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Current Genomics, 2013, *14*, 425-440 425

NBN Gene Polymorphisms and Cancer Susceptibility: A Systemic Review

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Abstract: The relationship between DNA repair failure and cancer is well established as in the case of rare, high penetrant genes in high cancer risk families. Beside this, in the last two decades, several studies have investigated a possible association between low penetrant polymorphic variants in genes devoted to DNA repair pathways and risk for developing cancer. This relationship would be also supported by the observation that DNA repair processes may be modulated by sequence variants in DNA repair genes, leading to susceptibility to environmental carcinogens. In this framework, the aim of this review is to provide the reader with the state of the art on the association between common genetic variants and cancer risk, limiting the attention to single nucleotide polymorphisms (SNPs) of the *NBN* gene and providing the various odd ratios (ORs). In this respect, the NBN protein, together with MRE11 and RAD50, is part of the MRN complex which is a central player in the very early steps of sensing and processing of DNA double-strand breaks (DSBs), in telomere maintenance, in cell cycle control, and in genomic integrity in general. So far, many papers were devoted to ascertain possible association between common synonymous and non-synonymous *NBN* gene polymorphisms and increased cancer risk. However, the results still remain inconsistent and inconclusive also in meta-analysis studies for the most investigated E185Q NBN miscoding variant.

Received on: June 29, 2013- Revised on: August 30, 2013- Accepted on: September 02, 2013

Keywords: NBN, Polymorphisms, Cancer, DNA repair, DSBs, E185Q, SNPs.

1. INTRODUCTION

NBN (formerly known as NBS1) is a protein of 754 amino acid composed of three regions: the *N*-terminus (containing a forkhead associated domain (FHA) and two breast cancer 1 (BRCA1) carboxy-terminal (BRCT) tandem domains), a central region (containing sites phosphorylated by the Ataxia-Telangiectasia Mutated (ATM) kinase), and the *C*-terminus (containing the MRE11- and ATM-binding domains) [1-11]. The NBN protein is a member of the MRE11/RAD50/NBN (MRN) complex, which is involved in nearly all aspects of the DNA double-strand break (DSB) metabolism, from lesion recognition, to DNA repair by both non-homologous end-joining (NHEJ) and homologous recombination repair (HRR) pathways, to cell cycle control [12-18]. Remarkably, DNA damage may arise as the consequence of physiological cellular metabolism or produced by the exposure to environmental pollutants [19-21]. As a consequence of the pivotal role of the MRN complex in the maintenance of genomic stability, any genetic variation of the *NBN* gene may have detrimental effects on cells capability to properly face with DNA damage, and consequently may predispose to cancer and to the genetic disease named Nijmegen Breakage Syndrome (NBS) [13, 22-24].

NBS is an autosomal recessive disorder characterized by microcephaly, immunodeficiency, spontaneous chromosomal instability, sensitivity to ionizing radiations and a high incidence of malignancy [25-27]. Cancer, and in particular malignancy of lymphoid origin, is the primary cause of death among NBS affected individuals. More than 70% of the malignancies were non-Hodgkin lymphoma [28-32], though solid tumours as medulloblastoma [33-35], rabdomiosarcoma of the perianal region [36], melanoma [37], breast [38-41], prostate [42], ovarian [43], lung [44] and colorectal cancers [45] were also represented.

The most common *NBN* mutation is due to the deletion of five base pairs (bps) in exon 6 (657del5), which leads to protein truncation. In addition to this mutation, which affects mostly Central Europe populations, at least 11 other truncating and missense mutations have been reported so far in NBS patients [2, 46-53]. Interestingly, some evidences point to a possible correlation between cancer risk and *NBN* at the heterozygous status, as it occurs in blood relatives of NBS patients [22, 23]. Furthermore, such a relationship has been corroborated by additional studies which identified carriers for the *NBN* 657del5, R215W and I171V mutations overrepresented in cancer patients [23, 30-32, 37, 41, 54-62]. The observation that in tumors recovered from NBN carriers the inactivating mutation was not detected on the second allele, seems to suggest a dominant negative mechanism. Such an effect in *NBN* monoallelic mutated tumors could be due to truncated NBN proteins as result of an alternative NBN translation [9, 63].

2. *NBN* SINGLE NUCLEOTIDE POLYMORPHISMS AND CANCER RISK

Beside classical miscoding mutations associated with either clinical signs of the NBS disorder or a functionally

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1875-5488/13 $58.00+.00 ©2013 Bentham Science Publishers

alterated NBN protein, a certain number of both low- and high-frequency polymorphisms have been reported to be distributed over the 16 exons of the *NBN* gene. According to the Environmental Genome Project (EGP), so far 675 single nucleotide polymorphisms (SNPs) have been reported for the *NBN* gene [64]. Among them, 84 are considered common based on a minor allele frequency of >5% [65]. As for *NBN* mutations, also for *NBN* gene polymorphisms acting as slow-penetrance genes a possible association with different kinds of malignancy has been evaluated in the last 15 years, in that DNA polymorphisms may bring to subtle structural alterations of proteins and consequently modulation of cancer susceptibility. In (Table **1**) is reported a list of a selected panel of *NBN* genetic variants, their effects on amino acid change, and their localization into protein's domains.

Here we provide the reader with the state of the art on this topic, limiting the attention to SNPs of the sole *NBN* gene, though in many of the presented works a large panel of polymorphisms in gene involved in DNA repair, cell cycle control, and metabolism of genotoxics was also investigated. The risk of cancer associated with *NBN* SNPs appears to differ by cancer type. In particular, based on the published papers, the association of *NBN* SNPs has been restricted to a panel of hematological and solid tumors (Table **1** and **2**).

