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A comprehensive analysis of genome-wide association studies to identify prostate cancer susceptibility loci for the Romanian population

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Abstract

The aim of this study is to examine a large dataset of single nucleotide polymorphism known to be associated with prostate cancer from previous genome-wide association studies and create a dataset of single nucleotide polymorphisms that can be used in replication studies for the Romanian population. This study will define a list of markers showing a significant association with this phenotype. We propose the results of this study as a starting point for any Romanian genome-wide association studies researching the genetic susceptibility for prostate cancer.

Keywords: prostate cancer, genome-wide association study, cancer predisposition genes, single nucleotide polymorphism, prostate cancer screening.

Introduction

Genome-wide association studies (GWASs) have emerged a new approach for investigating the genetic causes of complex diseases, providing a powerful tool to identify common, low-penetrance disease loci without prior knowledge of location or function [1].

In oncology, GWASs for almost all common cancers have been performed and more than 110 cancer predisposition genes have been identified. Genomic variation in GWAS reported to date is largely represented by single base pair changes known as SNPs [1, 2].

Genomic variation has not yet contributed to patient management in cancer care, but more than 50 GWAS studies that have been performed for over 15 malignancies have generated interesting association for clinical utility of this tool. These examples provide evidence that GWAS can identify genomic variations associated with disease risk and known biology [2].

Prostate cancer has a highest number of susceptibility loci identified through GWAS. The first and one of the most important regions was 8q24 [3]. This region was discovered through linkage studies by the deCODE group, followed-up by association analyses and separately through admixture mapping in African-Americans [3]. It is possible that genomic variation at this locus marks a carcinogenic pathway common to many cancers, and recent evidence suggests a role in regulation of the myc oncogene.

Identifying whether a cancer is the result of an underlying cancer predisposition genes mutation has significant impact for the cancer patients and their relatives. As such, cancer predisposition genes (CPGs) testing has become standard for many genes [1, 4].

GWASs have identified more than 50 common variants associated with susceptibility to prostate cancer (PrCa) [4]. These variants explain less than 1/3 of the familial risk of the disease, indicated that there are many others susceptibility loci that remain to be identified.

Current set of single nucleotide polymorphisms contributes to prostate cancer risk prediction, but overall they do not discriminate patients who will develop aggressive disease, a clinically more relevant outcome.

Genomic variation, either rare variants associated with specific disease or locus linked with various malignancies, such as 8q24 has the capacity to identify potentially targetable pathways important in oncogenesis, in prostate cancer pathogenesis and the result from prostate cancer GWAS completed to date begin to set the stage for further studies.

This study is an attempt to provide an overview of the results of GWAS studies and subsequent comparison of these data with data that will be obtained on Romanian population.

Materials and Methods

In an attempt to find susceptibility loci associated with prostate cancer for future replication, we assembled a database of single nucleotide polymorphisms from the

published results of 28 major prostate cancer genome-wide association studies. A complete list of reviewed papers can be found in Table 1.

Table 1 – *Complete list of reviewed papers*

1. Multiple newly identified loci associated with prostate cancer susceptibility [5].
2. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer [6].
3. A genome-wide association study of breast and prostate cancer in the NHLBI's Framingham Heart Study [7].
4. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24 [8].
5. Multiple loci identified in a genome-wide association study of prostate cancer [9].
6. A genome-wide search for loci interacting with known prostate cancer risk-associated genetic variants [10].
7. Genome-wide association scan for variants associated with early-onset prostate cancer [11].
8. A genome-wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity [12].
9. A study based on whole-genome sequencing yields a rare variant at 8q24 associated with prostate cancer [13].
10. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes [14].
11. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24 [15].
12. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21 [16].
13. Genome-wide association study identifies new prostate cancer susceptibility loci [17].
14. Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study [18].
15. Genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer [19].
16. Sequence variants at 22q13 are associated with prostate cancer risk [20].
17. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility [21].
18. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study [22].
19. New variants at 10q26 and 15q21 are associated with aggressive prostate cancer in a genome-wide association study from a prostate biopsy-screening cohort [23].
20. Evaluating genetic risk for prostate cancer among Japanese and Latinos [24].
21. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array [25].
22. Genome-wide association study in Chinese men identifies two new prostate cancer risk loci at 9q31.2 and 19q13.4 [26].
23. A meta-analysis of genome-wide association studies to identify prostate cancer susceptibility loci associated with aggressive and non-aggressive disease [2].
24. Genetic variation in prostate-specific antigen-detected prostate cancer and the effect of control selection on genetic association studies [27].
25. A two-stage genome-wide association study to identify single nucleotide polymorphisms associated with development of urinary symptoms after radiotherapy for prostate cancer [28].
26. A meta-analysis of 87 040 individuals identifies 23 new susceptibility loci for prostate cancer [29].
27. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1 [30].
28. Genome-wide association study identifies a region on chromosome 11q14.3 associated with late rectal bleeding following radiation therapy for prostate cancer [31].

