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Review Article

The structure and function of *NKAIN2*-a candidate tumor suppressor

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Abstract: The deletion of chromosomal region 6q was commonly found in several types of human cancers, although the tumor suppressor genes (TSGs) located within this genomic region are not well established. Our recent work detected recurrent chromosomal truncation at the Na^+/K^+ transporting ATPase interacting 2 (*NKAIN2*) gene in prostate cancer, which was also found to be truncated in leukemia and lymphoma, suggesting that *NKAIN2* is potentially one of the TSGs located in the 6q commonly deleted region in human cancers. *NKAIN2* gene consists of eight coding exons that span approximately 1 Mb of genomic DNA on chromosome 6q and there are four main splice variants. The function of this gene is not well investigated and the limited knowledge of this gene pointed to nervous system development. The chromosomal translocations in nervous development disorders usually lead to inactivation of this gene. In human tumors, both chromosomal deletion and translocation may also inactivate this gene and consequently contribute to tumorigenesis. Further genetic and cellular functional studies are required to establish its tumor suppressor role.

Keywords: Chromosomal deletion, genomic rearrangement, tumor suppressor gene, *NKAIN2 (TCBA1)*

Introduction

Deletions of 6q are frequently found in human cancers, including prostate cancer [1-3], breast cancer [4], pancreatic cancer [5], renal cell carcinoma [6], lung adenocarcinoma [7], malignant melanoma [8], esophageal squamous cell cancer [9], lymphoblastic leukemia [10], and non-Hodgkin's B-cell lymphomas [11]. Several studies on the loss of heterozygosity (LOH) have also suggested that chromosome 6q is involved in the pathogenesis of various human malignancies, including prostate cancer [12], acute lymphoblastic leukemia [13], non-Hodgkin's B-cell lymphoma [13], ovarian carcinoma [14], breast carcinoma [15], malignant melanoma [16], renal cell carcinoma [17], hepatocellular carcinoma [18], salivary gland adenocarcinoma [19], pancreatic cancer [20], and parathyroid adenoma [21]. Re-introducing a normal chromosome 6 into melanoma cells suppresses tumorigenesis [3] and a potential tumor metastasis suppressor locus has been functionally linked to 6q16.3-q23 [3]. These studies suggest that chromosome 6 may harbor one or more genes that suppress tumorigenesis and metastasis. However, while several candidate TSGs have been proposed, such as MAP3K7 [22], PLAGL1 [23], and LATS1 [24], no TSGs have been well established. In our recent study of prostate cancer genomic alterations, we found that in prostate cancer the majority of genomic truncations occurred at TSGs rather than oncogenes, indicating that genomic truncation is also a major mechanism causing TSG inactivation in prostate cancer [25]. Na^+/K^+ transporting ATPase interacting 2 (*NKAIN2*) is one of the genes recurrently truncated by chromosomal rearrangement [25] and our unpublished data showed that *NKAIN2* was generally under-expressed in prostate cancer cell compare to adjacent non-malignant prostate tissues, suggesting that *NKAIN2* is potentially one of the TSGs located on 6q. In the present article, we review the biological function of *NKAIN2* and existing evidence to support its role in tumorigenesis. We speculate that *NKAIN2* could be a novel tumor suppressor on the 6q

Table 1. Basic information of NKAINs family members

Gene	Location	Expression	Interaction	Involvement in diseases
NKAIN1	1p35.2	Neuron-specific	Interact with the b1 subunit of the Na, K-ATPase	alcohol dependence.
NKAIN2	6q22.31	Neuron-specific		genital herpes, alcohol dependence, lymphoma, neuroblastoma, prostate cancer, type 2 diabets mellitus.
NKAIN3	8q12.13	Neuron-specific		
NKAIN4	20q13.33	Ubiquitous		

