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 suppressor genes; BRCA; TMPRSS2-ERG fusion; SPOP.

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]. We describe here 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. 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.

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 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 10.4-11kb, 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 complex that repairs double-strand breaks in DNA. 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].

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 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 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 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. By blocking the activation of Akt, PTEN regulates cellular processes such as cell cycling, translation, 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, 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.

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 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 tumor [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 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].

3. Conclusions:

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 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. 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).

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.

References:

1. Beiki, O., Ekbom, A., Allebeck, P. and Moradi, T., Risk of prostate cancer among Swedish born and foreign born men in Sweden, 1961–2004. International journal of cancer, 124(8), (2009) pp.1941-1953.
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 9, no. 10 (2011) 748-55.
3. Shen, M.M. and Abate-Shen, C., Molecular genetics of prostate cancer: new prospects for old challenges. Genes & development, 24(18), (2010) pp.1967-2000.
4. Edwards, S.M., Kote Jarai, Z., Hamoudi, R. and Eeles, R.A., An improved high throughput heteroduplex mutation detection system for screening BRCA2 mutations—fluorescent mutation detection (FMD). Human mutation, 17(3), (2001) pp.220-232.

5. Tryggvadóttir, L., Vidarsdóttir, L., Thorgeirsson, T., Jonasson, J.G., Ólafsdóttir, E.J., Ólafsdóttir, G.H., Rafnar, T., Thorlacius, S., Jonsson, E., Eyfjord, J.E. and Tulinius, H., Prostate cancer progression and survival in BRCA2 mutation carriers. Journal of the National Cancer Institute, 99(12), (2007) pp.929-935.
6. Kirchhoff, T., Kauff, N.D., Mitra, N., Nafa, K., Huang, H., Palmer, C., Gulati, T., Wadsworth, E., Donat, S., Robson, M.E. and Ellis, N.A., BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clinical Cancer Research, 10(9), (2004) pp.2918-2921.
7. Mitra, A., Fisher, C., Foster, C.S., Jameson, C., Barbachanno, Y., Bartlett, J., Bancroft, E., Doherty, R., Kote-Jarai, Z., Peock, S. and Easton, D., 2008. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. British journal of cancer, 98(2), (2008) pp.502-507.