2.1. Basal Cell Carcinoma

Basal cell carcinoma (BCC) is considered the most common neoplasia of the skin, accounting for more than 75% of all skin malignancies [66, 67]. Though locally invasive and slow-growing, BCC is characterized by recurrence and tissue destruction [68]. Regarding the etiology of BCC, it has been proposed that both genetic factors and environmental determinants, as exposure to ultraviolet (UV) radiation, may contribute to the development of this kind of cancer [69, 70]. Therefore, genes whose products are enzymes involved in the removal of DNA lesions introduced by UV-light exposure may play a critical role in the etiology of BCC. In this respect, non-synonymous SNPs known for their potential capability to modulate gene functions are worth to be analysed [71].

The association of the rs1805794 *NBN* genetic variant with BBC risk was assessed in two case-control studies on Caucasian individuals in Europe. The first one comprised cohorts of patients (241) and controls (574) from Sweden and Finland [72]. Genotype distributions for the common rs1805794 variant were in accordance with those expected from Hardy-Weinberg equilibrium. No differences between controls and carriers of the rs1805794 *NBN* variant were observed with respect to BCC risk [72].

The second study, considered one of the largest association study, was conducted on a cohort of 529 BCC patients from Central Europe countries (*i.e.*, Hungary, Romania, and Slovakia) and 533 matched healthy control individuals [73]. Also in this study, the only polymorphism analyzed for a possible association with BCC was the rs1805794. No deviation from Hardy-Weinberg equilibrium distribution was detected for cases and controls. Interestingly, the authors found a gender relationship between the *NBN* SNP and BCC, in that in men homozygous for the C-allele an odd ratio (OR) of 2.19 (95% CI, 1.23-3.91) was calculated, whereas in women the calculated OR was 0.84. In addition, a multiplicative gene-gene interaction effect was found on the BCC risk association among men carrying the genotype CC *XRC3*/CC *NBN*, with an OR reaching the value of 8.79 (95% CI, 2.10-36.8), compared to the genotype TT *XRC3*/GG *NBN* [73].

2.2. Bladder Cancer

Urinary bladder cancer ranks ninth in worldwide cancer incidence, and particularly it represents the seventh most common malignancy in men and the seventeenth in women [74-77]. Some risk factors for bladder cancer have been recognized in environment exposure to aromatic amines, cigarette smoking exposure and uptake of several compounds as phenacetin and cyclophosphamide [78, 79]. However, a growing body of evidence has emerged indicating that culture-mediated and socioeconomic factors contribute substantially to the etiology of bladder tumors and may play an even more important role than the occupational environment [80].

The exposure to environmental agents and by-products of cellular metabolism results in DNA damage, which, if left un-repaired, can lead to carcinogenesis [81, 82]. A certain number of studies have been conducted in order to establish an association between urinary bladder cancer risk and genetic polymorphisms for a large panel of genes involved in DNA repair (*e.g.*, *BRCA1*, *RAD51*, *XPC*, *XPD*, *XRCC1*, *XRCC2*, *XRCC3*, *XRCC4*, etc), in the metabolism of genotoxic carcinogens (*e.g.*, *GSTT1*, *NAT1*, *NAT2*, *NQO1*, *MTHFR*, etc), and in cell cycle control (*e.g.*, *cyclin D1*) [83-93]. In particular, only few studies have analyzed the possible role of the *NBN* genetic variants in cancer susceptibility. In a case-control study in which 299 Caucasian bladder cancer patients from hospitals in the Stockholm area and 278 matched controls were gathered, the genotype distribution of SNPs was in accordance with Hardy Weinberg equilibrium, and the frequency of the common rs1805794 SNP in CC homozygous condition, between healthy controls and bladder cancer cases indicated a marginal significant difference (OR 1.64, 95% CI, 0.92-2.90, P=0.09) [82]. No association was detected between 1086 Caucasian bladder cancer patients and 1020 controls with respect to four *NBN* genetic variants (*i.e.*, rs1063045, rs1805794, rs867185, rs1063053) [88]. Similarly, in a case-control study on 771 bladder cancer cases and 800 controls of both Caucasian and non-Caucasian ethnicity, the association of bladder cancer risk with nine NBN variants, located at the 3'-UTR (*i.e.*, rs14448, rs9995, rs13312986, rs1063054, rs13312981, rs2735383, rs1063053) and in coding regions (*i.e.*, rs1805794, rs769420) was evaluated [90].

2.3. Breast Cancer

Brest cancer is the most common form of cancer among women, for which both genetic and environmental factors have been reported [94]. Although the cause of breast cancer is still obscure in the majority of cases, for a significant fraction of cases the age at the first child's birth and the family history represent well-established risk factors [95]. Remarkably, it has been also reported that breast cancer patients might be deficient in the repair of DNA damage [96]. Indeed, approximately 5% to 10% of breast cancers are

Table 1. *NBN* Gene Polymorphisms Reported in the Paper

Database SNP ID	Polymorphism	Exon/intron	Amino Acid Substitution	Location in the Protein
rs13312842	c.-905T>C; NBS1_5(-905)T/C	5'UTR		
	924T>C°	5'UTR		
rs36226237	c110242delAGTA; NBS1_5UTR_(-352)_del(AGTA)	5'UTR		
rs1063045	102G>A; Ex2+65G>A; NBSI_X2_(102)_G/A;	Exon 2	L34L	FHA
rs1805796	c.320+208G>A	Intron 3		
rs1805794	553G >C; 8360G>C; EX6-32G>C; NBSI_X5_(553)_G/C	Exon 5	E185Q	BRCT1
rs61754796	c.628G>T	Exon 6	V210F	Tandem BRCT linker region
rs769420	797C>T	Exon 7	P266L	BRCT2
rs1805790	c.994+1937A>G	Intron 8		
rs867185	IVS9+1488C>T	Intron 8		
rs2234744	c.1124+18C>T; IVS9+18C/T	Intron 9		
rs1805818	c.1124+91C>A; ISV9+91C/A	Intron 9		
	30537G>C°	Intron 9		
rs709816	c.1197T>C	Exon 10	D399D	Downstream of tandem BRCT domains
rs2308962	c.1915-7A>G; IVS12-7A>G	Intron 12		
rs3736639	c.2071-30A>T	Intron 13		
rs3736640	c.2071-61A>T; IVS13-61A/T	Intron 13		
rs1061302	c.2016A>G; NBSI_X13_(2016)_A/G	Exon 13	P672P	MRE11 binding domain
rs1063053	c.*273G>A; EX17+304G>A; NBSI_3UTR_(+27)_G/A	3' UTR		
rs2735383	c.*541G>C	3'UTR		
rs13312981	c.*757A>G	3'UTR		
rs1063054	c.*1209A>C	3'UTR		
rs13312986	c.*1692A>G	3'UTR		
rs9995	c.*1754T>C	3'UTR		
rs14448	c.*1977T>C	3'UTR		

