disease among men of European and African Descent. 101th Annual American Association for Cancer Research Conference, Washington, DC, April 17-21, 2010.

E3. POSTER PRESENTATIONS: LOCAL/REGIONAL MEETINGS

Lavender, N.A., Komolafe, O.O., Vancleave, T.T., Srivastava, D.S., Thacker, B., States, J.C., Brock, G.N. Interplay Between Xeroderma Pigmentosum Complementation Group D and Multi-drug Resistant 1 Genes (*XPD and MDR1*) and Prostate Cancer Risk. James Graham Brown Cancer Center Retreat, Louisville, KY, November 29, 2006.

Komolafe, O.O., Vancleave, T.T., Srivastava, D.S., Thacker, B., **Lavender, N.A.**, Doll, M., Hein, D.W., Brock, G.N., Kidd, L.R. Multifaceted Analytical Approach for Predicting Prostate Cancer Susceptibility Among African-American Men. School of Public Health and Information Sciences, University of Louisville, Louisville, KY, April 24, 2007.

Lavender, N.A., Komolafe, O.O., Brock, G., Moore, J.H., Vancleave, T.T., Srivastava, D.S., Benford, M.L., States, J.C., Kittles, R., Kidd, L.R. Variant Base and Nucleotide Excision Repair Alleles and Prostate Cancer Risk among African-American Men. Research!Louisville, Louisville, KY, October 16, 2007.

Zhu, Y., **Lavender, N.A.**, Benford, M.L., Vancleave, T.T., Kidd, L.R. TaqMan Allelic Discrimination Validation of Angiogenesis-associated Biomarkers. Research!Louisville, Louisville, KY, October 17, 2007.

Lavender, N.A., Komolafe, O.O., Brock, G.N., Moore, J.H., Vancleave, T.T., Srivastava, D.S., Benford, M.L., States, J.C., Kittles, R.A., Kidd, L.R. Influence of High Order Interactions between Variant DNA Repair Genes on Prostate Cancer Risk in African-American Men. James Graham Brown Cancer Center Retreat, Louisville, KY, November 28, 2007.

Zhu, Y., **Lavender, N.A.**, Benford, M.L., Vancleave, T.T., Kidd, L.R. TaqMan Assay for Genotyping of Single Nucleotide Polymorphisms (SNPs) in Genes Regulating Tumor

Angiogenesis. James Graham Brown Cancer Center Retreat, Louisville, KY, November 28, 2007.

Lavender, N.A., Zhu, Y., Benford, M.L., Vancleave, T.T., Kidd, L.R. Role of Glutathione S-Transferases (GSTs) Polymorphisms in Predicting Prostate Cancer Risk Among African-American Men. Research!Louisville, University of Louisville, Louisville, KY, October 21, 2008.

Zhu, Y., Benford, M.L., Vancleave, T.T., **Lavender, N.A.**, Zeng, J., Kidd, L.R. Interplay of Genetic Polymorphisms and Prostate Cancer Risk. Research!Louisville, University of Louisville, Louisville, KY, October 22, 2008.

Vancleave, T.T., Brock, G. N., Benford, M. L., **Lavender, N.A.**, Zhu, Y., Kruer, T. L., Wittliff, J.L., Kidd, L. R. Clinical Relevance of Angiogenesis SNP Profiles in Breast Cancer Recurrence. Research!Louisville, University of Louisville, Louisville, KY, October 22, 2008.

Lavender, N.A., Zhu, Y., Benford, M.L., Vancleave, T.T., Kidd, L.R. Role of Glutathione S-Transferases (GSTs) Polymorphisms in Predicting Prostate Cancer Risk Among African-American Men. James Graham Brown Cancer Annual Retreat, University of Louisville, Louisville, KY, October 29, 2008.

Vancleave, T.T., Brock, G.N., Benford, M.L., **Lavender, N.A.**, Zhu, Y., Kruer, T.L., Wittliff, J.L., Kidd, L.R. Clinical Relevance of Angiogenesis SNP Profiles in Breast Cancer Recurrence. James Graham Brown Cancer Annual Retreat, University of Louisville, Louisville, KY, October 29, 2008.

Zhu, Y., Benford, M.L., Vancleave, T.T., **Lavender, N.A.**, Zeng, J., Kidd, L.R. Interplay of Genetic Polymorphisms and Prostate Cancer Risk. James Graham Brown Cancer 7th Annual Retreat, University of Louisville, Louisville, KY, October 29, 2008.