For covering markers that can be expected to be found in the Romanian population, we choose to only include in the study markers with p-values less than 1×10^{-6}. We choose this threshold above genome-wide association as an inclusion criterion for our study due to the small sample size available right now in Romania for genome-wide association studies.

In the process of finding only the best markers from each loci, a python script was created and used for filtering any duplicated marker and extracting only the one with the best odds ratio and p-value. The script compares the exact position of each marker splinting the chromosomal position in two separate values: number of the chromosome and the exact base pair location, and compares the result with any single nucleotide polymorphism with the same two values. If the first two conditions are fulfilled, a second comparison is done on the p-values and odds ratios of both markers. The script only outputs the markers with the best p and odds ratios values. In this manner, 66 markers were excluded from the study.

One of the advantages of using this standardized method of comparing markers is the replicability of the process for future use in the effort of permanently updating the database.

Results

The study included a total of 239 unique single nucleotide polymorphisms. A complete list of RS (reference SNP cluster ID) names, p-values and odd ratios can be found in Table 2.

Table 2 – *A complete list of 239 unique single nucleotide polymorphisms associated with prostate cancer (NR: Not reported)*

RS number	Chromosome	Position	Reported effect	Reported *p*-value
rs7210100	17	49359387	0	0.05
rs6983267	8	127401060	0	0.53
rs10861905	12	108373556	0.01	0.0000008
rs5971305	23	28214936	0.02	0.000008
rs16861326	1	17967993	0.02	0.000002
rs17142289	6	6550516	0.02	0.000004
rs872690	23	37995474	0.03	0.000009
rs3802458	9	94978992	0.04	0.000004
rs16901979	8	127112671	0.04	3E-14
rs7582141	2	159042977	0.04	5E-11
rs11595238	10	100170652	0.04	0.000002
rs2788612	1	111873741	0.05	6E-16
rs188140481	8	127179427	0.054	6E-34
rs7153648	14	60655808	0.06	0.000000002
rs10194115	2	47012873	0.07	0.0000005
rs10090154	8	127519892	0.08	0.000003
rs9832625	3	29287529	0.08	0.000003
rs11650494	17	49267824	0.08	0.000000002
rs817826	9	107394019	0.084	5E-14
rs2823779	21	16396204	0.09	0.000007
rs12336160	9	33283584	0.09	0.000001
rs6862844	5	125030274	0.09	0.000004
rs1447295	8	127472793	0.11	2E-19
rs2660753	3	87061524	0.11	0.00000003
rs5965182	23	66386851	0.12	0.000006
rs4242382	8	127505328	0.12	3E-19
rs9443189	6	75786165	0.14	0.00000004
rs2716734	2	39720581	0.14	0.000002
rs10255878	7	97388483	0.14	0.000004
rs17694493	9	22041999	0.14	0.00000004
rs16902094	8	127308101	0.15	6E-15
rs3771570	2	241443449	0.15	0.000000005
rs2806864	1	116927159	0.15	0.0000006
rs2273669	6	108963986	0.15	0.000000008