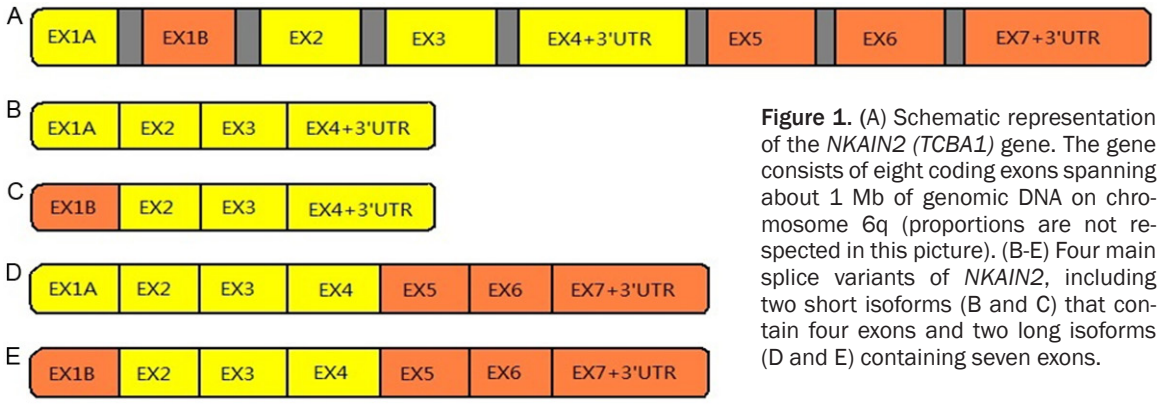

Figure 1. (A) Schematic representation of the *NKAIN2 (TCBA1)* gene. The gene consists of eight coding exons spanning about 1 Mb of genomic DNA on chromosome 6q (proportions are not respected in this picture). (B-E) Four main splice variants of *NKAIN2*, including two short isoforms (B and C) that contain four exons and two long isoforms (D and E) containing seven exons.

commonly deleted chromosomal region in human cancer and propose further researches required to investigate its potential tumor suppresser role. With the deepening of its involvement in human cancer and its cellular functions, the role of NKAIN2 in tumorigenesis will be uncovered, which may impact the treatment of human malignancy.

Basic structure and cellular function of *NKAIN2*

NKAIN2 was originally named T-cell lymphoma breakpoint associated target 1 (*TCBA1*), because it was involved in chromosome 6q aberrations in T-cell lymphoma and leukemia cell lines [26]. Potential functions of *NKAIN2* can be predicted based on its genetic structure. Searching the Sanger Center Pfam (Protein Families) database (http://www.sanger.ac.uk/resources/databases/pfam.html) for the product of *NKAIN2* identifies a family of proteins (Pfam05640/DUF798) with several members that are phylogenetically well conserved. The common feature shared by these proteins is the presence of the DUF798 domain, the function of which is not known. Most of the members of this family are classified as hypothetical proteins and no information is available about their function. In human, *NKAIN2* belongs to a superfamily of transmembrane proteins that interact with the b1 subunits of Na^+/K^+-ATPase and that are encoded by four genes, *NKAIN1*, *NKAIN2*, *NKAIN3* and *NKAIN4* [27] (**Table 1**).

NKAIN genes do not show any similarities to any other known genes, but they do share striking evolutionary conservation among species, there is a striking amino acid conservation in the first two transmembrane domains from Drosophila to human, which is considered a good indicator of their functional significance [27]. Preliminary data concerning the putative *C. elegans* homolog gene (T13H5.6) suggest that its expression pattern is also conserved among phylogenetically diverse species [28]. The *NKAIN2* gene consists of eight coding exons that span approximately 1 Mb of genomic DNA on chromosome 6q [28]. Four main splice variants have been identified, including two short isoforms that contain four exons and two long isoforms containing seven exons [26, 28] (**Figure 1**). A PSI-BLAST analysis, which allows the identification of distantly related proteins, has revealed a string of 70 residues that perfectly match a mouse protein similar to B-RAF [29]. In addition to the matching 70-residue sequence, this protein mainly consists of a serine/threonine kinase domain homologous to mouse B-RAF. Raf proteins, which are encoded by known proto-oncogenes, belong to the family of serine/threonine kinases and are intracellular signal transducers that are associated with membrane receptors [30-32].

Involvement of *NKAIN2* in human malignance

Chromosomal rearrangements, including translocations, inversions, deletions, and duplications, are the hallmarks of human cancer [33, 34]. Those chromosomal rearrangements can either activate oncogenes by deregulating them and even generate novel tumorigenic fusion product or inactivate TSGs by deleting the whole or part of the genes. As mentioned above, *NKAIN2* is located within the 6q commonly deleted region in human cancers, thus reducing expression by loss of genomic copies and potentially causing haploid insufficiency. In addition, chromosome translocations affecting *NKAIN2* genomic region can also lead to loss of function of this gene, both in developmental diseases and human malignancies [26, 28, 35].