° rs number not available in the database.

related to an inherited gene mutation. Of these cases, 84% of hereditary breast cancers and more than 90% of hereditary ovarian cancers are caused by mutations in either *BRCA1* or *breast cancer 2* (*BRCA2*) genes. Familial aggregation involving genes other than *BRCA1* and *BRCA2* seems to be the result of the additive effect of multiple low penetrant genes [97]. Overall, pathogenic mutations in *TP53, ATM, CHEK2, BRIP1* and *PALB2*, together with *BRCA1* and *BRCA2* mutations, account for less than 20-25% of the excess familial risk of breast cancer, thus supporting the notion that also other cancer susceptibility genes may play a role in the pathogenesis of breast cancer. Based on the recognized role of both BRCA1 and BRCA2 in different aspects of DSBs damage response and repair [98], many association studies have been carried out with respect to genes involved in the NHEJ and HRR repair, and particular between *NBN* and breast cancer risk. Indeed, several SNPs identified in genes involved in the HRR pathway (*e.g.*, *XRCC2*, *XRCC3*, *NBN*, and *RAD51*) may influence the repair capacity of breast cancer patients and, in turn, confer genetic predisposition to disease [99].

Table 2. Association of Individual *NBN* Polymorphisms and Cancer Risk

	Population	n° cases	n° controls	Polymorphisms and association (OR) reported as significant	References
Basal Cell Carcinoma	Caucasian Caucasian	241 529	574 533	No (rs1805794) 2.19 Men (rs1805794CC), No women (rs1805794)	[72] [73]
Bladder	Caucasian Caucasian Mixed	299 1086 771	278 1020 800	1.64 (rs1805794 CC) No (rs1063045, rs1805794, rs867185, rs1063053) No (rs14448, rs9995, rs13312986, rs1063054, rs133312981, rs2735383, rs1063053)	[82] [89] [90]
Breast	Caucasian Caucasian Afroamerican Caucasian Chinese Caucasian Afroamerican Caucasian Caucasian Taiwanese Non-hispanic Caucasian	2205 223 766 1273 220 336 63 97 289 559 421	1826 319 681 1136 310 416 78 74 548 1125 423	No (rs1063045, rs1805794, rs709816, rs1061302) No (rs1805794) No (rs1805794) No (rs1805794) No (rs1805794) No (rs1805794) Significant trend (rs1805794) No (rs1805794), 3.4 (rs36226237) No (rs1805794) No (rs1805794) No (rs1805794, rs1061302, rs1063045), 1.2 (rs1805790 GG) 1.3 (rs1805794 GG) 1.83 (rs1805794 CC), 4.5 (rs924 CC)	[100] [102] [101] [101] [103] [104] [104] [105] [95] [106] [107]
Colorectal	Caucasian	532	532	No (rs1805794)	[111]
Head and Neck	Caucasian Chinese	175 1052	275 1168	No (rs1063045, rs2234744, rs709816, rs1061302, rs3736639) 1805794GC lower in laryngeal cancer No (rs2735383)1.7 (rs1805794 CC) 3.7 (rs1805794 GC) East China No (rs2735383)1.5 (rs1805794CC) 3.9 (rs1805794GC) South China	[116] [126]
Hepatic Cancer	Chinese	865	900	1.4 (rs1805794 GC) 2.27 (rs1805794 CC) No (rs2735383)	[132]
Leukaemia	Caucasian Chinese Chinese	157 175 428	275 360 600	No (rs1063045, rs1805794, rs709816, rs1061302, rs2234744) 1.8 (rs376639 TT) 3.4 (rs1805794 CC), No (rs2735383) 1805794 CC as reference GG e GC were associated with decreased risk of cancer, No (rs2735383)	[148] [65] [149]
Lymphoma	NI Mixed Mixed	91 797 200	154 793 220	No (rs1063045, rs1805794, rs2234744, rs709816, rs1061302, rs2308962) No (rs13312842, rs36226237, rs1805796, rs1063053, rs1063045, rs1805794, rs1061302) No (rs1805794)	[28] [145] [146]
Lung	Mixed Chinese Caucasian Caucasian	611 1559 343 177	1040 1679 413 154	1.6 (rs1061302GG), 1.6 (rs1063054) No (rs14448,13312986) 1.4 (rs2735383 CC recessive model) 1.7 (rs2735383 CC recessive model for never smokers) No (rs1805794) 2.2 non-smoking women, 1.5 low-dose smoking women (rs 805794)	[160] [64] [199 [200]
Medulloblastoma	NI	42 tumor samples	-	No (rs1063045, rs709816, rs1061302, rs1805794, rs2234744, rs1805818, rs2308962, rs3736640)	[168]
Melanoma	Caucasian	632	615	No (rs9995, rs867185, rs1063045)	[37]

(Table 2) contd….

	Population	n° cases	n° controls	Polymorphisms and association (OR) reported as significant	References
Ovarian	Caucasian	643-732	1246-1695	No (rs1063045, rs1805794, rs769420, rs1061302)	[182]
Prostate	Caucasian Caucasian	200 239 early cancer 186 advanced cancer	200 NI	No (rs1805794) No (rs1805794) 1.8 (rs1805794 GG)	[57] [186]
Renal Cell Carcinoma	Caucasian	326	335	2.13 (rs1805794 CC)	[190]
Thyroid Cancer	Caucasian	109	217	No (rs1805794)	[191]

Abbreviations: NI: not indicated; No: no significant association found; OR: odds ratio.

