Major candidate genes associated with risk of hereditary and sporadic prostate cancer

Abstract

Prostate cancer risk factors gain more awareness in the world nowadays, due to the increasing incidents, which vary among different ethnic groups. Researches about genetic risk factors might help for more understanding of the initiation and development of prostate cancer and estimating risk values among individuals, and develop multi-perspective therapy approaches. Many efforts were achieved to study and evaluate high-risk variants associated with prostate tumors; through different populations. This evaluation depended on the high frequencies of these variants and the role of such variants in cell cycle and DNA repairing system. In this review, we highlighted the major candidate genes and molecular events of prostate cancer: BRCA, CHEK2, HOXB13, ELAC2, SPOP, PTEN, TMPRSS2-ERG Fusion and other less effective variants, in an attempt to explore the molecular seriousness and relative risk of suspected variants associated with hereditary and sporadic prostate cancer. The definition of particular groups of genes that lead prostate cancer prognosis is a difficult task, since the genetic and proteomic studies detected numerous susceptibility alleles complicated with risk of prostate tumors. The estimation of high-risk variants may be a key issue regarding prostate cancer diagnosis and therapy.

Keywords: Prostate cancer; tumor suppressors; BRCA; TMPRSS2-ERG fusion; SPOP; Elac2; risk factor, apoptosis

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Introduction:

Prostate cancer (PCa) is the most common cancer diagnosed among men in most western countries; about 75% of patients are diagnosed after 65 years. The incidence of prostate cancer varies between countries and between different ethnic groups, the highest incidence rates have been observed in North America especially among African-Americans, and in the Scandinavia region, whereas the lowest rates have been observed in India, China, and Japan. However, there is a general increase in incidences in most countries [1; 2]. Recently, identifying genetic risk factors for prostate cancer is an active area of medical research, as inherited variations in dozens of genes have been considered as possible risk factors for prostate cancer work as tumor suppressors through different cellular pathways. Alterations in these genes probably contribute to overall prostate cancer risk. But many cases of prostate cancer are not related to inherited gene changes, these cancers are associated with somatic mutations that occur only in certain cells in the infected organ. Tumor suppressor genes negatively regulate normal cell growth; they are involved in the inhibition of cell proliferation, regulation of the cell cycle and apoptosis, cell adhesion and transcriptional regulation and repair DNA damages [3; 4]. This review aimed to describe the major candidate genes of prostate cancer intensively investigated in few last decades, with a short focus on the original function of the gene, the pathway as tumor suppressor gene, and the risk susceptibility in different ethnic groups.

BRCA1 and BRCA2

The potential association between BRCA1 and BRCA2 mutations and the progression of prostate cancer after diagnosis have been discussed for decades. BRCA mutations might be associated with aggressive prostate disease since the relative risk of developing prostate cancer in BRCA1 and BRCA2 mutation carriers reach 1.8 times and 7–23 times, respectively [5]. The families with deleterious mutations in BRCA1 and BRCA2 had an increased number of prostate cancer infections compared with families without known inherited predisposition. The risk of developing prostate cancer is increased if BRCA1 or BRCA2 mutations are present [6]. Furthermore, males BRCA2

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mutation carriers who develop prostate cancer (PCa) may have a shorter disease-specific life expectancy than men with PCa in the general population [7]. Furthermore, BRCA2 mutation carriers have a five to seven-fold increase in risk [8]. Whilst a family history of early-onset breast cancer/ovarian cancer is a strong predictor of BRCA2 mutation positivity; the ascertainment by the early onset of PCa is the greatest predictor of BRCA2 mutation positivity concerning PCa susceptibility. The BRCA1 gene or breast cancer gene 1 is a tumor suppressor gene, which expressed in the cells, where it can repair damaged DNA as a protein complex, or destroys cells if DNA cannot be repaired in certain mechanisms. BRCA1 along with other tumor suppressors, sensors and signal transducers form protein complex called BRCA1-associated genome surveillance complex (BASC); Involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double-strand breaks [9].

The human BRCA1 gene is located on chromosome 17 and contains 27 exons distributed over about 70 kb of genomic DNA and gives rise to a transcript of 10.4 kb, coding for a protein of 3418 amino acids. The four major BRCA1 protein domains; the Znf C3HC4- RING domain, the BRCA1 serine domain, and two BRCT domains, encode approximately 27% of BRCA1 protein [10]. BRCA1 is part of a protein complex that repairs DNA errors during cell cycle. Double strand breaks occur after the cross-links are removed. The double-strand repair mechanism in which BRCA1 participates in homologous recombination, which depends on utilizing a template of the identical homologous intact sequence from a sister chromatid, forming a homologous chromosome, or forming the same chromosome. DNA repair takes place with the DNA in the cell nucleus, wrapped around the histone, several proteins, including BRCA1, arrive at the histone-DNA complex for this repair [11]. Of course, the defective BRCA1 protein is unable to help to fix DNA damage leading to mutations in other genes. Such mutations can accumulate and may allow cells to divide abnormally to initiate a tumor. Thus, BRCA1 inactivating mutations lead to a predisposition for cancer. In addition to prostate cancer; mutations in the BRCA1 gene also increase the risk of ovarian, precancerous lesions (dysplasia), leukemias and lymphomas [12].

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As same as BRCA1, BRCA2 cancer type 2 susceptibility proteins are responsible for repairing DNA [13]. Genetic characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair. Thirty-nine amino acid repeats of BRCA2 binding to RAD51 (a key protein in DNA recombinational repair) and resistance to methyl methanesulphonate treatment. The BRCA2 consists of a four-helix cluster core (alpha 1, alpha 8, alpha 9, alpha 10) and two successive beta-hairpins: beta 1 to beta 4 [14]. BRCA2 participates in repairing the DNA process by binding the single-strand DNA and directly interacts with the recombinase RAD51 to stimulate strand invasion, a vital step of homologous recombination [11]. Researchers have identified hundreds of mutations in the BRCA2 gene, many of which cause an increased risk of cancer. BRCA2 mutations are usually insertions or deletions of a small number of DNA base pairs in the gene [12; 15]. In addition to prostate cancer, mutations in BRCA2 also lead to an increased risk of ovarian, fallopian tube, pancreatic cancers, malignant melanoma, and ovarian cancer, as well as breast cancer in men and women. There is a piece of evidence for loss of heterozygosity of the BRCA2 region in prostate cancer, particularly those at an advanced stage. The relative risk of developing prostate cancer by age 56 years from a deleterious germline BRCA2 mutation was 23-fold, in some studies. This confirms that BRCA2 is a high-risk prostate cancer susceptibility gene [6]. It's not reported that whether mutations in BRCA1 are related to BRCA2 in the same cells or one patient case, this hypothesis should be examined due to the confident relation of their proteins participating in the DNA repairing mechanism.