It is well established that translocation and genomic fusion can deregulate oncogenes or generate gain of function tumorigenic genes. The generation of fusion proteins is a well-known mechanism capable of promoting oncogene activation, because the fusion proteins often have novel functional features such as the unscheduled expression or constitutive activation of an intrinsic function [36, 37]. Nowell and Hungerford's discovery of the Philadelphia chromosome in chronic myeloid leukemia (CML) [38], the first consistent chromosome change seen in human malignancy, clearly supports the notion that chromosomal abnormalities, especially translocations and their corresponding gene fusions, play an important role in the initiation of carcinogenesis. Fusion genes and the accompanying deregulation of oncogenes associated with chromosomal rearrangements have been extensively studied in hematological malignancies and soft tissue sarcomas [33], and can frequently be used to define tumor subtypes and predict prognosis. In last 10 years, the commonness and importance of fusion genes in carcinomas have also been revealed [39]. *TMPRSS2:ERG,* for instance, is the most frequently found fusion gene in human malignancies and occurs in about 50% of prostate cancer cases [2, 33]. However, in the case of chromosomal translocation and genomic fusion involving *NKAIN2*, this gene is inactivated rather than gain of function both in malignant and non-malignant diseases.

Translocation involving *NKAIN2* has been identified in both T-cell lymphoma and leukemia cell lines [26]. In a T-cell lymphoblastic lymphoma cell line, HT-1, *NKAIN2* was found to be fused to *SUSP1* (SUMO-1-specific protease), creating a *SUSP1-NKAIN2* chimeric gene. However, this fusion was not in frame, which led to the production of a abnormal SUPS1 protein and loss of NKAIN2 protein from this chromosome [26]. In an adult T-cell leukemia cell line, ATN-1, aberrant *NKAIN2* transcripts were produced and no chimeric gene was detected. Therefore, in both cases, the chromosomal rearrangements affecting this genomic region led to loss of function of *NKAIN2* [26]. Translocations of t(1;6)(q32.3;q22.3) and t(2;6)(q24.3;q22.31) with breakpoint at *NKAIN2* have been reported in developmental delay [35] and neurological disorders [28] respectively, and in both cases, the consequence is constitutional inactivation of the *NKAIN2* gene.

In our SNP array analysis of 71 samples from patients with prostate cancer, *NKAIN2* was truncated in 5 cases and deleted in 10 cases [25]. Importantly, in two of the five cases where *NKAIN2* was truncated, a small genomic deletion event occurred that covered nearly the entire gene but very little of the adjacent genomic regions [25]. This finding suggests that *NKAIN2* is also inactivated by not only chromosome deletion but also genomic truncation in prostate cancer. Further supporting this proposition, Kanishka Sircar *et al.* [40] have reported that *NKAIN2* is downregulated and deleted in castration-resistant prostate cancer (CRPC), which appears at the early stage of the development of castration resistance. These data support the hypothesis that *NKAIN2* is an important prostate cancer TSG in the frequently deleted 6q region.

In addition to chromosome loss, mutation and promoter methylation can also result in inactivation of TSG. The expression of NKAIN2 is downregulated in human brain and CNS cancer (Data from Oncomine database http://www.oncomine.org/resource/login). In addition, 80 mutations affecting the NKIAN2 coding region have been characterized and NKAIN2 gene mutation recurrence has been found in breast carcinoma (4/1233 samples), endometrioid carcinoma (4/494 samples), clear cell renal cell carcinoma (2/878 samples), lung adenocarcinoma (7/639 samples), lung squamous cell

carcinoma (4/531 samples), oesophagus adenocarcinoma (2/151 samples), skin malignant melanoma (13/526 samples), stomachadenocarcinoma (6/338 samples), bladder carcinoma (2/327 samples) (Data from COSMIC database http://cancer.sanger.ac.uk/cosmic and International Genome Cancer Consortium database http://dcc.icgc.org/). All these data reveals that NKAIN2 maybe a TSG inactivated in many types of human cancers.

However, based on the tissue type involved, *NKAIN2* may not only act as a TSG, but also promotes tumorigenesis in tissue types where it is required for cell proliferation, such as the neurons. In fact, Romania *et al*. revealed that *NKAIN2* expressed at high mRNA levels in affected siblings in peripheral blood and tumor samples, in a study involving an Italian family with three neuroblastoma patients [41]. Elevated *NKAIN2* was also detected in MYCN-amplified neuroblastoma cell lines, in the most aggressive neuroblastoma lesions and on the cell membranes of neuroblasts in the peripheral blood of a large cohort of neuroblastoma patients. These data indicate that *NKAIN2* contribute to neuroblastoma development and/or progression, which is consistent with its role in neuron cell growth.