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) pp.1-15.
9. Wang, Y., Cortez, D., Yazdi, P., Neff, N., Elledge, S.J. and Qin, J., BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes & development, 14(8), (2000) pp.927-939.
10. Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P.A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L.M., Ding, W. and Bell, R., Isolation of BRCA1, the 17q-linked breast and ovarian cancer susceptibility gene. Science, 266(667), (1994) p.1.
11. Boulton, S.J., Cellular functions of the BRCA tumour-suppressor proteins. Biochemical Society Transactions, 34(5), (2006) pp.633-645.
12. Friedenson, B., The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC cancer, 7(1), (2007) p.152.
13. Antoniou, A.C., Pharoah, P.D.P., McMullan, G., Day, N.E., Stratton, M.R., Peto, J., Ponder, B.J. and Easton, D.F., A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. British journal of cancer, 86(1), (2002) pp.76-83.
14. Chen, P.L., Chen, C.F., Chen, Y., Xiao, J., Sharp, Z.D. and Lee, W.H., The BRC repeats in BRCA2 are critical for RAD51 binding and resistance to methyl methanesulfonate treatment. Proceedings of the National Academy of Sciences, 95(9), (1998) pp.5287-5292.
15. Shaughnessy, J., Tian, E., Sawyer, J., Bumm, K., Landes, R., Badros, A., Morris, C., Tricot, G., Epstein, J. and Barlogie, B., High incidence of chromosome 13 deletion in multiple myeloma detected by multiprobe interphase FISH. Blood, 96(4), (2000) pp.1505-1511.
16. Matsuoka S., HuangM., ElledgeS.J.. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase, Science , vol. 282 (1998) pp. 1893-1897
17. Cybulski, C., Huzarski, T., Górski, B., Masojć, B., Mierzejewski, M., Dębniak, T., Gliniewicz, B., Matyjasik, J., Złowocka, E., Kurzawski, G. and Sikorski, A., A novel founder CHEK2 mutation is associated with increased prostate cancer risk. Cancer research, 64(8), (2004) pp.2677-2679.
18. Dong, X., Wang, L., Taniguchi, K., Wang, X., Cunningham, J.M., McDonnell, S.K., Qian, C., Marks, A.F., Slager, S.L., Peterson, B.J. and Smith, D.I., Mutations in CHEK2 associated with prostate cancer risk. The American Journal of Human Genetics, 72(2), (2003) pp.270-280.
19. Zannini, L., Delia, D., Buscemi G.,; CHK2 kinase in the DNA damage response and beyond, *Journal of Molecular Cell Biology*, Volume 6, Issue 6, 1 (2014) Pages 442–457, https://doi.org/10.1093/jmcb/mju045
20. Brzezniak, L.K., Bijata, M., Szczesny, R.J. and Stepien, P.P., Involvement of human ELAC2 gene product in 3'end processing of mitochondrial tRNAs. RNA biology, 8(4), (2011) pp.616-626.
21. Rökman, A., Ikonen, T., Mononen, N., Autio, V., Matikainen, M.P., Koivisto, P.A., Tammela, T.L., Kallioniemi, O.P. and Schleutker, J., ELAC2/HPC2 involvement in hereditary and sporadic prostate cancer. Cancer research, 61(16), (2001) pp.6038-6041.