CHEK2

Human gene Checkpoint kinase 2 (CHEK2) is a tumor suppressor gene that encodes the protein CHK2, a serine-threonine kinase. CHK2 operates in an intricate network of proteins to elicit DNA repair, cell cycle arrest or apoptosis in response to DNA damage [16]. Three deletion variants in the kinase domain in exon 10 and a missense mutation in the FHA domain in exon 3 were linked to inherited susceptibility of the lung, colon, kidney, thyroid cancers, certain brain

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tumors, osteosarcoma as well as prostate. Certainly variants: CHEK2 1100delC mutation, and I157T missense mutation through many demographic or ethnic backgrounds [17, 18]. Those two mutations have been mentioned widely, to my knowledge regarding hereditary prostate cancer; no reports about other important CHEK2 variants. The exact mechanism of CHEK2 participation in the DNA damage repairing system is unknown. Nevertheless, several mechanisms have been suggested the role of TTK/hMps1, STRAP, p21, and p53 genes in such mechanism [19].

ELAC2

The elaC ribonuclease Z 2 (ELAC2) gene encodes a protein that is 92 kDa in size and is localized to the mitochondrion [20]. ELAC2 involves in hereditary and sporadic prostate cancer. Multiple mutations including truncation and missense mutations are known to cause prostate cancer [21]. Two ELAC2 missense variants (Ser217Leu and Ala541Thr) were reported as risk variants of developing prostate cancer with different risk profiles, were also observed when cases were stratified by disease aggressiveness. And neither variant was associated with more aggressive prostate cancer phenotypes. Such reports estimated the Ser217Leu genotype may account for approximately 14% of less aggressive prostate cancer cases, and 9% of all sporadic cases in the general United States population of white men <age 65 years [22]. Another finding of a nonsense mutation in the ELAC2 gene confirms its potential role in genetic susceptibility to prostate cancer [23]. However, other results cannot rule out the possibility of a highly penetrate prostate cancer gene at (Ser217Leu and Ala541Thr) locus [24]. There are shortages observed regarding ELAC2 mechanism researches instead of hereditary prostate cancer development or other subtypes of prostate tumors.

HOXB13

Homeobox transcription factor gene HOXB13, a checkpoint kinase Gene and other genes, form a gene cluster on chromosome 17 in the 17q21-22 region forming homeobox proteins family [25]. Germline mutation G84E of HOXB13 was reported in hereditary prostate cancer. This mutation associated with an

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elevated risk of prostate cancer in men of European descent and European-American men [26]. One percent of the population carrying the variant (rs138213197: G84E of HOXB13). But at the same time, it's associated with a 3 to 5 fold increased risk of prostate cancer. In a statistical conclusion: one-third of G84E carriers will be diagnosed with prostate cancer. This risk is even higher among cases with an early age (≤55 years) or a family history of the disease [27]. However, the role of this variant plays in PCa development still uncertain. But it's thought that The G84E variant likely modulates the interaction between the HOXB13 protein and the androgen receptor and affecting FOXA1. Furthermore, the expression of HOX genes likely up or down-regulated in human tumors including colon, lung, and prostate cancer [25; 28]. In the case of HOXB13 G84E alterations; it is beneficial to explore other variants that might affect the structure and function of the transcription factor that belongs to the homeobox gene family, in parallel with a deep understanding of HOXB genes mechanism in prostate tissues. And a very important matter to understand is the HOXB13 role in vertebrate embryonic development.

SPOP

Speckle type BTB/POZ protein SPOP gene (17q21.33), encodes a protein that modulates the transcriptional repression functions of death-associated protein 6 (DAXX). The SPOP gene contains three domains: an N-terminal MATH domain that recruits substrates, an internal BTB domain, and a C-terminal nuclear localization sequence [29]. Several mutations in SPOP lead to a type of hereditary prostate tumor which involved 10-14.4% of all prostate tumors in various populations, there is no correlation between SPOP mutations with ethnicity, clinical, or pathologic parameters. The expression and mutational status of SPOP, defining a new biotype of prostate cancer associated with a worse prognosis according to accumulated shreds of evidence [30]. Recently the substitutions missense variants Y87N, F133V, G111E, and F102C, suggested as pathogenic. Other findings consider other variants as pathogenic instead of prostate cancer, namely: S14L, N296I, and P133L [31]. When we reviewed the SPOP mutation databases including SNPs, nonsense and missense variants; there are a series of variants that have been recorded to be

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risky through valued epidemiological and clinical researches, this database could form a driving base to explore the real structural and functional effects on the related protein [32].

PTEN

Phosphatase and tensin homolog (PTEN), a tumor suppressor located at chromosome 10, the protein encoded by this gene is a phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphatase. PTEN is a phosphatase that dephosphorylates phosphatidylinositol (3, 4, 5) triphosphate (PtdIns-3, 4, 5-P3), an important intracellular second messenger, lowering its level within the cell. PtdIns-3, 4, 5-P3 is necessary for the activation of Akt, a serine/threonine kinase involved in cell growth and survival. PTEN act to block the Akt, this permits cell cycle goes correctly, same as other crtical translations and apoptosis. [33]. Mutations of this gene are a step in the development of many cancers, as this gene was identified mutated in a large number of cancers at high frequencies. Indeed, up to 70% of men with prostate cancer are estimated to have lost a copy of the PTEN gene at the time of diagnosis. Furthermore, loss of PTEN function is a common event in glioblastoma, melanoma, endometrial carcinoma, prostate adenocarcinoma, renal cell carcinoma, and head and neck squamous carcinoma. Due to the vital role of PTEN in the regulation of metabolic pathways and cell motility, many studies tried to reveal the PTEN variants involved loss its function related to tumor progressions [84; 85].