Lavender, N.A., Zhu, Y., Benford, M.L., Vancleave, T.T., Kidd, L.R. Role of Glutathione S-Transferases (GSTs) Polymorphisms in Predicting Prostate Cancer Risk Among African-American Men. 1st University of Louisville Graduate Research Symposium, University of Louisville, Louisville, KY, March 6, 2009.

Lavender, N.A., Zhu, Y., Benford, M.L., Vancleave, T.T., Kidd, L.R. Role of Glutathione S-Transferases (GSTs) Polymorphisms in Predicting Prostate Cancer Risk Among African-American Men. Environmental Health Science Fellows Showcase, University of Cincinnati, Cincinnati, OH, September 18, 2009.

Lavender, N.A., Komolafe, O.O., Brock, G.N., Moore, J.H., Vancleave, T.T., Benford, M.L., States, J.C., Kittles, R.A., Kidd, L.R. Influence of High Order Interactions between Variant DNA Repair Genes on Prostate Cancer Risk in African-American Men. 12th Annual

Midwest DNA Repair Symposium, University of Louisville, Louisville, KY, May 14-15, 2010.

F. RESEARCH SUPPORT

F.1 ACTIVE GRANTS

Clinical & Translational Science Pilot grant (Kidd) 10/01/10-present
Clinical & Translational Science Pilot Program
Innate Immune Response Predictors of Prostate Cancer Outcomes.
This project utilizes a case-cohort to evaluate whether patients who inherit compromised innate immunity markers will suffer shortened disease-free relapse and even death. Increased prostate cancer risk, disease progression, poor prognosis may be partially attributed to inheritance of variant innate immunity-related loci linked with enhanced pro-inflammatory, presumably due to alterations macromolecules that may lead to changes in responsiveness to pathogens by toll-like receptors and their cytokine/chemokine production. These biochemical changes may result in chronic inflammation and other microenvironment changes that support tumor growth and disease progression.
Role: Research Assistant

F2. COMPLETED GRANT AWARDS

NIEHS T32 Training Program Grant 10/01/08 - 09/30/10
National Institute of Environmental Health Sciences, NIEHS
Joint Modifying Effects of Variant Oxidative Stress and Apoptosis Markers and Second Hand Cigarette Smoke in Relation to Prostate Cancer Risk in African-American Men.
The goal of this project is to examine the impact of complex interactions among oxidative stress, apoptosis, and second hand smoke on prostate cancer risk and disease progression among men of African-descent. These complex interactions will be analyzed using traditional and advanced bioinformatic approaches, including multifactor dimensionality reduction. This multi-faceted approach is designed to capture gene-environment interactions that would remain undetected using conventional strategies such as logistic regression models.
Role: Principal Investigator

Intramural Award (Kidd) 04/15/06 - 03/15/07
Bales Medical Research Fund
Impact of DNA Repair Genes on Prostate Cancer Risk Among Men of African Descent.
Determine the role of variations in base excision (*OGG1, XRCC1, APEX1*) alone or in combination with nucleotide excision repair genes (*XPA, XPD*) in the risk of developing prostate cancer among African-American men.
Role: Research Assistant

Intramural Award 02/01/07 - 01/31/08
JGBCC Pilot Program Initiative 2007 (Kidd)
Genomic Approach to Predicting Breast Cancer Recurrence.
The purpose of this study is to identify important SNP or mRNA signatures to optimize breast cancer.
Role: Research Assistant

2006 Competition Awards Program (Kidd) 02/1/07 - 01/31/08
Prostate Cancer Foundation
Combined Genetic Assessment of Angiogenesis Pathway Variants Predictive of Prostate Cancer Risk.
Systematically evaluate the interaction among 12 highly variant angiogenesis genes and their combined modifying effects on prostate cancer risk and disease progression within a unique and large case-control study. This assessment involves genetic profiles collected from 918 men of African-descent (220 cases and 698 controls) using highly advanced statistical tools. The project tests the hypothesis that variations within regulatory or coding regions within selected angiogenesis markers genes will individually or jointly modulate prostate cancer risk and disease progression (i.e., high tumor grade), presumably due to alterations in mRNA/protein expression critical to tumor vasculature formation capacity.
Role: Research Assistant