22. Stanford, J.L., Sabacan, L.P., Noonan, E.A., Iwasaki, L., Shu, J., Feng, Z. and Ostrander, E.A., Association of HPC2/ELAC2 polymorphisms with risk of prostate cancer in a population-based study. Cancer Epidemiology and Prevention Biomarkers, 12(9), (2003) pp.876-881.
23. Wang, L., McDonnell, S.K., Elkins, D.A., Slager, S.L., Christensen, E., Marks, A.F., Cunningham, J.M., Peterson, B.J., Jacobsen, S.J., Cerhan, J.R. and Blute, M.L., Role of HPC2/ELAC2 in hereditary prostate cancer. Cancer research, 61(17), (2001) pp.6494-6499.
24. Xu, J., Zheng, S.L., Carpten, J.D., Nupponen, N.N., Robbins, C.M., Mestre, J., Moses, T.Y., Faith, D.A., Kelly, B.D., Isaacs, S.D. and Wiley, K.E., Evaluation of linkage and association of HPC2/ELAC2 in patients with familial or sporadic prostate cancer. The American Journal of Human Genetics, 68(4), (2001) pp.901-911.
25. Decker B, Ostrander EA. Dysregulation of the homeobox transcription factor gene HOXB13: role in prostate cancer. Pharmgenomics Pers Med. 5;7 (2014) 193-201. doi: 10.2147/PGPM.S38117.
26. Breyer, J.P., Avritt, T.G., McReynolds, K.M., Dupont, W.D. and Smith, J.R., Confirmation of the HOXB13 G84E germline mutation in familial prostate cancer. Cancer Epidemiology and Prevention Biomarkers, 21(8), (2012) pp.1348-1353.
27. Karlsson, R., Aly, M., Clements, M., Zheng, L., Adolfsson, J., Xu, J., Grönberg, H. and Wiklund, F., A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. European urology, 65(1), (2014) pp.169-176.
28. Bhatlekar S, Fields JZ, Boman BM. HOX genes and their role in the development of human cancers. J Mol Med (Berl). 92(8) (2014) 811-23. doi: 10.1007/s00109-014-1181-y.
29. Zhuang, M., Calabrese, M.F., Liu, J., Waddell, M.B., Nourse, A., Hammel, M., Miller, D.J., Walden, H., Duda, D.M., Seyedin, S.N. and Hoggard, T., Structures of SPOP-substrate complexes: insights into molecular architectures of BTB-Cul3 ubiquitin ligases. Molecular cell, 36(1), (2009) pp.39-50.
30. Blattner, M., Lee, D.J., O'Reilly, C., Park, K., MacDonald, T.Y., Khani, F., Turner, K.R., Chiu, Y.L., Wild, P.J., Dolgalev, I. and Heguy, A., SPOP mutations in prostate cancer across demographically diverse patient cohorts. Neoplasia, 16(1), (2014) pp.14W8-20W10.
31. Wang, H., Barbieri, C. E., He, J., Gao, Y., Shi, T., Wu, C., ... & Mosquera, J. M., Quantification of mutant SPOP proteins in prostate cancer using mass spectrometry-based targeted proteomics. Journal of translational medicine, 15(1), (2017)175.
32. Tomlins, S.A., Rhodes, D.R., Yu, J., Varambally, S., Mehra, R., Perner, S., Demichelis, F., Helgeson, B.E., Laxman, B., Morris, D.S. and Cao, Q., The role of SPINK1 in ETS rearrangement-negative prostate cancers. Cancer cell, 13(6), (2008) pp.519-528.
33. Simpson, L. and Parsons, R., PTEN: life as a tumor suppressor. Experimental cell research, 264(1), (2001) pp.29-41.
34. Guo, X.Q., Gui, Y.T. and Cai, Z.M., The progress of TMPRSS2-ETS gene fusions and their mechanism in prostate cancer. Yi chuan= Hereditas, 33(2), (2011) pp.117-122.
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. J Cancer Sci Ther 4: (2012) 094- 101. doi:10.4172/1948-5956.1000119
36. Magi-Galluzzi, C., Tsusuki, T., Elson, P., Simmerman, K., LaFargue, C., Esgueva, R., Klein, E., Rubin, M.A. and Zhou, M., TMPRSS2–ERG gene fusion prevalence and class are significantly different in prostate cancer of caucasian, african-american and japanese patients. The Prostate, 71(5), (2011) pp.489-497.
37. Dai, M.J., Chen, L.L., Zheng, Y.B., Chen, W., Tao, Z.H., Weng, Z.L., Wu, X.L., Li, C.D., Chen, Z.G., Chen, X.D. and Shi, S.B., Frequency and transcript variant analysis of gene fusions between TMPRSS2 and ETS transcription factor genes in prostate cancer. Zhonghua yi xue za zhi, 88(10), (2008) pp.669-673.