TMPRSS2-ERG gene fusion

Transmembrane protease serine 2 (TMPRSS2) related confidentially with androgenic hormones. Fusions of the TMPRSS2 prostate-specific gene with the ERG transcription factor; consider an oncogenic event, which commonly found in prostate tumors. The ERG over-expression induced by TMPRSS2-ERG gene fusion contributes to the development of prostate cancer, which can be easily detected in urine [34]. A fusion between the prostate-specific androgen-regulated TMPRSS2 gene and the ETS genes ERG, ETV1, or ETV4; has been described in clinical prostate tumors, and occurs at a high frequency: approximately 50% of prostate cancers. In a study by Magi-Galluzzi, et al, 2011,

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TMPRSS2-ERG gene fusion translocation, deletion, or both, it was present in 50% (21/42) of Caucasians, 31.3% (20/64) of African-Americans, and 15.9% (7/44) of Japanese [35, 36]. Other studies distinguish between TMPRSS2/ERG and TMPRS22/ETV1 fusion genes with different subtypes that exist in the tissues of prostate cancer. TMPRSS2/ERG and TMPRSS2/ETV1 fusion genes may be used successfully as diagnostic tools for prostate cancer [37]. The specific complication of chromosomal rearrangement related to TMPRSS2/ERG needs more enlightenment, as well as how this fusion interferes with prostate tumors initiation.

The relative risk of prostate cancer of eight candidate genes: BRCA1, BRCA2, CHEK2, HOXB13, ELAC2, SPOP, PTEN, and TMPRSS2-ERG FUSION, versus maximum mutations rate, is given in figure 1 based on the risk criteria genes reviewed in this study.

2.9 More other candidate genes associated with hereditary prostate cancer

SPINK1 serine peptidase inhibitor, Kazal type 1 (5q32), the protein encoded by this gene is a trypsin inhibitor, this pancreatic origin protein, which found in pancreatic juice secreted from acinar cells. The known function is inhibiting trypsin-catalyzed premature activation of zymogens in the pancreas. At the same time, SPINK1 is responsible for a small protein (56 amino acids) secreted in the prostate gland whose function is to inhibit serine proteases. Some reports suggested a role of SPINK1 in ETS rearrangement may represent a link to the risk of prostate cancer progression, but not an aggressive disease [32]. p300 transcriptional co-activator protein alterations correlate individually with aggressive features in prostate cancer by inducing quantifiable nuclear alterations [38]. Other data suggested that the genetic variation in gene encodes a member of the Eph receptor family of receptor tyrosine kinase transmembrane glycoproteins; might increase the risk of sporadic PCa among African-Americans [39]. And downregulation of EZH2 (enhancer of zeste homolog 2), might affect prostate tumor cell growth [40]. Mutational analyses of

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macrophage scavenger receptor 1 MSR1, revealed P275A, INDEL7, P346P, 3'UTR 70006, P346P G allele (AG 1 GG), R293X and D174Y of MSR1 variants; are associated with an increased risk of sporadic prostate cancer, particularly in African-Americans, China, Asia and other populations worldwide [41, 42]. The signal transducer and activator of transcription 3 (STAT3) significantly impaired the ability of prostate cancer cells to initiate the development of the prostate tumors [43]. Besides, Glycine N-methyltransferase GNMT, considered as a tumor susceptibility gene for prostate cancer, especially the rs10948059 variant. In addition to STRP1 variants are associated with prostate cancer risk in men of European descent [44; 45]. Ribonuclease L (RNASEL) mutations, and some variants like Arg462Gln and Asp541Glu; are associated with the risk of presenting prostate cancer have been reported elsewhere [46]. Two independent variants in HNF1 homeobox B (HNF1B), considered also as susceptibility loci for prostate cancer risk [47]. Since genetic variation within the Ldl receptor-related protein 2 megalin gene may serve as a means for the malignant cell to increase androgen uptake; it's found to be associated with prostate cancer [48]. Genetic variant Leu1074Phe in the DNA repair gene Werner syndrome RecQ like helicase (WRN) in Chinese subjects [49], and germline 3381del allele of ATBF1 (16q22) coding for cell cycle active protein were linked to risk of prostate tumors [50]. Choi et al. study revealed a relation between steroid 5 alpha-reductase 2 SRD5A2 SNPs and prostate cancer in the Korean population [51], in contrast, another study from Turkey, concluded that there was no evidence of an association between SRD5A2 polymorphism and PCa risk in the Turkish population [52]. In addition, other data suggested that transforming growth factor-beta receptor 1 TGFBR1*6A, does not contribute to the development of prostate cancer [53], as well as Suarez et al., who revealed that there is no compelling evidence for an association of the variant in exon 1 of the TGFBR1 gene *6A variant with prostate cancer [54]. The overexpression of mediator complex subunit 12 (MED12), found to be a frequent event in castration-resistant prostate cancer (CRPC), in comparison with androgen-sensitive PCa and is directly implicated in TGFb signaling [55]. While Nibrin (NBN) gene overexpression associated with prostate cancer risk, maybe PCa predictive biomarker [56]. A suspected relation of prostate cancer initiation and development with each of: KAL1/CD82, Kruppel like factor 6 (KLF6) splice

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variants expression, overexpression of insulin-like growth factor 2 (IGF2), Plexin B1, interactor 1 dimerization protein MXI1, micro semino protein beta (MSMB), mitotic arrest deficient like 1 (MAD1L1) mutations; were discussed elsewhere [57-63]. A summary of genes variants detected, frequency of alleles, population studied, and association with PCa collected from various sources in the literature; are given in Table (1).