In this respect, any association for the rs1063045, rs1805794, rs709816, and rs1061302 *NBN* SNPs was found in 2205 Caucasian patients and 1826 controls (age range 45-74 years) [100]. In a similar way, no association was found between the rs1805794 polymorphism and breast cancer risk in another hospital-based study performed on 766 African-American (681 matched controls) and 1273 Caucasian women with breast cancer (1136 matched controls) (age range 21-74 years) [101].

In a series of other relatively small studies, conducted on 221 Finnish sporadic breast cancer patients and Poland familial cases [102], 220 Chinese population patients [103], 336 Caucasian patients [104], 97 cases selected from high-risk families from the French-Canadian population [105], and 289 Caucasian Portuguese patients [95], no association between the rs1805794 and breast cancer risk was reported.

On the contrary, a certain number of studies pointed to a significant association between *NBN* gene variants and sporadic breast cancer risk. A study carried out in the genetic homogeneous Taiwanese population analyzed the rs1805794, rs1805790, rs709816, rs1061302, and rs1063045 SNPs of the *NBN* gene in 559 female breast cancer patients and 1125 healthy female controls [106]. In this study, a significant 1.29-fold increase in risk (95%, CI 1.00-1.69) was reported for the only rs1805790 variant in the form of the GG homozygous genotype [106].

The rs36226237 promoter variant was found significantly increased in a cohort of 97 high-risk non-*BRCA1* and non-*BRCA2* breast cancer families from the French-Canadian population compared with 74 unrelated healthy controls from the same origin [105]. In another study, the rs1805794, 924T>C*, and 30537G>C* *NBN* genetic variants were analyzed in a hospital-based case-control study of 421 relatively young non-Hispanic Caucasian women (≤55 years: range 22-55 years). An association of the variant rs1805794GG (in an allele-dose response manner; GC OR: 1.33, 95% CI 1.00-1.78; CC OR: 1.83, 95% CI 1.14-2.94) and of carriers of the homozygote rare variant 924CC (OR: 4.55, 95% CI 1.51-13.7) with breast cancer risk was found [107]. Such an association was also found for haplotype analysis in allele/dose response manner, but not for the 30537G>C polymorphism. A similar result, showing a significant trend of breast cancer risk with increasing numbers of GC/CC genotypes of the rs1805794 variant in a very small sample of African-American patients (63 cases and 78 controls) was reported [104].

2.4. Colorectal Cancer

Colorectal cancer is a common neoplasia in both men and women, and ranks as the second worldwide [108, 109]. In the last decades the incidence is greatly increased in Europe, and in particular in the central Europe region, with Czech Republic having the highest rate in the world for rectal cancer and the third highest incidence for colorectal cancers [109-111]. Colorectal cancer may occur in three different forms, and namely: the sporadic form (about 85% of cases), the familial form (less than 10%) and the form transmitted as a Mendelian trait (5%), which include familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) [112]. In the etiopathology of the sporadic form of the malignancy, both genetic and environmental factors, as diet, drinking and smoking habits, seem to play a relevant role [113, 114]. Other factors (*e.g*., genetic variants with low penetrance) may be involved in the modulation of colorectal risk. Indeed, with respect to a possible association between *NBN* polymorphisms and the risk of colorectal cancer, only one case-control study carried out in 532 Caucasian cases and 532 control in Czech Republic and restricted to the rs1805794 *NBN* genetic variant was found in the literature [111]. Genotype frequencies in control cases were tested for their accordance with Hardy-Weinberg expectation. The OR for the three genotypic combinations of the *NBN* SNP showed no association with the risk of colorectal cancer [111].

2.5. Head and Neck Tumors

Excluding skin and thyroid cancers, virtually all carcinomas that occur in the head and neck region arise within the upper aerodigestive tract and connected adenexal structures. Taken together, carcinomas of the upper aerodigestive tract, also termed head and neck cancer, account for only 3.2% of all incident malignancies in the United States [115] and for approximately 5% of all newly diagnosed cancer cases in the northern and Western European countries [116]. The overwhelming majority of these head and neck cancers are head and neck squamous cell carcinomas (HNSCC) with most of

* For these two *NBN* variants the rs numbers are not available.

the remainder being salivary gland carcinomas. To better understand etiologic associations and clinical management/outcomes, head and neck cancers are subcategorized by their site of origin and annually account for approximately 17,000 cancers of the oral cavity, 10,000 of the larynx, 10,000 of the oropharynx, and 2500 of the hypopharynx [115, 117, 118]. Despite recent advances in the diagnosis and treatment of HNSCC, survival rates of patients affected by these tumors still remain at low levels (40% to 50%) [116]. Smoking and alcol drinking are recognized as relevant factor in the development of HNSCC, though some genetic factors have been invoked to explain individual differences in susceptibility. In a study carried out on 175 Polish men patients with a single laryngeal cancer (*i.e.*, 104 patients with multiple tumors in the larynx and 60 patients with multiple primary tumors localized in the head and neck region excluded laryngeal cancer) together with 275 healthy controls, a possible association between 6 *NBN* SNPs and head and neck cancer risk was tested [116]. The *NBN* genetic variants analysed were both synonymous and non-synonymous (*i.e.*, rs1063045, rs1805794, rs2234744, rs709816, rs1061302, rs3736639). The genotypes distributions were tested for its accordance with Hardy-Weinberg expectation. The frequency of the *NBN* rs1805794 variant genotype at the GC heterozygous status was significantly lower in laryngeal cancer (OR: 1.79, CI 95%, 1.18-2.70, p=0.0055) and multiple cancer patients (excluded laryngeal cancer) with respect to normal controls (OR: 2.03, CI 95%, 1.09-3.78, p = 0.0234). In a similar way, the C allele (GC+CC) was less represented in patients with laryngeal tumor (49% versus 60% in controls, p=0.029, OR 1.52). The rs2234744 SNP frequency was 48% CT and 62% CT+TT in controls vs 30% CT and 15% CT+TT in patients with multiple cancer patients (excluded laryngeal cancer). The calculated differences were statistically significant with an OR value of 2.28 (p=0.008) and 1.97 (p=0.016), respectively. The heterozygous genotype AG of the rs1061302 variant was more common in controls (46%) than in patients affected with laryngeal cancer (34%; OR: 1.65, 95% CI 1.09-2.50, p=0.017). Similar was the situation for the AT genotype of the rs3736639 which was more represented among controls (47%) compared with laryngeal cancer group (34%, OR: 1.64, 95% CI 1.08-2.48, p= 0.018). On the contrary, no association between the remaining *NBN* polymorphisms and the three groups of patients were found [116].