Biological function of *NKAIN2* and its involvement in human diseases

The biological function of *NKAIN2* remains unclear. *NKAIN2* is transcribed in different splice variants and abundantly expressed in the brain tissues [27]. Several studies have suggested that *NKAIN2* is highly specific to the central nervous system and is necessary for nervous system health and development [28, 35, 42-44]. Bocciardi *et al.* described the characterization of a *de novo* balanced translocation, t(2;6)(q24.3;q22.31), in a patient with a severe neurologic phenotype that included epileptic encephalopathy with spastic tetraparesis, severe psychomotor retardation associated with cerebral atrophy and involvement of the periventricular white matter [28]. Calboli *et al.* analyzed 430,000 autosomal SNPs together with an additional 1.2 million SNPs with high estimated quality from the International Hap Map Project's CEU samples and demonstrated that neuroticism is one of the primary effects associated with SNPs in *NKAIN2* [42]. Yue *et al.* found that *NKAIN2* is disrupted in intron 4 by a *de novo* balanced translocation, t(1;6)(q32.2;q22.3), in a child with developmental delay and recurrent infections [35]. In an Australian twin-family based association analysis of alcohol dependence in the Collaborative Study on the Genetics of Alcoholism (COGA) study of two cohorts of Australian twins and their spouses, Wang *et al.* revealed that rs637547 in *NKAIN2* at 6q21 showed a strong association with alcohol dependence [43]. Lind *et al.* performed a meta-analysis of Australian and Dutch Data and found that rs594664 in the *NKAIN2* intron was the thirty most significant association with nicotine dependence, although it failed to reach genome-wide significance ($P = 2.63 \times 10^{-5}$) [44].

In addition to the strong expression in brain tissues [26, 35], *NKAIN2* was also expression in thymus [26], skeletal muscle [28], spinalcord, and ovary (Data from GeneCards http://www.genecards.org). However, the role of *NKAIN2* in those tissues is unknown. *NKAIN2* expression was detected in hematological malignancy cell lines but not those T cell derived malignant cell lines with *NKAIN2* truncation, suggesting its potential involvement in hematological cell differentiation, which is also supported by the recurrent infection in the case with constitutional t(1;6)(q32.2;q22.3) [35].

NKAIN2 in prostate cancer and the difference between Chinese and western populations

Despite numerous investigations into the molecular mechanisms underlying the pathogenesis of the disease, the genetic changes driving prostate cancer development and progression are incompletely characterized [45]. The chromosomal regions that are most commonly lost in prostate cancer are 1p, 6q, 8p21.2, 10p15, 10q21, 10q23.31, 12p12-13, 13q21, 16q22, 21q22.2 [2, 46]. Prostate cancer has been shown commonly to involve very complex chromosome rearrangements, which lead to many chromosome breakpoints and gene fusions, including the most common fusion gene in human malignancies, *TMPRSS2:ERG* [47, 48]. The fusions frequently involve the ETS family of transcription factors, which are placed under the control of genes highly active in prostate epithelial cells, predominately as *TMPRSS2*, but also including *SLC45A3*, *HERV-K_22q11.23*, *C15orf21,* and *HNRPA2B1* [49-52]. However, in our recent work, we found that

chromosome breakpoints in prostate cancer may more frequently lead to TSG inactivation than oncogene activation [25].

By analyzing 71 clinical prostate cancer cases and 6 prostate cancer cell lines using Affymetrix array 6.0 and 500K SNP microarrays, we identified many recurrent breakpoints ($n \geq 2$) and 41 located at known TSGs, oncogenes and genes previously identified as partner genes in gene fusion events. While the *ERG* and *TMPRSS2* genes were affected by the frequent breakpoints (identified in 18/77 and 15/77 cases, respectively), there was a preferential involvement of TSGs (n = 27) compared to oncogenes (n = 6) at the breakpoints [25]. *NKAIN2* was also recurrently truncated by chromosomal rearrangement [25]. Together with our unpublished data that *NKAIN2* was generally underexpressed in prostate cancer cell compare to adjacent non-malignant prostate tissues, it suggests that *NKAIN2* is potentially a TSG in prostate cancer.