3. Conclusion:

Men with particular variations in particular genes have a risk of developing prostate cancer. But a wide difference of variant frequencies was obtained among many populations. Consequently, these differences lead to differences in relative risk associated with hereditary prostate cancer or the importance of such variants as a biomarker for the early development of prostate cancer. There are hundreds of mutations in BRCA1 gene have been estimated, to be associated with an increased risk of prostate cancer, this gene is widely studied among different populations, with hundreds of variants, major of them are deleterious, and many mutations estimated in BRCA2 gene related to prostate cancer risk. The majority of results confirmed that BRCA1, BRCA2, PTEN are a high risk prostate cancer susceptibility genes. Genetic variations of CHEK2 are associated with inherited susceptibility to prostate cancers, as well as missense variants (Ser217Leu and Ala541Thr) in the ELAC2 gene. The HOXB13 G84E missense mutation represents a unique variant increases the risk of prostate cancer in European-American men. Whilst the SPOP is mutated in patients with prostate cancer across different ethnic and demographic backgrounds. TMPRSS2-ERG gene fusion has been suggested as a biomarker for prostate cancer, but there are confusing conclusions about use SPINK1 as biomarkers for prognostication of early-stage prostate cancer. Other variants have been detected as genetic risk factors of prostate cancer by different degrees of risk.

The molecular biology of prostate cancer is very complex, this complexity originates from multi genetic factors interfere with prostate tumorigenesis, or may due to the complexity of prostate gland function originally, and slow, long

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time initiation of prostate tumors. For decades, hundreds of variants were screened and evaluated to determine the risk degree of such variants on prostate cancer. Along with studies progression, researches range increased significantly. Today; we have big knowledge about genes functions that affect prostate cancer tumors, but some areas still not demonstrated clearly. Such as detailed mechanisms, genes interactions involved in the tumorigenesis process. Furthermore, there is some mistiness about what genes leads strongly this vital process, and the value of other genes as prospective therapy targets, or diagnosis biomarkers. Besides, more studies are needed to estimate more major high-risk candidate genes of hereditary and sporadic prostate cancer or establish special local databases related to these genetic variations among different regions and populations. The purpose of this review was not to discuss the detailed mechanisms but to highlights the generally accepted about the role of major candidate genes instead of prostate cancer. For the reason that the mutations mentioned in this review, have been estimated in wide range of human tumors and through many ethnic and demographic sites, it's the time to go forward to explore the certain mechanisms and the other genes complicated with, in order to pave the way for serious steps toward drug designs, or other specialized gene therapy processes.

Legends:

Table (1): Summary of genes variants detected, frequency of alleles, population studied, and association with PCa. (D: Different Ethnic Group, *Not estimated, 1 Associated, 2 Not Associated, A.A: African American, A.E: American European, PCa: Prostate Cancer).

Figure 1: Relative risk of prostate cancer of eight candidate genes: BRCA, CHEK2, HOXB13, ELAC2, SPOP, PTEN, and TMPRSS2-ERG fusion, versus maximum mutations rate according to the researches listed in this review.

Conflict of interest: None.

Ethical Approval:

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As per international standard, ethical approval has been collected and preserved by the author(s).

References:

1. Beiki O, Ekbom A, Allebeck P, Moradi T. Risk of prostate cancer among Swedish- born and foreign- born men in Sweden, 1961–2004. International journal of cancer. 2009 Apr 15;124(8):1941-53.
2. Sundararajan, Srinath, Aisha Ahmed, and Oscar B. Goodman Jr. "The relevance of BRCA genetics to prostate cancer pathogenesis and treatment." Clin Adv Hematol Oncol. 2011; 9(10) 748-55.
3. Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes & development. 2010 Sep 15;24(18):1967-2000.
4. Edwards SM, Kote- Jarai Z, Hamoudi R, Eeles RA. An improved high throughput heteroduplex mutation detection system for screening BRCA2 mutations—fluorescent mutation detection (F- MD). Human mutation. 2001 Mar;17(3):220-32.
5. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, Jonasson JG, Ólafsdóttir EJ, Ólafsdóttir GH, Rafnar T, Thorlacius S, Jonsson E, Eyfjord JE, Tulinius H. Prostate cancer progression and survival in BRCA2 mutation carriers. Journal of the National Cancer Institute. 2007 Jun 20;99(12):929-35.
6. Kirchhoff T, Kauff ND, Mitra N, Nafa K, Huang H, Palmer C, Gulati T, Wadsworth E, Donat S, Robson ME, Ellis NA. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clinical Cancer Research. 2004 May 1;10(9):2918-21.
7. Mitra A, Fisher C, Foster CS, Jameson C, Barbachanno Y, Bartlett J, Bancroft E, Doherty R, Kote-Jarai Z, Peock S, Easton D. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. British journal of cancer. 2008 Jan;98(2):502.
8. Darves-Bornoz, A., Park, J., Katz, A., Philippou, Y., Dev, H., Sooriakumaran, P., Oxley, J., Cheetham, P.J., Richenberg, J., Smith, N.J. and Cross, W.R., Prostate Cancer Epidemiology. Prostate Cancer: Diagnosis and clinical management. 2014; 1-15.
9. Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes & development. 2000 Apr 15;14(8):927-39.
10. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994 Oct 7:66-71.
11. Boulton SJ. Cellular functions of the BRCA tumour-suppressor proteins. Biochemical Society Transactions. 2006 Oct 1;34(5):633-45.
12. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC cancer. 2007 Dec;7(1):152.
13. Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, Easton DF. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. British journal of cancer. 2002 Jan;86(1):76.
14. Chen PL, Chen CF, Chen Y, Xiao J, Sharp ZD, Lee WH. The BRC repeats in BRCA2 are critical for RAD51 binding and resistance to methyl methanesulfonate treatment. Proceedings of the National Academy of Sciences. 1998 Apr 28;95(9):5287-92.
15. Shaughnessy J, Tian E, Sawyer J, Bumm K, Landes R, Badros A, Morris C, Tricot G, Epstein J, Barlogie B. High incidence of chromosome 13 deletion in multiple myeloma detected by multiprobe interphase FISH. Blood. 2000 Aug 15;96(4):1505-11.