RS number	Chromosome	Position	Reported effect	Reported *p*-value
rs11135910	8	26034626	0.16	8E-11
rs823123	1	205756218	0.16	5E-13
rs5944185	23	25835497	0.16	0.000007
rs636291	1	10496040	0.16	0.00000002
rs7064929	23	65147139	0.17	0.0000007
rs902774	12	52880120	0.17	0.000000005
rs2268363	2	48974189	0.18	0.00000005
rs6983561	8	127094635	0.18	4E-13
rs2807031	23	52867918	0.18	9E-10
rs721048	2	62904596	0.19	0.000000008
rs10519410	4	137213427	0.2	0.000001
rs11228565	11	69211113	0.2	7E-12
rs6869841	5	173512423	0.21	0.00000005
rs7126629	11	2207722	0.21	0.00000002
rs9623117	22	40056115	0.21	0.0000005
rs130067	6	31150734	0.21	0.00000003
rs17599629	1	150685811	0.22	6E-11
rs115457135	6	30105999	0.22	0.00000002
rs16958536	15	46737708	0.22	0.000004
rs7584330	2	237478585	0.22	0.000000003
rs1465618	2	43326810	0.23	0.00000002
rs12155172	7	20954872	0.23	5E-13
rs103294	19	54293995	0.238	5E-16
rs17779457	9	27488094	0.25	0.0000007
rs2292884	2	237534583	0.25	0.00000004
rs5925696	23	22873960	0.26	0.000003
rs11902236	2	9977740	0.27	0.00000003
rs1775148	1	205788696	0.27	0.00000004
rs4962416	10	125008303	0.27	0.0000002
rs10934853	3	128319530	0.28	3E-10
rs6049375	20	24077771	0.28	0.000008
rs9364554	6	160412632	0.29	6E-10
rs7120482	11	93058934	0.29	0.00000005
rs11122834	2	120943713	0.29	0.000005
rs10875943	12	49282227	0.31	7E-12
rs10210358	2	141038051	0.31	0.000002
rs9948	2	96835063	0.31	0.000006
rs10009409	4	72989536	0.32	2E-10
rs2840044	17	35565049	0.33	0.000008
rs6741148	2	38050689	0.33	0.000004
rs12051443	16	71657426	0.34	0.00000003
rs575018	5	101043689	0.34	0.0000007
rs2121875	5	44365443	0.34	0.00000004
rs5945572	23	51486831	0.35	4E-13
rs5945619	23	51498820	0.36	0.000000002
rs1512268	8	23668950	0.36	0.000005
rs684232	17	715725	0.36	5E-15
rs2901964	1	15465931	0.37	0.000005
rs339331	6	116888889	0.37	2E-12
rs9600079	13	73154002	0.38	0.000000003
rs4844289	23	71188133	0.39	0.000000001
rs3096702	6	32224554	0.4	0.000000005
rs6625711	23	70920000	0.41	6E-12
rs1983891	6	41568689	0.41	0.00000008
rs10993994	10	46046326	0.42	0.0000002
rs219553	2	21354871	0.42	0.000007
rs12653946	5	1895715	0.43	0.0000003
rs1527243	2	122533446	0.43	0.000001
rs1041449	21	41529494	0.44	0.0000003
rs13385191	2	20688505	0.44	0.00000008
rs4631830	10	46052478	0.45	7E-11
rs6763931	3	141383991	0.45	0.00000002
rs56232506	7	47397647	0.45	0.000000002
rs1218582	1	154861707	0.45	0.00000002
rs12500426	4	94593458	0.46	1E-11
rs9287719	2	10570604	0.46	0.00000002
rs10505477	8	127395198	0.49	0.000000009
rs1270884	12	114247766	0.49	7E-11
rs2153904	1	205673662	0.5	1E-13
rs7141529	14	68660027	0.5	3E-10
rs6679073	1	205787356	0.5	4E-15
rs11228583	11	69241647	0.52	0.0000002
rs1894292	4	73483441	0.52	5E-13
rs10896449	11	69227200	0.52	0.000000002
rs4713266	6	11218797	0.52	0.00000004
rs10936632	3	170412314	0.52	7E-22
rs4430796	17	37738049	0.52	0.000008
rs5759167	22	43104206	0.53	6E-29
rs8102476	19	38244973	0.54	2E-11
rs13254738	8	127092098	0.54	4E-10
rs7679673	4	105140377	0.55	3E-14
rs11568818	11	102530930	0.56	2E-11
rs1933488	6	153119944	0.59	4E-18
rs8014671	14	70625539	0.59	0.00000001
rs10187424	2	85567174	0.59	3E-15
rs7611694	3	113556777	0.59	4E-13
rs2427345	20	62440555	0.63	0.00000004
rs445114	8	127310936	0.64	5E-10
rs17021918	4	94641726	0.65	4E-15
rs115306967	6	32433162	0.65	0.000000003
rs2659051	19	50842312	0.66	9E-21
rs7241993	18	79013973	0.7	0.000000002
rs6062509	20	63731211	0.7	4E-16
rs3850699	10	102654464	0.71	5E-10
rs11214775	11	113936459	0.71	0.00000003
rs4245739	1	204549714	0.75	2E-11
rs10486567	7	27936944	0.77	0.000002
rs2405942	23	9846095	0.79	2E-10
rs2238776	22	19770369	0.8	0.0000002
rs5919432	23	67801708	0.81	0.00000001
rs2242652	5	1279913	0.81	3E-24
rs8008270	14	52905612	0.82	2E-14
rs2735839	19	50861367	0.85	2E-18
rs76934034	10	45587537	0.91	0.000000005
rs80130819	12	48025835	0.91	0.00000004
rs17632542	19	50858501	0.92	0.0000001
rs12480328	20	50911385	0.93	0.0000002
rs12621278	2	172446825	0.94	9E-23
rs4345897	10	98387303	NR	2E-91
rs4793529	17	71122495	NR	2E-13
rs10456809	6	17813594	NR	0.000005
rs1926657	13	95222702	NR	0.000002
rs1016343	8	127081052	NR	4E-10
rs9567349	13	44063269	NR	0.000004
rs998124	18	45145697	NR	0.000005
rs6005451	22	27456222	NR	0.000004
rs3764913	2	210210185	NR	4E-29
rs1876206	15	48608389	NR	0.000006
rs4489787	12	48417317	NR	0.000001
rs3789080	2	111039954	NR	0.000004
rs7789197	7	40925528	NR	0.000003
rs17181170	3	87124174	NR	0.00000003
rs12628051	22	40258272	NR	0.000003
rs4351	17	63492371	NR	9E-13
rs11199874	10	121273005	NR	3E-10
rs458685	21	29805194	NR	0.000006
rs1154865	12	73596057	NR	0.0000007
rs11045879	12	21229685	NR	5E-15
rs174549	11	61803910	NR	2E-30
rs6766510	3	12510308	NR	0.000002
rs1529276	13	103275657	NR	0.000002
rs13398206	2	198304372	NR	0.000004
rs4242384	8	127506309	NR	2E-24
rs11672691	19	41479679	NR	2E-12