38. Debes, J.D., Sebo, T.J., Heemers, H.V., Kipp, B.R., De Anna, L.H., Lohse, C.M. and Tindall, D.J., p300 modulates nuclear morphology in prostate cancer. Cancer research, 65(3), (2005) pp.708-712.
39. Robbins, C.M., Hooker, S., Kittles, R.A. and Carpten, J.D., EphB2 SNPs and sporadic prostate cancer risk in African American men. PLoS One, 6(5), (2011) p.e19494.
40. Tamgue, O., Chai, C.S., Hao, L., Zambe, J.C.D., Huang, W.W., Zhang, B., Lei, M. and Wei, Y.M., Triptolide inhibits histone methyltransferase EZH2 and modulates the expression of its target genes in prostate cancer cells. Asian Pacific Journal of Cancer Prevention, 14(10), (2013) pp.5663-5669.
41. Sun, J., Hsu, F.C., Turner, A.R., Zheng, S.L., Chang, B.L., Liu, W., Isaacs, W.B. and Xu, J., Meta analysis of association of rare mutations and common sequence variants in the MSR1 gene and prostate cancer risk. The Prostate, 66(7), (2006) pp.728-737.
42. Hsing, A.W., Sakoda, L.C., Chen, J., Chokkalingam, A.P., Sesterhenn, I., Gao, Y.T., Xu, J. and Zheng, S.L., MSR1 variants and the risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China. Carcinogenesis, 28(12), (2007) pp.2530-2536.
43. Han, Z., Wang, X., Ma, L., Chen, L., Xiao, M., Huang, L., Cao, Y., Bai, J., Ma, D., Zhou, J. and Hong, Z., Inhibition of STAT3 signaling targets both tumor-initiating and differentiated cell populations in prostate cancer. Oncotarget, 5(18), (2014) pp.8416-8428.
44. Huang, Y.C., Lee, C.M., Chen, M., Chung, M.Y., Chang, Y.H., Huang, W.J.S., Ho, D.M.T., Pan, C.C., Wu, T.T., Yang, S. and Lin, M.W., Haplotypes, loss of heterozygosity, and expression levels of glycine N-methyltransferase in prostate cancer. Clinical Cancer Research, 13(5), (2007) pp.1412-1420.
45. Chen, M., Huang, Y.L., Huang, Y.C., Shui, I.M., Giovannucci, E., Chen, Y.C. and Chen, Y.M.A., Genetic polymorphisms of the glycine N-methyltransferase and prostate cancer risk in the health professionals follow-up study. PloS one, 9(5), (2014) p.e94683.
46. San Francisco, I.F., Rojas, P.A., Torres Estay, V., Smalley, S., Cerda Infante, J., Montecinos, V.P., Hurtado, C. and Godoy, A.S., 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, 18(1), (2014) pp.125-133.
47. Berndt, S.I., Sampson, J., Yeager, M., Jacobs, K.B., Wang, Z., Hutchinson, A., Chung, C., Orr, N., Wacholder, S., Chatterjee, N. and Yu, K., Large-scale fine mapping of the HNF1B locus and prostate cancer risk. Human molecular genetics, (2011) p.ddr213.
48. Holt, S.K., Karyadi, D.M., Kwon, E.M., Stanford, J.L., Nelson, P.S. and Ostrander, E.A., Association of megalin genetic polymorphisms with prostate cancer risk and prognosis. Clinical Cancer Research, 14(12), (2008) pp.3823-3831.
49. Wang, L., Kaku, H., Huang, P., Xu, K., Yang, K., Zhang, J., Li, M., Xie, L., Wang, X., Sakai, A. and Watanabe, M., Single nucleotide polymorphism WRN Leu1074Phe is associated with prostate cancer susceptibility in Chinese subjects. Acta Medica Okayama, 65(5), (2011) pp.315-323.
50. Xu J, Sauvageot J, Ewing CM, et al. Germline ATBF1 mutations and prostate cancer risk. Prostate; 66(10) (2006) 1082-5.
51. Choi, S.Y., Kim, H.J., Cheong, H.S. and Myung, S.C., The association of 5-alpha reductase type 2 (SRD5A2) gene polymorphisms with prostate cancer in a Korean population. Korean journal of urology, 56(1), (2015) pp.19-30.
52. Onen, I.H., Ekmekci, A., Eroglu, M., Polat, F. and 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, 26(2), (2007) pp.100-107.
53. Kaklamani, V., Baddi, L., Rosman, D., Liu, J., Ellis, N., Oddoux, C., Ostrer, H., Chen, Y., Ahsan, H., Offit, K. and Pasche, B., No major association between TGFBR1* 6A and prostate cancer. BMC genetics, 5(1), (2004) p.28.