Cancer Prevention R03 (Kidd) 06/1/07 - 5/31/09
National Cancer Institute, NIH
A Pharmacogenetic Approach to Prostate Cancer Susceptibility.
The purpose of the study is to systematically evaluate the capacity of an innovative panel of genetic variants within carcinogen-biotransformation, -transport, and -DNA repair pathways to predict prostate cancer susceptibility among men of African descent. In order to accomplish this high-impact research objective, the proposed project will use a multi-faceted statistical strategy that combines orthodox statistical methods with computation algorithms and hierarchical interaction graphs.
Role: Research Assistant

CODRE/Graduate School Diversity Grant for Graduate Students 06/01/09 - 05/31/10
UofL Commission on Diversity and Racial Equality
Joint Modifying Effects of Variant Oxidative Stress and Apoptosis Markers and Smoking in Relation to Prostate Cancer Risk in African-American Men.
This study aims to identify and evaluate whether a complex array of oxidative stress-related genetic and environmental markers can detect PCA risk, disease aggressiveness and treatment response using a combination of traditional and innovative advanced mathematical methodologies.
Role: Principal Investigator

G. ADMINISTRATIVE AND COMMUNITY SERVICES

G1. SERVICE TO THE DEPARTMENT

Interviewer, Department of Pharmacology & Toxicology, Spring 2008 – present
University of Louisville, School of Medicine, Louisville, KY

Responsibilities:

- Interview and recommend prospective graduate students
- Address questions/concerns regarding graduate school
- Disseminate recruitment materials
- Follow-up with interested candidates

G2. SERVICE TO THE UNIVERSITY

Member, Academic Grievance Committee, September 2009-2010
University of Louisville, School of Medicine, Louisville, KY

Responsibilities:

- Handle grievances from medical students, graduate students and post-doctoral trainees

G3. SERVICE TO THE PROFESSION

Manuscript Peer Reviews
Cancer Epidemiology, review submitted March 19, 2010

- Polymorphisms of Glutathione S-Transferase M1 and T1 and Prostate Cancer Risk in a Tunisian population, manuscript reference number: CANEP-D-10-00055

Disease Markers, review submitted September 28, 2010

- Association of GSTM1 and GSTT1 polymorphism and tobacco usage with oxidative stress in benign prostate hyperplasia and prostate cancer, manuscript reference number: DMA0910

G4. SERVICE TO THE COMMUNITY

Volunteer Activities
Team member/participant, American Cancer Society Relay For Life, May 15, 2010
Mentor, YMCA Black Achievers Program, 2008-present
Mentor/advisor, Nativity Academy at Saint Boniface Science Fair, Spring 2008

H. PUBLICATIONS, BOOK CHAPTERS, MONOGRAPHS AND TEXTBOOKS

H1. PEER-REVIEWED MANUSCRIPTS

Lavender N.A., Benford M.L., VanCleave T.T., Brock G.N., Kittles R.A., Moore J.H., Hein D.W., and Kidd L.R. Examination of polymorphic glutathione S-transferase (GST) genes, tobacco smoke and prostate cancer risk: A case-control study. BMC Cancer. 2009 Nov 16; 9:397.

Lavender N.A., Komolafe O.O., Benford M.L., Brock G.N., Moore J.H., VanCleave T.T., States J.C., Kittles R.A., and Kidd L.R. No association between variant DNA repair genes and prostate cancer risk among men of African descent. Prostate. 2010 Feb 1; 70(2):113-9.

Kidd L.R., Brock G.N., VanCleave T.T., Benford M.L., **Lavender N.A.**, Kruer T., Wittliff J.L. Angiogenesis-associated Sequence Variants Relative to Breast Cancer Recurrence and Survival. Cancer Causes and Control. 2010 Oct; 21(10):1545-57.

Benford M.L., VanCleave T.T., **Lavender N.A.**, Kittles R.A., Kidd L.R. 8q24 Sequence Variants in Relation to Prostate Cancer Risk among Men of African Descent. BMC Cancer. 2010 Jun 28; 10:334.

I. SCIENTIFIC MEETINGS, WORKSHOPS, SEMINARS

James Graham Brown Cancer Center Memorial Lecture Series, weekly seminars September 2006 to present
James Graham Brown Cancer Center, University of Louisville
Louisville, KY

Pharmacology and Toxicology Departmental Seminars, weekly seminars September 2006 to present
University of Louisville, School of Medicine
Louisville, KY

Grant Workshop: NIH Training and Career Development Programs, October 18, 2007
Research Louisville!
University of Louisville, School of Medicine
Louisville, KY

Third American Association for Cancer Research Conference: The Science of Cancer Health Disparities, September 30-October 3, 2010
Loews Miami Beach Hotel
Miami, FL