RS number	Chromosome	Position	Reported effect	Reported *p*-value
rs12682851	9	8012418	NR	0.000002
rs4463179	5	13505322	NR	0.000002
rs731174	1	37731169	NR	0.000005
rs5751168	22	22490916	NR	0.000004
rs1866967	1	29712815	NR	0.000005
rs12317459	12	82770777	NR	0.000004
rs4821941	22	40279087	NR	0.000004
rs13258681	8	123702482	NR	0.000004
rs11605083	11	15333700	NR	0.000004
rs10940579	5	57834991	NR	0.000004
rs16867225	2	180176559	NR	0.000003
rs7629490	3	87192347	NR	0.0000001
rs10498792	6	51801833	NR	0.000003
rs7501939	17	37741165	NR	3E-18
rs3123078	10	46070851	NR	1E-19
rs8057939	16	49360365	NR	0.000005
rs12485321	3	108303	NR	0.000003
rs7694725	4	113079800	NR	0.000002
rs345013	3	145456001	NR	0.000005
rs6465657	7	98187015	NR	0.00000002
rs7837688	8	127527115	NR	1E-25
rs1327301	23	51467205	NR	2E-10
rs7717572	5	67537429	NR	0.000003
rs4775302	15	46347610	NR	0.00000004
rs10277209	7	109363517	NR	0.000004
rs742134	22	43122269	NR	0.000006
rs7931342	11	69227030	NR	0.000001
rs1456315	8	127091692	NR	1E-12
rs1859962	17	71112612	NR	2E-16
rs10795917	10	12009817	NR	0.0000007
rs4466137	5	83689920	NR	0.000003
rs11704416	22	40040969	NR	0.0000004
rs9311171	3	37954986	NR	0.000002
rs10503733	8	23676505	NR	0.00000008
rs1978503	18	55997051	NR	0.000001
rs16944141	13	90213292	NR	0.000003
rs2219968	8	78044423	NR	0.0000006
rs11720607	3	173125487	NR	0.000005
rs1002979	3	112779033	NR	0.000003
rs9351730	6	68584593	NR	0.000005
rs735172	4	5757142	NR	0.000002
rs10263639	7	67594280	NR	0.000003
rs7127900	11	2212344	NR	0.0000001
rs7130881	11	69228491	NR	8E-13
rs2400997	14	101260770	NR	0.000003
rs13252298	8	127082911	NR	0.000004
rs1916284	3	57409039	NR	0.000001
rs9757252	3	86845328	NR	0.000005
rs784411	15	48747600	NR	0.0000001
rs10490113	2	59272212	NR	0.000005
rs543686	15	34776108	NR	0.000004
rs1243647	14	20556460	NR	0.000001
rs11637980	15	96459423	NR	0.000002
rs2057681	7	95308945	NR	7E-15
rs6763848	3	1470903	NR	0.000004
rs10885582	10	114567791	NR	0.000004
rs2108622	19	15879621	NR	9E-24
rs6507016	18	33347811	NR	0.000004
rs2075555	17	50196930	NR	0.00000008
rs290258	9	90793457	NR	0.000001
rs9284813	3	87103019	NR	0.000000005
rs17023900	3	87085650	NR	0.00000006
rs2711721	12	46978487	NR	0.000002
rs9649213	7	98391899	NR	0.000001
rs7847271	9	115068533	NR	0.000004
rs10505483	8	127112950	NR	7E-15
rs6556756	5	164462274	NR	0.0000005
rs651164	6	160160342	NR	0.000000002
rs6545977	2	63074029	NR	0.0000005
rs13192613	6	122961796	NR	0.000003
rs13264970	8	82161594	NR	0.000004