16. Matsuoka S, Huang M, Elledge SJ. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. Science. 1998 Dec 4;282(5395):1893-7.
17. Cybulski C, Huzarski T, Górski B, Masojć B, Mierzejewski M, Dębniak T, Gliniewicz B, Matyjasik J, Złowocka E, Kurzawski G, Sikorski A. A novel founder CHEK2 mutation is associated with increased prostate cancer risk. Cancer research. 2004 Apr 15;64(8):2677-9.
18. Dong X, Wang L, Taniguchi K, Wang X, Cunningham JM, McDonnell SK, Qian C, Marks AF, Slager SL, Peterson BJ, Smith DI. Mutations in CHEK2 associated with prostate cancer risk. The American Journal of Human Genetics. 2003 Feb 1;72(2):270-80.
19. Zannini L, Delia D, Buscemi G. CHK2 kinase in the DNA damage response and beyond. Journal of molecular cell biology. 2014 Nov 17;6(6):442-57.
20. Brzezniak LK, Bijata M, Szczesny RJ, Stepien PP. Involvement of human ELAC2 gene product in 3'end processing of mitochondrial tRNAs. RNA biology. 2011 Jul 1;8(4):616-26.
21. Rökman A, Ikonen T, Mononen N, Autio V, Matikainen MP, Koivisto PA, Tammela TL, Kallioniemi OP, Schleutker J. ELAC2/HPC2 involvement in hereditary and sporadic prostate cancer. Cancer research. 2001 Aug 15;61(16):6038-41.
22. Stanford JL, Sabacan LP, Noonan EA, Iwasaki L, Shu J, Feng Z, Ostrander EA. Association of HPC2/ELAC2 polymorphisms with risk of prostate cancer in a population-based study. Cancer Epidemiology and Prevention Biomarkers. 2003 Sep 1;12(9):876-81.
23. Wang L, McDonnell SK, Elkins DA, Slager SL, Christensen E, Marks AF, Cunningham JM, Peterson BJ, Jacobsen SJ, Cerhan JR, Blute ML. Role of HPC2/ELAC2 in hereditary prostate cancer. Cancer research. 2001 Sep 1;61(17):6494-9.
24. Xu J, Zheng SL, Carpten JD, Nupponen NN, Robbins CM, Mestre J, Moses TY, Faith DA, Kelly BD, Isaacs SD, Wiley KE. Evaluation of linkage and association of HPC2/ELAC2 in patients with familial or sporadic prostate cancer. The American Journal of Human Genetics. 2001 Apr 1;68(4):901-11.
25. Decker B, Ostrander EA. Dysregulation of the homeobox transcription factor gene HOXB13: role in prostate cancer. Pharmacogenomics and personalized medicine. 2014;7:193.
26. Breyer JP, Avritt TG, McReynolds KM, Dupont WD, Smith JR. Confirmation of the HOXB13 G84E germline mutation in familial prostate cancer. Cancer Epidemiology and Prevention Biomarkers. 2012 Aug 1;21(8):1348-53.
27. Karlsson R, Aly M, Clements M, Zheng L, Adolfsson J, Xu J, Grönberg H, Wiklund F. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. European urology. 2014 Jan 1;65(1):169-76.
28. Bhatlekar S, Fields JZ, Boman BM. HOX genes and their role in the development of human cancers. Journal of molecular medicine. 2014 Aug 1;92(8):811-23.
29. Zhuang M, Calabrese MF, Liu J, Waddell MB, Nourse A, Hammel M, Miller DJ, Walden H, Duda DM, Seyedin SN, Hoggard T. Structures of SPOP-substrate complexes: insights into molecular architectures of BTB-Cul3 ubiquitin ligases. Molecular cell. 2009 Oct 9;36(1):39-50.
30. Blattner M, Lee DJ, O'Reilly C, Park K, MacDonald TY, Khani F, Turner KR, Chiu YL, Wild PJ, Dolgalev I, Heguy A. SPOP mutations in prostate cancer across demographically diverse patient cohorts. Neoplasia (New York, NY). 2014 Jan;16(1):14.
31. Wang H, Barbieri CE, He J, Gao Y, Shi T, Wu C, Schepmoes AA, Fillmore TL, Chae SS, Huang D, Mosquera JM. Quantification of mutant SPOP proteins in prostate cancer using mass spectrometry-based targeted proteomics. Journal of translational medicine. 2017 Dec;15(1):175.
32. Tomlins SA, Rhodes DR, Yu J, Varambally S, Mehra R, Perner S, Demichelis F, Helgeson BE, Laxman B, Morris DS, Cao Q. The role of SPINK1 in ETS rearrangement-negative prostate cancers. Cancer cell. 2008 Jun 10;13(6):519-28.
33. Simpson L, Parsons R. PTEN: life as a tumor suppressor. Experimental cell research. 2001 Mar 10;264(1):29-41.
34. GUO XJ, GUI YT, CA ZM. The progress of TMPRSS2-ETS gene fusions and their mechanism in prostate cancer. Hereditas (Beijing). 2011 Feb 25;33(2):117-22.