Among head and neck cancers, nasopharyngeal carcinoma (NPC) is considered a leading cause of death in South China, and is characterized by a high incidence of nodal and distant metastasis [119]. Beside environmental factors as drinking, smoking, nitrosamines, and salty food, the main etiological factor seems to be Epstein-Barr virus infection [120-125]. Individual genetic susceptibility in genes devoted to the maintenance of genome stability has been invoked as a possible contributor in the development of NPC. A multiple-center case-control study was performed to assess the association between the rs1805794 and rs2735383 (located at the 3'-UTR of *NBN*) SNPs and NPC risk in 1052 ethnically homogeneous cases drawn from the Eastern and Southern Chinese population and 1168 controls [126]. Hardy-Weinberg equilibrium was tested, but it did not reveal differences between observed and expected genotype frequencies. Genotyping results showed a significant association of the miscoding rs1805794 variant with the NPC risk in both the Chinese populations [126]. The OR values for the homozygous rare allele CC and the heterozygous GC one were 1.73 and 3.75, respectively, compared with the GG genotype in the Eastern Chinese population (p<0,001). In the Southern population the OR values were 1.51 (95% CI 1.09-2.15, p<0.001) and 3.91 (95% CI 2.53-6.20, p<0.001). Overall, while an allele-dose response association between the rs1805794 SNP with NPC cancer risk was found, no association was detected for the 3'UTR *NBN* polymorphism [126].

2.6. Hepatic Cancer

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, representing 70% to 85% of primary hepatic malignancies in adults. HCC is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected [127]. The incidence of HCC is increasing, likely attributable to the increased prevalence of hepatitis C and possibly nonalcoholic fatty liver disease [128]. The incidence of HCC is highest in Asia and Africa, where the endemic high prevalence of hepatitis B and hepatitis C strongly predisposes to the development of chronic liver disease and subsequent development of hepatocellular carcinoma [127, 129]. Indeed, a large cohort of patients infected with hepatitis C several decades ago are now expected to seek medical care and present with complications of cirrhosis [130]. Because HCC tends to arise in the setting of cirrhosis, liver transplant is the ultimate life-saving modality because it removes the diseased liver along with macroscopic and microscopic cancer cells [131]. Although there is a growing understanding of the molecular mechanisms that induce hepatocarcinogenesis, real mechanisms of hepatocarcinogenesis have not been completely elucidated. However, cumulative knowledge regarding the molecular mechanisms of carcinogenesis revealed that the development and progression of HCC are caused by the accumulation of genetic changes, thus resulting in altered expression of cancer-related genes [129].

To our knowledge only a paper was devoted to the investigation of the association between genetic variations in the *NBN* gene and HCC risk. The study was carried out in an ethnically homogenous Chinese population of 865 HCC patients and 900 cancer-free healty controls looking at the rs1805794 and rs2735383 variants [132]. It was found that the rs1805794 SNP was associated with increased risk of developing HCC malignancy in an allele-dose response manner, in particulare the GC genotype presented an OR value of 1.41 (95% CI 1.11-1.80), whereas the CC carriers had an OR of 2.27 (95% CI 1.68-3.14). In addition the risk effect was more pronounced in ever-drinking HCC patients. On the contrary, no association was detected for the rs2735383 3'UTR *NBN* polymorphism [132].

2.7. Lymphoma and Acute Lymphoblastic Leukemia

Lymphoid cancer and leukemia are common malignancies in childhood [54, 133-137] associated with specific chromosomal translocations, as immunoglobulin and T-cell receptor loci or rearrangements involving chromosomes 9 and 22 [138-140]. Translocations occur as result of incorrect

processing of DSBs produced during antigen receptor rearrangements, physiological processes, and as an effect of clastogenic agents as ionizing radiations or chemotherapeutic agents [141-144]. Therefore, processing of DNA lesions arising physiologically or as response to DNA damaging agents is a critical step for the maintenance of genome stability. As a consequence, alterations in genes, as *NBN*, whose products taking active part in DNA damage repair may led to misrepair and chromosomal aberrations which in turn contribute to cancer development [13, 23].

Several studies have been carried out to evaluate the potential role of the *NBN* SNPs and hematological malignancies. In a study performed in the United States on 91 cases of sporadic Non-Hodgkin lymphoma (NHL) (B-cell and T-cell origin) and 154 controls, the frequencies of six common *NBN* polymorphisms (*i.e.*, rs1063045, rs1805794 rs2234744, rs709816, rs2308962, rs1061302) were analyzed and no association with lymphoid tumors was found [28].

No association between NHL and the *NBN* variants rs13312842, rs36226237, rs1805796, rs1063053, rs1063045, rs1805794, and rs1061302 was reported in a Canadian study carried out on 797 cases with an ethnical background that included Caucasian, Asian, South Asian, mixed populations and 793 matched controls [145]. Coding and non-coding DNA was sequenced, as well as 1000 bps upstream of the transcription start, and no association between NHL risk and seven *NBN* polymorphisms was found [145]. In a similar way, in another study no association was detected for the rs1805794 variant in 200 Hodgkin lymphoma (HL) patients and 220 controls, though in combination allelic variants in *XPC, XRCC1, XRCC3* and *NBN* genes modified the risk of developing HL [146].