54. Suarez, B.K., Pal, P., Jin, C.H., Kaushal, R., Sun, G., Jin, L., Pasche, B., Deka, R. and Catalona, W.J., TGFBR1* 6A is not associated with prostate cancer in men of European ancestry. Prostate cancer and prostatic diseases, 8(1), (2005) pp.50-53.
55. Shaikhibrahim, Z., Offermann, A., Braun, M., Menon, R., Syring, I., Nowak, M., Halbach, R., Vogel, W., Ruiz, C., Zellweger, T. and Rentsch, C.A., MED12 overexpression is a frequent event in castration-resistant prostate cancer. Endocrine-related cancer, 21(4), (2014) pp.663-675.
56. Berlin, A., Lalonde, E., Sykes, J., Zafarana, G., Chu, K.C., Ramnarine, V.R., Ishkanian, A., Sendorek, D.H., Pasic, I., Lam, W.L. and Jurisica, I., NBN gain is predictive for adverse outcome following image-guided radiotherapy for localized prostate cancer. Oncotarget, 5(22), (2014) p.11081.
57. Jee, B., Jin, K., Hahn, J.H., Song, H.G. and Lee, H., Metastasis-suppressor KAI1/CD82 induces homotypic aggregation of human prostate cancer cells through Src-dependent pathway. Experimental & molecular medicine, 35(1), (2003) p.30.
58. Chiam, K., Ryan, N.K., Ricciardelli, C., Day, T.K., Buchanan, G., Ochnik, A.M., Murti, K., Selth, L.A., Butler, L.M., Tilley, W.D. and Bianco-Miotto, T., Characterization of the prostate cancer susceptibility gene KLF6 in human and mouse prostate cancers. The Prostate, 73(2), (2013) pp.182-193.
59. Lubik, A.A., Gunter, J.H., Hendy, S.C., Locke, J.A., Adomat, H.H., Thompson, V., Herington, A., Gleave, M.E., Pollak, M. and Nelson, C.C., Insulin increases de novo steroidogenesis in prostate cancer cells. Cancer Research, 71(17), (2011) pp.5754-5764.
60. Damola, A., Legendre, A., Ball, S., Masters, J.R. and Williamson, M., Function of mutant and wildtype plexinB1 in prostate cancer cells. The Prostate, 73(12), (2013) pp.1326-1335.
61. Prochownik, E.V., Grove, L.E., Deubler, D., Zhu, X.L., Stephenson, R.A., Rohr, L.R., Yin, X. and Brothman, A.R., Commonly occurring loss and mutation of the MXI1 gene in prostate cancer. Genes, Chromosomes and Cancer, 22(4), (1998) pp.295-304.
62. Sjöblom, L., Saramäki, O., Annala, M., Leinonen, K., Nättinen, J., Tolonen, T., Wahlfors, T., Nykter, M., Bova, G.S., Schleutker, J. and Tammela, T.L., Microseminoprotein-Beta Expression in Different Stages of Prostate Cancer. PloS one, 11(3), (2016) p.e0150241.
63. Tsukasaki, K., Miller, C.W., Greenspun, E., Eshaghian, S., Kawabata, H., Fujimoto, T., Tomonaga, M., Sawyers, C., Said, J.W. and Koeffler, H.P., Mutations in the mitotic check point gene, MAD1L1, in human cancers. Oncogene, 20(25),(2001) p.3301.
64. Akbari, M.R., Trachtenberg, J., Lee, J., Tam, S., Bristow, R., Loblaw, A., Narod, S.A. and Nam, R.K., Association between germline HOXB13 G84E mutation and risk of prostate cancer. Journal of the National Cancer Institute, 104(16), (2012) pp.1260-1262.
65. Beebe-Dimmer, J.L., Hathcock, M., Yee, C., Okoth, L.A., Ewing, C.M., Isaacs, W.B., Cooney, K.A. and Thibodeau, S.N., The HOXB13 G84E mutation is associated with an increased risk for prostate cancer and other malignancies. Cancer Epidemiology and Prevention Biomarkers, 24(9), (2015) pp.1366-1372.
66. Chen, Z., Greenwood, C., Isaacs, W.B., Foulkes, W.D., Sun, J., Zheng, S.L., Condreay, L.D. and Xu, J., The G84E mutation of HOXB13 is associated with increased risk for prostate cancer: results from the REDUCE trial. Carcinogenesis, 34(6), (2013) pp.1260-1264.
67. Ewing, C.M., Ray, A.M., Lange, E.M., Zuhlke, K.A., Robbins, C.M., Tembe, W.D., Wiley, K.E., Isaacs, S.D., Johng, D., Wang, Y. and Bizon, C., Germline mutations in HOXB13 and prostate-cancer risk. New England Journal of Medicine, 366(2), (2012) pp.141-149.
68. Kote-Jarai, Z., Mikropoulos, C., Leongamornlert, D.A., Dadaev, T., Tymrakiewicz, M., Saunders, E.J., Jones, M., Jugurnauth-Little, S., Govindasami, K., Guy, M. and Hamdy, F.C., Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Annals of Oncology, 26(4), (2015) pp.756-761.