35. John JS, Powell K, Conley-LaComb MK, Chinni SR. TMPRSS2-ERG fusion gene expression in prostate tumor cells and its clinical and biological significance in prostate cancer progression. Journal of cancer science & therapy. 2012 Apr 26;4(4):94.
36. Magi- Galluzzi C, Tsusuki T, Elson P, Simmerman K, LaFargue C, Esgueva R, Klein E, Rubin MA, Zhou M. TMPRSS2–ERG gene fusion prevalence and class are significantly different in prostate cancer of caucasian, african- american and japanese patients. The Prostate. 2011 Apr;71(5):489-97.
37. Dai MJ, Chen LL, Zheng YB, Chen W, Tao ZH, Weng ZL, Wu XL, Li CD, Chen ZG, Chen XD, Shi SB. Frequency and transcript variant analysis of gene fusions between TMPRSS2 and ETS transcription factor genes in prostate cancer. Zhonghua yi xue za zhi. 2008 Mar;88(10):669-73.
38. Debes JD, Sebo TJ, Heemers HV, Kipp BR, De Anna LH, Lohse CM, Tindall DJ. p300 modulates nuclear morphology in prostate cancer. Cancer research. 2005 Feb 1;65(3):708-12.
39. Robbins CM, Hooker S, Kittles RA, Carpten JD. EphB2 SNPs and sporadic prostate cancer risk in African American men. PLoS One. 2011 May 16;6(5):e19494.
40. Tamgue O, Chai CS, Hao L, Zambe JC, Huang WW, Zhang B, Lei M, Wei YM. Triptolide inhibits histone methyltransferase EZH2 and modulates the expression of its target genes in prostate cancer cells. Asian Pacific Journal of Cancer Prevention. 2013;14(10):5663-9.
41. Sun J, Hsu FC, Turner AR, Zheng SL, Chang BL, Liu W, Isaacs WB, Xu J. Meta- analysis of association of rare mutations and common sequence variants in the MSR1 gene and prostate cancer risk. The Prostate. 2006 May 15;66(7):728-37.
42. Hsing AW, Sakoda LC, Chen J, Chokkalingam AP, Sesterhenn I, Gao YT, Xu J, Zheng SL. MSR1 variants and the risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China. Carcinogenesis. 2007 Sep 3;28(12):2530-6.
43. Han Z, Wang X, Ma L, Chen L, Xiao M, Huang L, Cao Y, Bai J, Ma D, Zhou J, Hong Z. Inhibition of STAT3 signaling targets both tumor-initiating and differentiated cell populations in prostate cancer. Oncotarget. 2014 Sep;5(18):8416.
44. Huang YC, Lee CM, Chen M, Chung MY, Chang YH, Huang WJ, Ho DM, Pan CC, Wu TT, Yang S, Lin MW. Haplotypes, loss of heterozygosity, and expression levels of glycine N-methyltransferase in prostate cancer. Clinical Cancer Research. 2007 Mar 1;13(5):1412-20.
45. Chen M, Huang YL, Huang YC, Shui IM, Giovannucci E, Chen YC, Chen YM. Genetic polymorphisms of the glycine N-methyltransferase and prostate cancer risk in the health professionals follow-up study. PloS one. 2014 May 6;9(5):e94683.
46. San Francisco IF, Rojas PA, Torres- Estay V, Smalley S, Cerda- Infante J, Montecinos VP, Hurtado C, Godoy AS. Association of RNASEL and 8q24 variants with the presence and aggressiveness of hereditary and sporadic prostate cancer in a Hispanic population. Journal of cellular and molecular medicine. 2014 Jan;18(1):125-33.
47. Berndt SI, Sampson J, Yeager M, Jacobs KB, Wang Z, Hutchinson A, Chung C, Orr N, Wacholder S, Chatterjee N, Yu K. Large-scale fine mapping of the HNF1B locus and prostate cancer risk. Human molecular genetics. 2011 May 16;20(16):3322-9.
48. Holt SK, Karyadi DM, Kwon EM, Stanford JL, Nelson PS, Ostrander EA. Association of megalin genetic polymorphisms with prostate cancer risk and prognosis. Clinical Cancer Research. 2008 Jun 15;14(12):3823-31.
49. Wang L, Kaku H, Huang P, Xu K, Yang K, Zhang J, Li M, Xie L, Wang X, Sakai A, Watanabe M. Single nucleotide polymorphism WRN Leu1074Phe is associated with prostate cancer susceptibility in Chinese subjects. Acta Med Okayama. 2011 Oct 1;65(5):315-23.
50. Xu J, Sauvageot J, Ewing CM, Sun J, Liu W, Isaacs SD, Wiley KE, Diaz L, Zheng SL, Walsh PC, Isaacs WB. Germline ATBF1 mutations and prostate cancer risk. The Prostate. 2006 Jul 1;66(10):1082-5.
51. Choi SY, Kim HJ, Cheong HS, Myung SC. The association of 5-alpha reductase type 2 (SRD5A2) gene polymorphisms with prostate cancer in a Korean population. Korean journal of urology. 2015 Jan 1;56(1):19-30.