Interestingly, *NKAIN2* was truncated in four of the 39 Chinese prostate cancer cases but not in any of the 32 cases from UK. Remarkable disparities of prostate cancer incidence and mortality exist among different racial groups and the prevalence of prostate cancer in Asian countries is much lower than that observed in Western countries [53-56]. In our previous study, we have revealed that deletions of chromosomes 21 (causing *TMPRSS2:ERG* and consequently *ERG* overexpression) and 10q (inactivating *PTEN*) in Chinese patients are far less common than those reported in Western populations [53, 57]. Magi-Galluzzi *et al*. confirmed the difference in *ERG* rearrangement frequency between Western and Asian patients [58]. We have also found that different ERG proteins are expressed in prostate cancer from UK or Chinese patients and that this difference was detected in prostate cancer precursor lesion, high-grade prostatic intraepithelial neoplasia [59]. *PTEN* is a well-characterized TSG, recurrently deleted as a result of chromosome rearrangements [60]. AKT pathway activation resulting from PTEN inactivity is a commonly detected phenomenon in prostate cancers from Western countries, particularly during the progression of cancer from localized tumors to metastatic cancer lesions [53]. However, the activation of the AKT pathway through the inactivation of PTEN may have limited contribution to Chinese prostate cancer [53]. While *TMPRSS2:ERG* gene fusion and *PTEN* loss were detected much less frequently in Chinese than Western prostate cancer, recently we also found a higher frequency of *BRAF* and *RAF1* alterations in Chinese patients with prostate cancer than was observed in their Western counterparts [61]. All those observations suggest that UK and Chinese prostate cancer tumorigenesis may result from different genetic mechanisms and loss of function of NKAIN2 may contribute more significantly to prostate carcinogenesis in Chinese than the Western population. In fact, deletion of 6q was also more frequent in prostate cancers in Chinese than Western men, although 6q deletion occurred at a high frequency in the prostate cancer in the Western population.

Future directions

Clearly, there are limited studies on *NKAIN2*. It has been found to be involved in the nervous system developmental and genetic alterations affect its function lead to developmental diseases and mental disorders [28, 35, 42-44]. There are several lines of evidence suggest that *NKAIN2* is potentially a TSG [25, 26, 40], but much more extensive investigations are required to confirm its tumor suppressor role. It is necessary to continue to study the chromosomal alterations of *NKAIN2* gene and the functional consequence of those genomic alterations in prostate cancer and other human cancers. *NKAIN2* is currently known as a transmembrane protein, which interacts with Na^+/K^+-ATPase. Apart from this, little is known of its cellular functions; therefore it is unclear how it may play the role to suppress tumor growth. Extensive biological study of the cellular function of NAKIN2 is urgently required, in particular its involvement in tumorigenesis pathways. Until the cellular and biological functions of *NKAIN2* revealed, we will not be able to use it for the diagnosis and treatment of related diseases.

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Disclosure of conflict of interest

None.

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References

[1] Boström PJ, Bjartell AS, Catto JW, Eggener SE, Lilja H, Loeb S, Schalken J, Schlomm T and Cooperberg MR Genomic Predictors of Outcome in Prostate Cancer. Eur Urol 2015; 68: 1033-44.

[2] Boyd LK, Mao X and Lu YJ. The complexity of prostate cancer: genomic alterations and heterogeneity. Nat Rev Urol 2012; 9: 652-664.

[3] Sun M, Srikantan V, Ma L, Li J, Zhang W, Petrovics G, Makarem M, Strovel JW, Horrigan SG, Augustus M, Sesterhenn IA, Moul JW, Chandrasekharappa S, Zou Z and Srivastava S. Characterization of frequently deleted 6q locus in prostate cancer. Dna Cell Biol 2006; 25: 597-607.

[4] Fabris VT. From chromosomal abnormalities to the identification of target genes in mouse models of breast cancer. Cancer Genet 2014; 207: 233-246.

[5] Capurso G, Festa S, Valente R, Piciucchi M, Panzuto F, Jensen RT and Delle Fave G. Molecular pathology and genetics of pancreatic endocrine tumours. J Mol Endocrinol 2012; 49: R37-R50.

[6] Maher ER. Genomics and epigenomics of renal cell carcinoma. Semin Cancer Biol 2013; 23: 10-17.

[7] Yen C, Liang S, Jong Y, Chen Y, Lin C, Chen Y, Wu Y, Su W, Huang CF, Tseng S and Whang-Peng J. Chromosomal aberrations of malignant pleural effusions of lung adenocarcinoma: Different cytogenetic changes are correlated with genders and smoking habits. Lung Cancer 2007; 57: 292-301.

[8] van den Hurk K, Niessen HE, Veeck J, van den Oord JJ, van Steensel MA, Zur Hausen A, van Engeland M and Winnepenninckx VJ. Genetics and epigenetics of cutaneous malignant melanoma: A concert out of tune. Biochim Biophys Acta 2012; 1826: 89-102.

[9] Bellini MF, Silva AE and Varella-Garcia M. Genomic imbalances in esophageal squamous cell carcinoma identified by molecular cytogenetic techniques. Genet Mol Biol 2010; 33: 205-213.

[10] Borchers CH, Kast J, Foster LJ, Siu KW, Overall CM, Binkowski TA, Hildebrand WH, Scherer A, Mansoor M and Keown PA. The Human Proteome Organization Chromosome 6 Consortium: Integrating chromosome-centric and biology/disease driven strategies. J Proteomics 2014; 100: 60-67.