Regarding leukemia, it should be recalled that in children about 80% are acute lymphoblastic leukemia (ALL) [54, 134, 144, 147]. To study whether *NBN* polymorphisms may influence susceptibility to the development of childhood ALL, a case-control study has been carried out in 157 Polish children and 275 controls [148]. Six SNPs of the *NBN* gene have been analyzed (*i.e.*, rs1063045, rs1805794 rs2234744, rs709816, 1061302, rs3736639). Genotype frequencies distributions were in accordance with Hardy-Weinberg equilibrium. The only rare homozygous TT genotype of the rs3736639 variant was found to slightly increase in frequency among leukemia patients as compared to controls (OR: 1.82, 95% CI 1.00-3.32, p=0.04). No significant differences in both allele and genotypes frequencies were detected for the remaining five *NBN* polymorphisms [148].

Apart from the studies on the Caucasian populations, some studies on the association between *NBN* polymorphisms and risk of hematological malignancies have been performed in the Chinese population. Regarding ALL risk (both B-ALL and T-ALL), in a recent study conducted on 175 Chinese patients and 360 controls, an association with the rs1805794 variant was found, but not for the rs2735383 3'UTR SNP [65]. In particular, the C allele frequency was higher among patients (0.61) than in controls (0.40). Genotypic frequencies did not deviate from the expected Hardy-Weinberg equilibrium distributions. The frequencies of the three genotypic combinations (*i.e.*, GG, GC and CC) differed significantly from those observed in healthy controls ($p<10^{-5}$). In addition, carriers of the homozygous CC genotype presented an OR value of 3.4 (95% CI 1.47-8.01 p<0.0001) compared to the GG genotype [65].

In another Chinese hospital-based case-control study, the association between the rs1805794 and rs2735383 (located at the 3'-UTR of *NBN*) polymorphisms and acute myeloid leukemia (AML) risk was investigated in 428 ethnically homogeneous AML patients and 600 cancer-free controls [149]. Genotypes were distributed in accordance with Hardy-Weinberg equilibrium. The genotypic frequencies of the rs1805794 variants GG, GC and CC significantly differed between patients and controls. With respect to the rare homozygous CC genotype taken as reference, both GC and GG genotypes were associated with a significantly decreased risk of AML (OR: 0.5, 95% CI 0.37-0.67, p<0.0001 for GC genotype; and OR: 0.23, 95% CI 0.16-0.34, p<0.0001 for GG genotype). In addition, the C allele frequency was 56.8% in healthy controls and 39.3% in patients (p<0.0001). Overall, it was found that for the rs1805794 variant the genotypes GC+GG appeared to be protective against AML, and that the risk decreased as the number of G alleles increased. On the contrary, the 3'- UTR *NBN* polymorphism was not associated with AML [149].

The association between ALL and *NBN* haplotypes for the rs12680687, rs6470522, rs7840099, and rs709816 variants in both Hispanic and non-Hispanic ethnicity and matched controls was examined [144]. They found significant ALL cytogenetic subtype-specific *NBN* haplotype association with t(12;21) positive childhood ALL [144]. In addition, it was found that at least the rs709816 variant significantly influences the risk of second neoplasm after the treatment of childhood ALL [150].

2.8. Lung Cancer

Lung cancer is one of the most common cancers [151], and its incidence has increased generally worldwide during the last few years, especially in Asian countries [151, 152]. Though many advances in the treatment of lung cancer, it is still one of the leading causes of cancer mortality [153-156]. There are several types of lung cancers, including non-small cell lung cancer, small cell lung cancer, and lung adenocarcinoma [156, 157]. Currently, it is well accepted that lung cancer is a multi-factorial process that involves both environmental carcinogens and genetic factors [158]. Polymorphisms of genes involved in the repair of DNA damages caused by environmental carcinogens may be responsible for the hosts' susceptibility to cancers, since they affect the genetic susceptibility to carcinogens [159].

Several studies are available in the literature on the possible association between *NBN* gene polymorphisms and lung cancer risk. In a three-case control study investigating smoking-related cancers, including lung cancer (611 and 1040 controls of mixed ethnicity), an OR value of 1.6 (95% CI, 1.2-2.4) was found for the rs1061302 synonymous variant at the homozygous status [160]. Additionally, a positive correlation was found for the homozygous rs1063054 SNP located in the 3'-UTR region with lung cancer (OR: 1.6, 95% CI 1.0-2.3). Furthermore, the association was modified by the smoking status of patients, thus suggesting a role of *NBN* variants in tabacco-related carcinogenesis [160]. In an

other study carried out in 109 lung cancer patients of mixed origin it was found that the prevalence of *TP53* mutations was significantly higher among individual homozygous for the rs1805794 NBN variant than among individuals for the wild-type allele [161]. A similar association between the rs1805794 variant and the prevalence of of *TP53* mutations in lung tumors has been also reported by [162].

More recently, the association between SNPs located in the 3'-UTR region of the *NBN* gene and lung cancer risk was investigated in Southern and Eastern Chinese populations [64]. In particular, three SNPs have been genotyped (*i.e.*, rs2735383, rs13312986, rs14448) in two independent hospital-based case-control studies conducted in the Chinese population. While no association was detected for both rs13312986 and rs14448 in 1559 patients and 1679 controls, the CC homozygous genotype of the rs2735383 SNP was significantly associated with cancer risk under a recessive genetic model (OR: 1.4, 95% CI 1.18-1.66, p=0.001). For this variant, the OR value rose to 1.7 in never-smokers (95% CI 1.34-2.17, $p=1.3x10^{-5}$) [64].

2.9. Medulloblastoma

Medulloblastoma is known to be the most common form of cancer of childhood, and consists of a highly malignant and invasive embryonic tumor of the cerebellum [163-165]. Although the majority of medulloblastoma occur sporadically, some of them occur within familial cancer syndromes, including the nevoid basal cell carcinoma (Gorlin syndrome) associated with germ-line *PTCH* mutations [166] and the Turcot syndrome type 2 caused by germ-line *APC* mutations [167].