Using results from the ProMark project published in the paper: "Replication study of 34 common SNPs associated with prostate cancer in the Romanian population" [32], we compared results to our generated database.

Out of 34 SNPs examined by the previously mentioned study, 28 SNPs were found (rs5945572, rs12621278, rs1465618, rs721048, rs2660753, rs10934853, rs7679673, rs17021918, rs12500426, rs9364554, rs6465657, rs10486567, rs445114, rs1447295, rs6983267, rs16902094, rs16901979, rs1512268, rs4962416, rs10993994, rs11228565, rs7127900, rs1859962, rs4430796, rs2735839, rs8102476, rs5759167, rs9623117) in our study results.

Rs5945572 located on Xp11.22 was found in our collected database as the results of the paper "Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer" with the risk allele frequency of 0.35 and a *p*-value of 4×10^{-13} in an initial cohort of 1854 European ancestry cases, 21 372 European ancestry controls and was replicated in a second cohort of 8239 European ancestry cases, 7590 European ancestry controls [6]. In the same results, we also found rs721048 located on 2p15 with the risk allele frequency of 0.19 and a *p*-value of 8×10^{-9}.

Rs12621278 located on 2q31.1 was found in the results of the paper "Identification of seven new prostate cancer susceptibility loci through a genome-wide association study" with the risk allele frequency of 0.94 and a *p*-value of 9×10^{-23} in an initial cohort of 1854 European ancestry cases, 1894 European ancestry controls and was replicated in a second cohort of 19 879 cases and 18 761 controls of European, East Asian, African-American, Latino, and Hawaiian ancestry [22].

Rs1465618 located on 2p21 was found in the same paper as rs12621278 with the risk allele frequency of 0.23 and a *p*-value of 2×10^{-8} in the same initial cohort and replicated in the same second cohort.