[11] Honma K, Tsuzuki S, Nakagawa M, Tagawa H, Nakamura S, Morishima Y and Seto M. TNFAIP3/A20 functions as a novel tumor suppressor gene in several subtypes of non-Hodgkin lymphomas. Blood 2009; 114: 2467-2475.

[12] Konishi N, Shimada K, Ishida E and Nakamura M. Molecular pathology of prostate cancer. Pathol Int 2005; 55: 531-539.

[13] Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, Ishida E and Konishi N. Novel tumor suppressor loci on 6q22-23 in primary central nervous system lymphomas. Cancer Res 2003; 63: 737-741.

[14] Orphanos V, McGown G, Hey Y, Thorncroft M, Santibanez-Koref M, Russell SE, Hickey I, Atkinson RJ and Boyle JM. Allelic imbalance of chromosome 6q in ovarian tumours. Br J Cancer 1995; 71: 666-9.

[15] Smeds J, Wärnberg F, Norberg T, Nordgren H, Holmberg L and Bergh J. Ductal carcinoma in situ of the breast with different histopathological grades and corresponding new breast tumour events: Analysis of loss of heterozygosity. Acta Oncol 2005; 44: 41-49.

[16] Stark M and Hayward N. Genome-wide loss of heterozygosity and copy number analysis in melanoma using high-density single-nucleotide polymorphism arrays. Cancer Res 2007; 67: 2632-2642.

[17] Chen M, Ye Y, Yang H, Tamboli P, Matin S, Tannir NM, Wood CG, Gu J and Wu X. Genome-wide profiling of chromosomal alterations in renal cell carcinoma using high-density single nucleotide polymorphism arrays. Int J Cancer 2009; 125: 2342-2348.

[18] Maximin S, Ganeshan DM, Shanbhogue AK, Dighe MK, Yeh MM, Kolokythas O, Bhargava P and Lalwani N. Current update on combined hepatocellular-cholangiocarcinoma. European Journal of Radiology Open 2014; 1: 40-48.

[19] Namboodiripad PC. A review: Immunological markers for malignant salivary gland tumors. J Oral Biol Craniofac Res 2014; 4: 127-134.

[20] Sunamura M, Takeda K, Matsuno S, Yatsuoka T, Motoi F, Duda DG, Kimura M, Abe T, Yokoyama T, Inoue H and Oonuma M. Gene therapy for pancreatic cancer based on genetic characterization of the disease. J Hepatobiliary Pancreat Surg 2002; 9: 32-38.

[21] Correa P, Juhlin C, Rastad J, Akerstr M GR, Westin G and Carling T. Allelic loss in clinically and screening-detected primary hyperparathyroidism. Clin Endocrinol 2002; 56: 113-117.