In a study on 42 cases of medulloblastoma screened for *NBN* gene mutations, it was found that seven of them (corresponding to the 17%) carried a total of 15 *NBN* mutations: 10 missense point mutations and five intronic splicing mutations. Regarding miscoding mutations and SNPs, no differences in the frequencies detected in healthy controls and reported in the literature were observed for common variants (*i.e.*, rs1063045, rs709816, rs1061302, rs1805794) and intronic SNPs (*i.e.*, rs2234744, rs1805818, rs2308962), as well as for a rare intronic SNP (*i.e.*, rs3736640) [168]. However, neither genotype frequencies were reported nor was specified the ethnic characteristics of both the investigated patients and the reference healthy medulloblastoma-free population [168].

2.10. Melanoma

Skin melanoma is known for its extreme aggressivity, and its frequency is increased progressively in the last few years. Mutations in high-penetrance genes, *i.e. CDKN2A* and *CDK4*, have been identified as responsible for about 10% of all cases [37]. On the other hand, the genetic factors involved in the etiology of sporadic forms of melanoma are largely unknown [169] and the contribution of multiple low-penetrance and modifying genes has been proposed [170-177].

In a single study, the association of the *NBN* genetic variants with melanoma risk was analyzed in 376 Southern German patients [37]. By gene sequencing, three non-synonymous sequence variations within exon six of *NBN* were identified, that is V210F, F222L and R215W. Remarkably, the latter variation has been recognized as a true mutation since observed in compound heterozygosis with the classical 657del5 in two German twins affected by NBS [178]. Furthermore, in the same study reported above, a case-control study conducted on 632 melanoma patients and 615 controls of Southern Germany was performed, looking at three *NBN* SNPs (*i.e.*, rs9995, rs867185, rs1063045). No statistically significant association was found with melanoma risk for both the three SNPs and the different combination of haplotypes [37].

2.11. Ovarian Cancer

Epithelial ovarian cancer is the most lethal gynecologic malignancy, which accounts for up to 5% of all cancer types among women [179]. The origin and pathogenesis of epithelial ovarian cancer remains not fully understood, though epidemiological evidences point to a role of the ovulation process, that consists in the epithelial cellular proliferation necessary to repair the wound, with the consequent risk of DNA lesions accumulation connected to an increased cellular division [180, 181].

In the literature, we have found only one study devoted to assess the association of *NBN* polymorphisms with invasive epithelial ovarian cancer risk [182]. In a case-control study performed on Caucasians gathered from four separate genetic association studies and from three countries, four common *NBN* SNPs (one having functional effects (*i.e.*, rs1805794) and three non-coding variants (*i.e.*, rs1063045, rs709816, rs1061302)). Genotypes frequency in controls did not differ significantly from an Hardy-Weinberg equilibrium. No evidence for an association of the four SNPs with epithelial ovarian cancer was detected [182].

2.12. Prostate Cancer

Prostate cancer is one of the most common non-cutaneous malignancy among men of the Western countries [183]. Some factors, as increasing age, African-American ancestry, diet, obesity and environmental pollutants have been proposed as risk determinants for prostate cancer, though familial aggregation and family-based linkage studies suggest that genetic factors may also be involved in this pathology [184, 185].

To our knowledge, the number of studies devoted to the analysis of association between *NBN* genetic variants and such kind of cancer is very limited. In a study carried out by the International Consortium for Prostate Cancer Genetics, which collected samples from five centers, 1809 familial and 1218 sporadic cases of prostate cancer were analysed for *NBN* mutations [57]. The *NBN* gene sequencing in a subset of 20 of the youngest individuals from the Finnish group of familial cases, allowed the identification of the common rs1805794 SNP. However, the analysis of 200 patients failed to show any association of rs1805794 variant with prostate cancer [57].

In a recent case-control study comparing 239 Caucasian patients from Portugal diagnosed with early prostate cancer and 186 patients who presented advanced disease, the rs1805794 SNP was investigated [186]. It was found that the

GG carriers presented an almost two-fold increased risk for developing prostate malignancy (OR: 1.87, 95% CI 1.26-2.79, p= 0.002), thus suggesting a possible role for *NBN* in prostate cancer progression [186]. However, in this study, no mention was made to a reference control population.

2.13. Renal Cell Carcinoma

Among all the malignancies of the genito-urinary apparatus, renal cell carcinoma (RCC) represents the third cause of death. In United States approximately 51,000 people were diagnosed with RCC in 2007, and roughly one third of these patients will ultimately die from this disease [115]. Many and different factors have been identified as contributors of RCC development, including gender, obesity, smoking, analgesic and diuretic abuse, and environmental factors [187]. Host factors have been invoked to explain tumor development inter-individual differences that may be attributed to SNPs in genes involved in the repair of DNA damage induced by carcinogens [188, 189].

To our knowledge, only one study has been published on the role of *NBN* genetic variants and RCC [190]. A population-based case-control study that included 326 Caucasian RCC patients and 335 matched cancer-free controls has been carried out to evaluate the association of 13 SNPs in 10 candidate genes of the DSBs repair pathway [190]. Among the selected SNPs, the rs1805794 *NBN* variant was investigated. This SNP was reported to be in Hardy-Weinberg equilibrium. A significantly increased frequency of the minor homozygous variant CC genotype was found to be associated with an increased risk of RCC (OR: 2.13, 95% CI 1.17-3.86, p=0.01). Interestingly, the cancer risk increased as increased the number of adverse alleles for both the rs1805794 variant of *NBN* gene and the rs1805377 variant of the *XRCC4* gene [190].