Rs2660753 located on 3p12.1 was found in our study as a result reported in the paper "Multiple newly identified loci associated with prostate cancer susceptibility" [5] with the risk allele frequency of 0.11 and a *p*-value of 3×10^{-8} in an initial cohort of 1854 European ancestry cases, 1894 European ancestry controls and replicated in a second cohort of 3268 European ancestry cases, 3366 European ancestry controls.

Rs10934853 located on 3q21.3 was identified as a result from the paper "Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility" with the risk allele frequency of 0.28 and a *p*-value of 3×10^{-8} in a initial cohort of 1968 European ancestry cases, 35 382 European ancestry controls and was replicated in a second cohort of 11 806 European ancestry cases, 12 387 European ancestry controls [21].

A series of three markers: rs7679673, rs17021918 and rs12500426, all three located on 4q22, were confirmed in the results of the same paper as rs12621278 with the frequencies of 0.55, 0.65 and 0.46, and the *p*-values of

3×10^{-14}, 4×10^{-5} and 1×10^{-11} in the same European ancestry cohort [22].

Rs9364554 located on 6q25.3 and rs6465657 located on 7q21.3 were confirmed as results in the paper "Multiple newly identified loci associated with prostate cancer susceptibility" with the risk allele frequencies of 0.29 and 0.46 and *p*-values of 6×10^{-10} and 1×10^{-9} in a initial cohort of 1854 European ancestry cases, 1894 European ancestry controls and replicated in a second cohort of 8239 European ancestry cases, 7590 European ancestry controls [5].

Rs10486567 located on 7p15.2 was replicated in the paper "Multiple loci identified in a genome-wide association study of prostate cancer" with the risk allele frequency of 0.77 and a *p*-value 2×10^{-6} in a initial cohort of 1172 European ancestry cases, 1157 European ancestry controls and a replicated in a second cohort of 3941 European ancestry cases, 3964 European ancestry controls [9].

Rs445114, rs1447295 and rs16902094 located on 8q24.21 were confirmed in the paper "Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility" with the risk allele frequency of 0.64, 0.11 and 0.15 and a *p*-values 5×10^{-10}, 2×10^{-19} and 6×10^{-10} in a initial cohort of 1968 European ancestry cases, 35 382 European ancestry controls and replicated in a second cohort of 11 806 European ancestry cases, 12 387 European ancestry controls [21].

Rs16901979 located on 8q24.21 was identified as a result in the paper "Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24" with the risk allele frequency of 0.03 and a *p*-value of 1×10^{-12} in a initial cohort of 1453 European ancestry cases, 3064 European ancestry controls and replicated in a second cohort of 1210 European ancestry cases, 2445 European ancestry controls, 373 African-American cases, 372 African American [15].

Rs1512268 located on 8p21.2 was confirmed in the same paper as rs12621278 with the risk allele frequency of 0.45 and a *p*-value of 3×10^{-14} [22].

Rs4962416 located on 10q26.13 was confirmed in the paper "Multiple loci identified in a genome-wide association study of prostate cancer" with the risk allele frequency of 0.27 and a *p*-value of 2×10^{-7} in a initial cohort of 1172 European ancestry cases, 1157 European ancestry controls and replicated in a second cohort of 3941 European ancestry cases, 3964 European ancestry controls [9].

Another SNP confirmed as a result in the paper "Multiple newly identified loci associated with prostate cancer susceptibility" [5] is rs10993994 located on 10q11.22 with the risk allele frequency of 0.40 and a *p*-value of 9×10^{-23}.

Rs11228565 located on 11q13.3 was found in the same paper as rs445114, rs1447295 and rs16902094 with the risk allele frequency of 0.20 and a *p*-value of 7×10^{-12} [5].

Rs7127900 located on 11p15.5 was also confirmed in the paper "Identification of seven new prostate cancer susceptibility loci through a genome-wide association study" with the risk allele frequency of 0.20 and a *p*-value of 3×10^{-33} in the same cohort [22].