69. Xu, J., Lange, E.M., Lu, L., Zheng, S.L., Wang, Z., Thibodeau, S.N., Cannon-Albright, L.A., Teerlink, C.C., Camp, N.J., Johnson, A.M. and Zuhlke, K.A., HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Human genetics, 132(1), (2013) pp.5-14.
70. Hope, Q., Bullock, S., Evans, C., Meitz, J., Hamel, N., Edwards, S.M., Severi, G., Dearnaley, D., Jhavar, S., Southgate, C. and Falconer, A., Macrophage scavenger receptor 1 999C> T (R293X) mutation and risk of prostate cancer. Cancer Epidemiology and Prevention Biomarkers, 14(2), (2005) pp.397-402.
71. Maier, C., Vesovic, Z., Bachmann, N., Herkommer, K., Braun, A.K., Surowy, H.M., Assum, G., Paiss, T. and Vogel, W., Germline mutations of the MSR1 gene in prostate cancer families from Germany. Human mutation, 27(1), (2006) p.98.
72. Miller, David C., et al. "Germ-line mutations of the macrophage scavenger receptor 1 gene: association with prostate cancer risk in African-American men." Cancer research 63.13 (2003) 3486-3489.
73. Rennert, H., Zeigler-Johnson, C.M., Addya, K., Finley, M.J., Walker, A.H., Spangler, E., Leonard, D.G., Wein, A., Malkowicz, S.B. and Rebbeck, T.R., 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, 14(4), (2005) pp.949-957.
74. Seppälä, E.H., Ikonen, T., Autio, V., Rökman, A., Mononen, N., Matikainen, M.P., Tammela, T.L. and Schleutker, J., Germ-line alterations in MSR1 gene and prostate cancer risk. Clinical cancer research, 9(14), (2003) pp.5252-5256.
75. Meitz, J.C., Edwards, S.M., Easton, D.F., Murkin, A., Ardern-Jones, A., Jackson, R.A., Williams, S., Dearnaley, D.P., Stratton, M.R., Houlston, R.S. and Eeles, R.A., HPC2/ELAC2 polymorphisms and prostate cancer risk: analysis by age of onset of disease. British journal of cancer, 87(8), (2002) pp.905-908.
76. Rebbeck, T.R., Walker, A.H., Zeigler-Johnson, C., Weisburg, S., Martin, A.M., Nathanson, K.L., Wein, A.J. and Malkowicz, S.B., Association of HPC2/ELAC2 genotypes and prostate cancer. The American Journal of Human Genetics, 67(4), (2000) pp.1014-1019.
77. Vesprini, D., Nam, R.K., Trachtenberg, J., Jewett, M.A., Tavtigian, S.V., Emami, M., Ho, M., Toi, A. and Narod, S.A., HPC2 variants and screen-detected prostate cancer. The American Journal of Human Genetics, 68(4), (2001) pp.912-917.
78. Maier, C., Haeusler, J., Herkommer, K., Vesovic, Z., Hoegel, J., Vogel, W. and Paiss, T., Mutation screening and association study of RNASEL as a prostate cancer susceptibility gene. British journal of cancer, 92(6), (2005) pp.1159-1164.
79. Nakazato, H., et al. Role of genetic polymorphisms of the RNASEL gene on familial prostate cancer risk in a Japanese population. British journal of cancer 89.4 (2003) 691.
80. Wiklund, F., Jonsson, B.A., Brookes, A.J., Strömqvist, L., Adolfsson, J., Emanuelsson, M., Adami, H.O., Augustsson-Bälter, K. and Grönberg, H., Genetic analysis of the RNASEL gene in hereditary, familial, and sporadic prostate cancer. Clinical Cancer Research, 10(21), (2004) pp.7150-7156.
81. Gallagher, D.J., Gaudet, M.M., Pal, P., Kirchhoff, T., Balistreri, L., Vora, K., Bhatia, J., Stadler, Z., Fine, S.W., Reuter, V. and Zelefsky, M., Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clinical Cancer Research, 16(7), (2010) pp.2115-2121.
82. Leongamornlert, D., Mahmud, N., Tymrakiewicz, M., Saunders, E., Dadaev, T., Castro, E., Goh, C., Govindasami, K., Guy, M., O'brien, L. and Sawyer, E., Germline BRCA1 mutations increase prostate cancer risk. British journal of cancer, 106(10), (2012) pp.1697-1701.
83. FitzGerald, L.M., Karlins, E., Karyadi, D.M., Kwon, E.M., Koopmeiners, J.S., Stanford, J.L. and Ostrander, E.A., Association of FGFR4 genetic polymorphisms with prostate cancer risk and prognosis. Prostate cancer and prostatic diseases, 12(2), (2009) p.192.
84. Chen, Z., Trotman, L.C., Shaffer, D., Lin, H.K., Dotan, Z.A., Niki, M., Koutcher, J.A., Scher, H.I., Ludwig, T., Gerald, W. and Cordon-Cardo, C., Crucial role of p53-dependent cellular senescence in suppression of Ptendeficient tumorigenesis. Nature, 436(7051), (2005) pp.725-730.