[22] Roh YS, Song J and Seki E. TAK1 regulates hepatic cell survival and carcinogenesis. J Gastroenterol 2014; 49: 185-194.
[23] Zhou Y, Zhang X and Klibanski A. Genetic and epigenetic mutations of tumor suppressive genes in sporadic pituitary adenoma. Mol Cell Endocrinol 2014; 386: 16-33.
[24] Visser S and Yang X. LATS tumor suppressor: A new governor of cellular homeostasis. Cell Cycle 2010; 9: 3892-3903.
[25] Mao X, Boyd LK, Yanez-Munoz RJ, Chaplin T, Xue L, Lin D, Shan L, Berney DM, Young BD and Lu Y. Chromosome rearrangement associated inactivation of tumour suppressor genes in prostate cancer. Am J Cancer Res 2011; 1: 604-617.
[26] Tagawa H, Miura I, Suzuki R, Suzuki H, Hosokawa Y and Seto M. Molecular cytogenetic analysis of the breakpoint region at 6q21-22 in T-cell lymphoma/leukemia cell lines. Genes Chromosomes Cancer 2002; 34: 175-185.
[27] Gorokhova S, Bibert S, Geering K and Heintz N. A novel family of transmembrane proteins interacting with subunits of the Na, K-ATPase. Hum Mol Genet 2007; 16: 2394-2410.
[28] Bocciardi R, Giorda R, Marigo V, Zordan P, Montanaro D, Gimelli S, Seri M, Lerone M, Ravazzolo R and Gimelli G. Molecular characterization of a t(2;6) balanced translocation that is associated with a complex phenotype and leads to truncation of the. Hum Mutat 2005; 26: 426-436.
[29] Barnier JV, Papin C, Eychène A, Lecoq O and Calothy G. The mouse B-raf gene encodes multiple protein isoforms with tissue-specific expression. J Biol Chem 1995; 270: 23381-23389.
[30] Hindley A and Kolch W. Extracellular signal regulated kinase (ERK)/mitogen activated protein kinase (MAPK)-independent functions of Raf kinases. J Cell Sci 2002; 115: 1575-1581.
[31] Mercer KE and Pritchard CA. Raf proteins and cancer: B-Raf is identified as a mutational target. Biochim Biophys Acta 2003; 1653: 25-40.
[32] Wellbrock C, Karasarides M and Marais R. The RAF proteins take centre stage. Nat Rev Mol Cell Biol 2004; 5: 875-885.
[33] Mitelman F, Johansson B and Mertens F. The impact of translocations and gene fusions on cancer causation. Nat Rev Cancer 2007; 7: 233-245.
[34] Zhang C, Leibowitz ML and Pellman D. Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. Gene Dev 2013; 27: 2513-2530.
[35] Yue Y, Stout K, Grossmann B, Zechner U, Brinckmann A, White C, Pilz DT and Haaf T. Disruption of TCBA1 associated with a de novo t(1;6)(q32.2;q22.3) presenting in a child with developmental delay and recurrent infections. J Med Genet 2006; 43: 143-147.
[36] Alberti L, Carniti C, Miranda C, Roccato E and Pierotti MA. RET and NTRK1 proto-oncogenes in human diseases. J Cell Physiol 2003; 195: 168-186.
[37] Bystritskiy AA and Razin SV. Breakpoint clusters: Reason or consequence? Crit Rev Eukar Gene 2004; 14: 65-77.
[38] Nowell PC. A minute chromosome in human chronic granulocytic leukemia. Science 1960; 132: 1497.
[39] Qi M, Li Y, Liu J, Yang X, Wang L, Zhou Z, Han B. Morphologic features of carcinomas with recurrent gene fusions. Adv Anat Pathol 2012; 19: 417.
[40] Sircar K, Huang H, Hu L, Cogdell D, Dhillon J, Tzelepi V, Efstathiou E, Koumakpayi IH, Saad F, Luo D, Bismar TA, Aparicio A, Troncoso P, Navone N and Zhang W. Integrative Molecular Profiling Reveals Asparagine Synthetase Is a Target in Castration-Resistant Prostate Cancer. Am J Pathol 2012; 180: 895-903.
[41] Romania P, Castellano A, Surace C, Citti A, De Ioris MA, Sirleto P, De Mariano M, Longo L, Boldrini R, Angioni A, Locatelli F and Fruci D. High-Resolution Array CGH Profiling Identifies Na/K Transporting ATPase Interacting 2 (NKAIN2) as a Predisposing Candidate Gene in Neuroblastoma. PLoS One 2013; 8: e78481.
[42] Calboli FCF, Tozzi F, Galwey NW, Antoniades A, Mooser V, Preisig M, Vollenweider P, Waterworth D, Waeber G, Johnson MR, Muglia P and Balding DJ. A Genome-Wide Association Study of Neuroticism in a Population-Based Sample. PLoS One 2010; 5: e11504.
[43] Wang K, Liu X, Aragam N, Jian X, Mullersman JE, Liu Y and Pan Y. Family-based association analysis of alcohol dependence in the COGA sample and replication in the Australian twin-family study. J Neural Transm 2011; 118: 1293-1299.
[44] Lind PA, Macgregor S, Vink JM, Pergadia ML, Hansell NK, de Moor MH, Smit AB, Hottenga JJ, Richter MM, Heath AC, Martin NG, Willemsen G, de Geus EJ, Vogelzangs N, Penninx BW, Whitfield JB, Montgomery GW, Boomsma DI and Madden PA. A Genomewide Association Study of Nicotine and Alcohol Dependence in Australian and Dutch Populations. Twin Res Hum Genet 2010; 13: 10-29.
[45] Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K, Sivachenko AY, Sboner A, Esgueva R, Pflueger D, Sougnez C, Onofrio R, Carter SL, Park K, Habegger L, Ambrogio L, Fennell T, Parkin M, Saksena G, Voet D, Ramos AH, Pugh TJ, Wilkinson J, Fisher S, Winckler W, Mahan S, Ardlie K, Baldwin J, Simons JW, Kitabayashi N, MacDonald TY, Kantoff PW, Chin L, Gabriel SB, Gerstein MB, Golub TR, Meyerson M, Tewari A, Lander ES, Getz G, Rubin MA and Garraway LA. The genomic complexity of primary human prostate cancer. Nature 2011; 470: 214-220.