Rs1859962 located on 17q24.3 was confirmed in the same paper same as rs6983267 and rs10993994 with the risk allele frequency of 0.46 and a *p*-value of 1×10^{-6} [5].

Rs4430796 located on 17q12 was replicated in the paper "Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes" with the risk allele frequency of 0.49 and a *p*-value of 1×10^{-11} in a original cohort of 1501 European ancestry cases, 11 290 European ancestry controls and replicated in a second cohort of 1992 European ancestry cases, 3058 European ancestry controls [14].

Rs2735839 located in 19q13.33 was the last marker confirmed in the results of the paper "Multiple newly identified loci associated with prostate cancer susceptibility" with the risk allele frequency of 0.85 and a *p*-value of 2×10^{-8} [5].

The last marker replicated in our study from the paper "Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility" was rs8102476 located on 19q13.2 with the risk allele frequency of 0.54 and a *p*-value of 2×10^{-11} [21].

The last SNP found in the paper "Identification of seven new prostate cancer susceptibility loci through a genome-wide association study" is rs5759167 located on 22q13.2 with the risk allele frequency of 0.53 and a *p*-value of 6×10^{-14} [22].

Rs9623117 located on 22q13.1 was replicated in the paper "Sequence variants at 22q13 are associated with prostate cancer risk" with the risk allele frequency of 0.21 and a *p*-value 5×10^{-7} in a original cohort of 1235 European ancestry aggressive cases, 1599 European ancestry controls and was replicated in a second cohort of up to 11 806 European ancestry cases, 12 387 European ancestry controls [20].

More than 80% of the single nucleotide polymorphisms already confirmed by the previous mentioned Romanian study as being associated with prostate cancer are also present in our data set.

With this strong result validating our study, we believe future studies can use our results for validation of different replicating markers.

Discussion

Since the first GWAS on prostate cancer predisposition in 2006 [33], a great number of studies envisaged the genetic variants correlated with a higher risk for developing the disorder.

Prostate cancer is the most frequently diagnosed cancer, and the second leading cause of death from cancer among men [34]. The disease is more frequent in older men and is associated with a higher incidence in certain racial/ethnic backgrounds [35–38]; therefore, it is vital to detect the disease at an earlier stage [39–43]. Taking into account the racial background of a specific population plays a major factor for replication studies and identifying novel markers. Defining a complete collection of genetic markers associated with prostate cancer can be of great use for future genome-wide association studies in Romania.

Current statistical estimations state that inherited susceptibility stands for 40% of all prostate cancer cases worldwide, most of them correlated with low penetrance genetic variants [44]. Studies have shown that not just a single low penetrance allele triggers the prostate cancer,

but certain associations of a number of these polymerphisms seem to strongly increase the risk for developing the disorder [45, 46].

Knowledge of a large number of genetic variants correlated with prostate cancer susceptibility and understanding the biological pathways and interactions, which take place at a molecular level between them, would provide important information for possibly preventing the setting off of the disease. At the same time, mapping the genetic prostate cancer predisposition provides great progress in developing new-targeted individualized therapies and management strategies.

Identifying a list of clinically relevant genetic markers for predisposition to prostate cancer can also lead to develop of guidelines for genetic testing in order to achieve an effective prevention [47].

The need for a review of previously published single nucleotide polymorphisms (SNPs) associated with prostate cancer that show a strong association with the same phenotype in the Romanian population is needed as a starting point for further research.

Our study illustrates the value of combining multiple GWAS results into a larger database that can be easily accessed, updated and modified to reflect the known markers associated with prostate cancer.

Conclusions

Hence, prostate cancer is one of the main causes of death in the male population worldwide, it is very important for clinicians to have the possibility of identifying men with higher risk for the disease for targeted screening methods. Since most of these SNPs do not act individually, the use of risk profiling models could provide important information on the severity, stage of development and spread of the cancer and at the same time for detecting the disease at an earlier stage. For assembling risk profile models for the Romanian population, supporting the actual validity of GWAS results is needed. Our study provides a starting point for confirming markers identified in future genome-wide association studies for prostate cancer.

Conflict of interests

The authors confirm that there is no conflict of interests.

Author contribution

All the authors had equal contributions to the article.

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