52. Onen IH, Ekmekci A, Eroglu M, Polat F, Biri H. The Association of 5α-Reductase II (SRD5A2) and 17 Hydroxylase (CYP17) Gene Polymorphisms with Prostate Cancer Patients in The Turkish Population. DNA and cell biology. 2007 Feb 1;26(2):100-7.
53. Kaklamani V, Baddi L, Rosman D, Liu J, Ellis N, Oddoux C, Ostrer H, Chen Y, Ahsan H, Offit K, Pasche B. No major association between TGFBR1* 6A and prostate cancer. BMC genetics. 2004 Dec;5(1):28.
54. Suarez BK, Pal P, Jin CH, Kaushal R, Sun G, Jin L, Pasche B, Deka R, Catalona WJ. TGFBR1* 6A is not associated with prostate cancer in men of European ancestry. Prostate cancer and prostatic diseases. 2005 Mar;8(1):50.
55. Shaikhibrahim Z, Offermann A, Braun M, Menon R, Syring I, Nowak M, Halbach R, Vogel W, Ruiz C, Zellweger T, Rentsch CA. MED12 overexpression is a frequent event in castration-resistant prostate cancer. Endocr Relat Cancer. 2014 Aug 1;21(4):663-75.
56. Berlin A, Lalonde E, Sykes J, Zafarana G, Chu KC, Ramnarine VR, Ishkanian A, Sendorek DH, Pasic I, Lam WL, Jurisica I. NBN gain is predictive for adverse outcome following image-guided radiotherapy for localized prostate cancer. Oncotarget. 2014 Nov;5(22):11081.
57. Jee B, Jin K, Hahn JH, Song HG, Lee H. Metastasis-suppressor KAI1/CD82 induces homotypic aggregation of human prostate cancer cells through Src-dependent pathway. Experimental & molecular medicine. 2003 Feb;35(1):30.
58. Chiam K, Ryan NK, Ricciardelli C, Day TK, Buchanan G, Ochnik AM, Murti K, Selth LA, Australian Prostate Cancer BioResource, Butler LM, Tilley WD. Characterization of the prostate cancer susceptibility gene KLF6 in human and mouse prostate cancers. The Prostate. 2013 Jan;73(2):182-93.
59. Lubik AA, Gunter JH, Hollier BG, Ettinger S, Fazli L, Stylianou N, Hendy SC, Adomat HH, Gleave ME, Pollak M, Herington A. IGF2 increases de novo steroidogenesis in prostate cancer cells. Endocrine-related cancer. 2013 Apr 1;20(2):173-86.
60. Damola A, Legendre A, Ball S, Masters JR, Williamson M. Function of mutant and wild- type plexinB1 in prostate cancer cells. The Prostate. 2013 Sep;73(12):1326-35.
61. Prochownik EV, Grove LE, Deubler D, Zhu XL, Stephenson RA, Rohr LR, Yin X, Brothman AR. Commonly occurring loss and mutation of the MXI1 gene in prostate cancer. Genes, Chromosomes and Cancer. 1998 Aug;22(4):295-304.
62. Sjöblom L, Saramäki O, Annala M, Leinonen K, Nättinen J, Tolonen T, Wahlfors T, Nykter M, Bova GS, Schleutker J, Tammela TL. Microseminoprotein-beta expression in different stages of prostate cancer. PloS one. 2016 Mar 3;11(3):e0150241.
63. Tsukasaki K, Miller CW, Greenspun E, Eshaghian S, Kawabata H, Fujimoto T, Tomonaga M, Sawyers C, Said JW, Koeffler HP. Mutations in the mitotic check point gene, MAD1L1, in human cancers. Oncogene. 2001 May;20(25):3301.
64. Akbari MR, Trachtenberg J, Lee J, Tam S, Bristow R, Loblaw A, Narod SA, Nam RK. Association between germline HOXB13 G84E mutation and risk of prostate cancer. Journal of the National Cancer Institute. 2012 Jul 9;104(16):1260-2.
65. Beebe-Dimmer JL, Hathcock M, Yee C, Okoth LA, Ewing CM, Isaacs WB, Cooney KA, Thibodeau SN. The HOXB13 G84E mutation is associated with an increased risk for prostate cancer and other malignancies. Cancer Epidemiology and Prevention Biomarkers. 2015 Sep 1;24(9):1366-72.
66. Chen Z, Greenwood C, Isaacs WB, Foulkes WD, Sun J, Zheng SL, Condreay LD, Xu J. The G84E mutation of HOXB13 is associated with increased risk for prostate cancer: results from the REDUCE trial. Carcinogenesis. 2013 Feb 7;34(6):1260-4.
67. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y, Bizon C. Germline mutations in HOXB13 and prostate-cancer risk. New England Journal of Medicine. 2012 Jan 12;366(2):141-9.
68. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, Dadaev T, Tymrakiewicz M, Saunders EJ, Jones M, Jugurnauth-Little S, Govindasami K, Guy M, Hamdy FC. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Annals of oncology. 2015 Jan 16;26(4):756-61.

69. Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, Cannon-Albright LA, Teerlink CC, Camp NJ, Johnson AM, Zuhlke KA. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Human genetics. 2013 Jan 1;132(1):5-14.
70. Hope Q, Bullock S, Evans C, Meitz J, Hamel N, Edwards SM, Severi G, Dearnaley D, Jhavar S, Southgate C, Falconer A. Macrophage scavenger receptor 1 999C> T (R293X) mutation and risk of prostate cancer. Cancer Epidemiology and Prevention Biomarkers. 2005 Feb 1;14(2):397-402.
71. Maier C, Vesovic Z, Bachmann N, Herkommer K, Braun AK, Surowy HM, Assum G, Paiss T, Vogel W. Germline mutations of the MSR1 gene in prostate cancer families from Germany. Human mutation. 2006 Jan;27(1):98-102.
72. Miller DC, Zheng SL, Dunn RL, Sarma AV, Montie JE, Lange EM, Meyers DA, Xu J, Cooney KA. Germ-line mutations of the macrophage scavenger receptor 1 gene: association with prostate cancer risk in African-American men. Cancer research. 2003 Jul 1;63(13):3486-9.
73. Rennert H, Zeigler-Johnson CM, Addya K, Finley MJ, Walker AH, Spangler E, Leonard DG, Wein A, Malkowicz SB, Rebbeck TR. Association of susceptibility alleles in ELAC2/HPC2, RNASEL/HPC1, and MSR1 with prostate cancer severity in European American and African American men. Cancer Epidemiology and Prevention Biomarkers. 2005 Apr 1;14(4):949-57.
74. Seppälä EH, Ikonen T, Autio V, Rökman A, Mononen N, Matikainen MP, Tammela TL, Schleutker J. Germ-line alterations in MSR1 gene and prostate cancer risk. Clinical cancer research. 2003 Nov 1;9(14):5252-6.
75. Meitz JC, Edwards SM, Easton DF, Murkin A, Ardern-Jones A, Jackson RA, Williams S, Dearnaley DP, Stratton MR, Houlston RS, Eeles RA. HPC2/ELAC2 polymorphisms and prostate cancer risk: analysis by age of onset of disease. British journal of cancer. 2002 Oct;87(8):905.
76. Rebbeck TR, Walker AH, Zeigler-Johnson C, Weisburg S, Martin AM, Nathanson KL, Wein AJ, Malkowicz SB. Association of HPC2/ELAC2 genotypes and prostate cancer. The American Journal of Human Genetics. 2000 Oct 1;67(4):1014-9.
77. Vesprini D, Nam RK, Trachtenberg J, Jewett MA, Tavtigian SV, Emami M, Ho M, Toi A, Narod SA. HPC2 variants and screen-detected prostate cancer. The American Journal of Human Genetics. 2001 Apr 1;68(4):912-7.
78. Maier C, Haeusler J, Herkommer K, Vesovic Z, Hoegel J, Vogel W, Paiss T. Mutation screening and association study of RNASEL as a prostate cancer susceptibility gene. British journal of cancer. 2005 Mar;92(6):1159.
79. Nakazato H, Suzuki K, Matsui H, Ohtake N, Nakata S, Yamanaka H. Role of genetic polymorphisms of the RNASEL gene on familial prostate cancer risk in a Japanese population. British journal of cancer. 2003 Aug;89(4):691.
80. Wiklund F, Jonsson BA, Brookes AJ, Strömqvist L, Adolfsson J, Emanuelsson M, Adami HO, Augustsson-Bälter K, Grönberg H. Genetic analysis of the RNASEL gene in hereditary, familial, and sporadic prostate cancer. Clinical Cancer Research. 2004 Nov 1;10(21):7150-6.
81. Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K, Bhatia J, Stadler Z, Fine SW, Reuter V, Zelefsky M. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clinical cancer research. 2010 Apr 1;16(7):2115-21.
82. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, Goh C, Govindasami K, Guy M, O'brien L, Sawyer E. Germline BRCA1 mutations increase prostate cancer risk. British journal of cancer. 2012 May;106(10):1697.
83. FitzGerald LM, Karlins E, Karyadi DM, Kwon EM, Koopmeiners JS, Stanford JL, Ostrander EA. Association of FGFR4 genetic polymorphisms with prostate cancer risk and prognosis. Prostate cancer and prostatic diseases. 2009 Jun;12(2):192.
84. Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M, Koutcher JA, Scher HI, Ludwig T, Gerald W, Cordon-Cardo C. Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. Nature. 2005 Aug;436(7051):725.
85. You MJ, Castrillon DH, Bastian BC, O'Hagan RC, Bosenberg MW, Parsons R, Chin L, DePinho RA. Genetic analysis of Pten and Ink4a/Arf interactions in the