[46] Barbieri CE, Bangma CH, Bjartell A, Catto JWF, Culig Z, Grönberg H, Luo J, Visakorpi T and Rubin MA. The Mutational Landscape of Prostate Cancer. Eur Urol 2013; 64: 567-576.
[47] Mao X, James SY, Yanez-Munoz RJ, Chaplin T, Molloy G, Oliver RTD, Young BD and Lu Y. Rapid high-resolution karyotyping with precise identification of chromosome breakpoints. Gene Chromosome Canc 2007; 46: 675-683.
[48] van Bokhoven A, Caires A, Maria MD, Schulte AP, Lucia MS, Nordeen SK, Miller GJ and Varella-Garcia M. Spectral karyotype (SKY) analysis of human prostate carcinoma cell lines. Prostate 2003; 57: 226-244.
[49] Maher CA, Kumar-Sinha C, Cao X, Kalyana-Sundaram S, Han B, Jing X, Sam L, Barrette T, Palanisamy N and Chinnaiyan AM. Transcriptome sequencing to detect gene fusions in cancer. Nature 2009; 458: 97-99.
[50] Esgueva R, Perner S, LaFargue CJ, Scheble V, Stephan C, Lein M, Fritzsche FR, Dietel M, Kristiansen G and Rubin MA. Prevalence of TMPRSS2-ERG and SLC45A3-ERG gene fusions in a large prostatectomy cohort. Modern Pathol 2010; 23: 539-546.
[51] Pflueger D, Rickman DS, Sboner A, Perner S, LaFargue CJ, Svensson MA, Moss BJ, Kitabayashi N, Pan Y, de la Taille A, Kuefer R, Tewari AK, Demichelis F, Chee MS, Gerstein MB and Rubin MA. N-myc Downstream Regulated Gene 1 (NDRG1) Is Fused to ERG in Prostate Cancer. Neoplasia 2009; 11: 113-804.
[52] Pflueger D, Terry S, Sboner A, Habegger L, Esgueva R, Lin P, Svensson MA, Kitabayashi N, Moss BJ, MacDonald TY, Cao X, Barrette T, Tewari AK, Chee MS, Chinnaiyan AM, Rickman DS, Demichelis F, Gerstein MB and Rubin MA. Discovery of non-ETS gene fusions in human prostate cancer using next-generation RNA sequencing. Genome Res 2011; 21: 56-67.
[53] Mao X, Yu Y, Boyd LK, Ren G, Lin D, Chaplin T, Kudahetti SC, Stankiewicz E, Xue L, Beltran L, Gupta M, Oliver RTD, Lemoine NR, Berney DM, Young BD and Lu Y. Distinct Genomic Alterations in Prostate Cancers in Chinese and Western Populations Suggest Alternative Pathways of Prostate Carcinogenesis. Cancer Res 2010; 70: 5207-5212.
[54] Mahal BA, Aizer AA, Ziehr DR, Hyatt AS, Choueiri TK, Hu JC, Hoffman KE, Sweeney CJ, Beard CJ, D'Amico AV, Martin NE, Kim SP, Quoc-Dien T and Nguyen PL. Racial Disparities in Prostate Cancere-Specific Mortality in Men With Low-Risk Prostate Cancer. Clin Genitourin Cancer 2014; 12: E189-E195.
[55] Sim HG and Cheng C. Changing demography of prostate cancer in Asia. Eur J Cancer 2005; 41: 834-845.
[56] Gronberg H. Prostate cancer epidemiology. Lancet 2003; 361: 859-864.
[57] Mani RS and Chinnaiyan AM. Triggers for genomic rearrangements: insights into genomic, cellular and environmental influences. Nat Rev Genet 2010; 11: 819-829.
[58] Magi-Galluzzi C, Tsusuki T, Elson P, Simmerman K, LaFargue C, Esgueva R, Klein E, Rubin MA and Zhou M. TMPRSS2-ERG Gene Fusion Prevalence and Class Are Significantly Different in Prostate Cancer of Caucasian, African-American and Japanese Patients. Prostate 2011; 71: 489-497.
[59] Xue LY, Mao XY, Ren GP, Stankiewicz E, Kudahetti SC, Lin DM, Beltran L, Berney DM and Lu YJ. Chinese and Western prostate cancers show alternate pathogenetic pathways in association with ERG status. Am J Cancer Res 2012; 2: 736-744.
[60] Hollander MC, Blumenthal GM and Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nat Rev Cancer 2011; 11: 289-301.
[61] Ren G, Liu X, Mao X, Zhang Y, Stankiewicz E, Hylands L, Song R, Berney DM, Clark J, Cooper C and Lu Y. Identification of frequent BRAF copy number gain and alterations of RAF genes in chinese prostate cancer. Gene Chromosome Cancer 2012; 51: 1014-1023.