85. You, M.J., Castrillon, D.H., Bastian, B.C., O'Hagan, R.C., Bosenberg, M.W., Parsons, R., Chin, L. and DePinho, R.A., Genetic analysis of Pten and Ink4a/Arf interactions in the suppression of tumorigenesis in mice. Proceedings of the National Academy of Sciences, 99(3), (2002) pp.1455-1460.

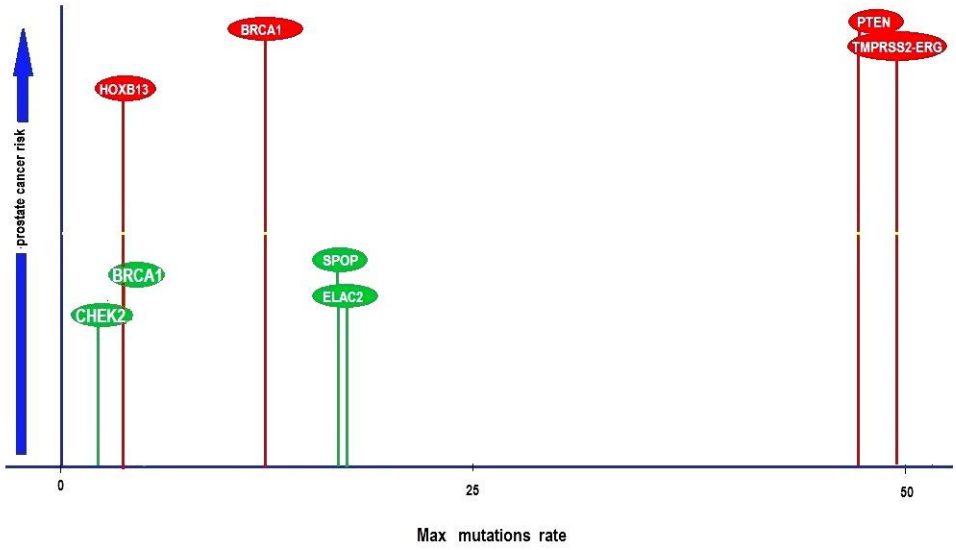

Table (1): Summary of genes variants detected, frequency of alleles, population studied, and association with PCa. (*D: Deferent Ethnic Group, *Not estimated, 1 Associated, 2 Not Associated, A.A: African American, A.E: American European, PCa: Prostate Cancer*).

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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