suppression of tumorigenesis in mice. Proceedings of the National Academy of Sciences. 2002 Feb 5;99(3):1455-60.

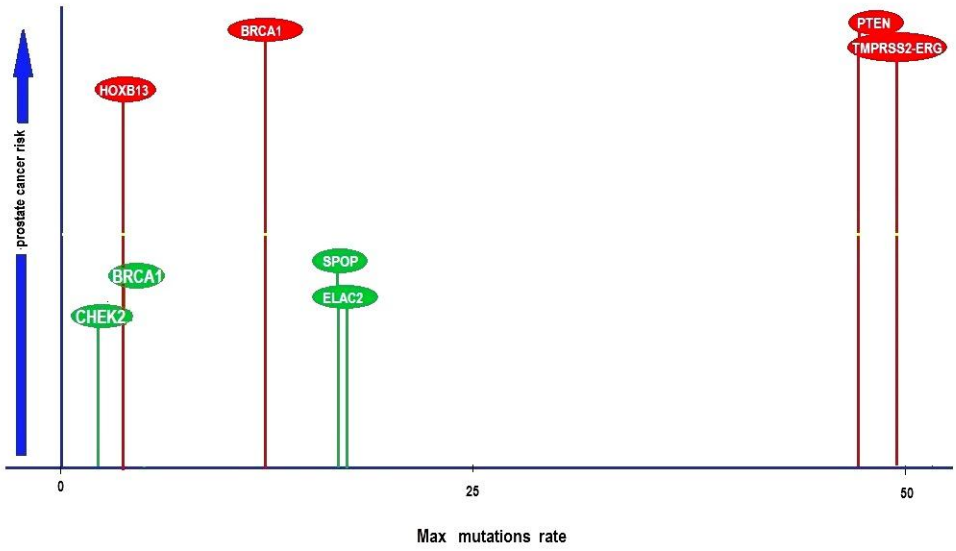

Figure 1: Relative risk of prostate cancer of eight candidate genes: BRCA, CHEK2, HOXB13, ELAC2, SPOP, PTEN, and TMPRSS2-ERG fusion, versus maximum mutations rate according to the researches listed in this review.

UNDER PEER

Table (1): Summary of genes variants detected, frequency of alleles, population studied, and association with PCa. (*D: Deferent Ethnic Group, *Not estimated, 1 Associated, 2 Not Associated, A.A: African American, A.E: American European, PCa: Prostate Cancer*).

Gene	Variant	Population	Variant Frequency	Association with PCa	Reference
HOXB13	G84E	D	0.7%	1	[64]
		D	0.5%	1	[65]
		D	0.99%	1	[66]
		European	1.4%	1	[67]
		British	1.5%	1	[68]
		D	5.0%	1	[69]
MSR1	999C>T (R293X)	D	0.027%	2	[70]
	c.877C4T (R293X)	German	1.9%	2	[71]
	Asp174Tyr	A.A	6.8%	1	[72]
	14,742 A > G	A.A	0.253%	1	[73]
	14,742 A > G	E.A	0.105%	1	[73]
	R293X, P275A, -14743A>G	Finnish	1.1% 3.9% 10.0%	2	[74]
ELAC2	Thr541	British	*	2	[75]
	Thr541 Leu217	D	2.9% 31.6%,	1	[76]
	650 C > T	A.A	0.211%	1	[73]
	650 C > T	E.A	0.301%	1	[73]
	Ala541Thr	D	6.3%	2	[77]
	Leu217	D	32.3%	1	[23]
	Thr541	D	5.4%	1	[23]
RNASEL	Arg462Gln and Asp541Glu	Chilean	Multiple	1	[46]
	E265X	German	1.4%	2	[78]
	G282A, G1385A and T1623G	Japanese	*	1	[79]
	1385 G > A	A.A	0.159%	1	[73]
	1385 G > A	E.A	0.370%	1	[73]
	E265X	Swedish	1.9%	2	[80]
BRCA	Clinical Pathological Features	Ashkenazi Jews	*	1	[81]
	BRCA1: 185delAG , 5382insC BRCA2: 6174delT	Ashkenazi Jews	5.2%	1	[6]
	Deleterious Mutations	British	0.45%	1	[82]
CHEK2	1100delC	Polish	1.6%	1	[17]
	Multiple	D	4.8%	1	[18]
GNMT	(STRP1), SNP : rs10948059	European	*	1	[45]
	4-bp insertion/deletion (INS/DEL)			2	
	Multiple	Taiwanese	Multiple	1	[44]
HNF1B SNPs	rs4430796, rs4430769, rs11649743	European	*	2	[47]
SPOP	Multiple Missense Mutations	D	8.1%	1	[29]
FGFR4	rs351855	Caucasian ,A.A	Multiple	2	[83]
Megalin SNPs	Multiple	Caucasian	Multiple	2	[48]
TGFBR1	(*9A) exon 1	D	0.086%	*2*	[53]
WRN	Leu1074Phe (rs1801195)	Chinese	41.5%	1	[49]

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