2.14. Thyroid Cancer

Thyroid cancer is the most frequent endocrine neoplasia, with nonfamilial papillary and follicular thyroid carcinomas being the most common histological subtypes. These two histological subtypes are two to four times more frequent in women than in men, thus making thyroid cancer the eighth most prevalent cancer in women [191]. Exposure to ionisng radiation (IR) is the only established cause of thyroid carcinogenesis in humans [192-194], although other factors have also been linked to this pathology. These include dietary iodine deficiency [193, 194] and exposure to various environmental xenobiotics, which are important chromosome-damaging agents [195]. In addition, hereditary factors are also important in the etiology of thyroid cancer. The interplay of these different risk factors leads to a specific molecular pathway that results in either follicular or papillary thyroid carcinoma [191].

In a hospital-based case-control study on a Caucasian Portoguese population of 109 thyroid cancer patients and 217 age and gender controls, no association was found between the rs1805794 *NBN* variant and individual susceptibility toward thyroid cancer of both papillary and follicular type [191].

3. META-ANALYSIS STUDIES

Since the association between *NBN* genetic variants and increased risk of cancer appear to be still inconsistent and controversial, as evidenced in the present review for the various SNPs analyzed, tumor type and ethnicity, efforts have been made toward meta-analysis studies restricted to either specific polymorphisms, as the miscoding rs1805794 which lead to the E185Q amino acid substitution, or specific tumors. The various meta-analysis studies available are herein reported.

A study, restricted to the rs1805794 *NBN* variant, was based on 16 eligible case-control studies (17 set data) comprising a total of 9734 patients and 10325 controls of mixed populations (14 studies on Caucasians, 1 on African-Americans and 2 for the Chinese population) [196]. The association was estimated using dominant (GC/CC vs GG), additive (CC vs GG) and recessive (CC vs CG/GG) genetic models. For the GC/CC dominant model an OR value of 1.06 (95% CI 1.00-1.12, p=0.05) was found. The effect of the rs1805794 variant was further analyzed in a stratification analysis, showing an increased risk of cancer particularly among the Caucasians (OR: 1.07; 95% CI 1.01-1.14 p=0.03) [196].

Concerning a possible association of the rs1805794 SNP and breast cancer risk, a systemic review and meta-analysis study was carried out based on 10 case-control eligible studies of 4452 cases and 5665 controls of mixed population (seven studies on Caucasians, two in African-Americans, and one in Asian population) [197]. The authors considered different genetic models: the allele contrast model (C vs G), the codominant model (CC vs GG; CG vs GG), the dominant model (CG/CC vs GG), and the recessive model (CC vs GG/CG). It was reported an OR value of 0.85 (95% CI, 0.74-0.98) for the codominant model CC vs GG, suggesting that the individuals carrying the CC genotype had a significant decreased risk to develop breast cancer, compared with those with the GG genotype. The recessive model, CC vs GG/CG, showed a borderline significant association with breast cancer, while no association was detected in subgroup analyzed for ethnicity [197].

In a recent systemic review and meta-analysis study, the association of the rs1805794 *NBN* variant with lung cancer risk was addressed [198]. Six eligible case-control studies (two studies performed among Caucasians and four studies performed among the Chinese population) were considered, for a total of 2348 lung cancer patients and 2401 cancer-free controls. The authors reported a significant risk of lung cancer development under the dominant comparison model (OR: 1.21, 95% CI, 1.07-1.37, p=000.2). In particular, subgroup analysis performed by ethnicity suggested a significant association of rs1805794 with lung cancer risk under a dominant comparison model in the Asiatic population (OR: 1.22, 95% CI, 1.06-1.41, p=0.005), but not in Caucasians (OR: 1.17, 95% CI, 0.91-1.50, p=0.220) [198]. OR values were not adjusted for confounding factors as age and smoking habits. Concerning the Caucasian population, the two studies included in the meta-analysis have shown either no association (343 Norwegian origin patients for non-small cell lung cancer and 413 healthy controls) [199] or a significant association only among a small sample of non-smoking women (OR: 2.2, 95% CI 1.0-4.8) and low-dose smoking women (OR: 4.8, 95% CI 1.5-15.7) [200] for the rs1805794 polymorphism.

Findings from pooled analysis and meta-analysis studies performed in Europe and in the United States, carried out on 5282 non-Latin white origin cases by the International Consortium of Bladder Cancer, clearly indicated a significant association of the rs1805794 with bladder cancer risk (OR: 1.09, 95%, CI, 1.00-1.21, P= 0.028) [201]. Interestingly, the strongest association was found among individuals that reported the highest smoking doses or smoking duration [201].

Interestingly, recent systematic reviewes and meta-analysis on the involvement of DNA repair polymorphisms in human cancers, based on the guidance "Venice criteria" for assessing cumulative epidemiologic evidence in genetic associations [202, 203], indicated an association of the rs1805794 SNP and bladder cancer risk according to the dominant model CG/CC vs GG [204].

4. CONCLUSIONS

Though many studies have been carried out to establish a possible association between *NBN* gene polymorphisms and increased risk of cancer, the results still remain inconclusive and sometimes contradictory (Table **2**).

Based on the "Venice criteria" so far strong epidemiological credibility was found for the NBN miscoding E185Q (rs1805794) variant and bladder cancer. Remarkably, the E185 aminoacid is located within the BRCT1 domain of NBN. This domain is involved in NBN interaction with BRCA1, allowing the formation of the BRCA1-associated genome surveillance complex (BASC) that is responsible for the recognition and repair of DNA DSBs [205].

Meta analysis studies have the advantage of collecting a large number of cases, however some of them need to be considered with caution since they are not adjusted for relevant confounders, such as age and lifestyle, in particular smoking habits. Gene-gene and gene-environmental interactions need to be taken into account in future studies, since the carcinogenic mechanisms involving alteration in DNA repair pathways are affected by exposure to environmental agents, and more relevance should be put to report about the level of exposure. It has been stressed that, whereas genotyping is accurate, environmental exposure is often classified with a high degree of uncertainty [204]. In addition, association studies would greatly benefit from analysis of haplotypes and combined effect of several SNPs in multiple and different genes taking part in DNA repair, since it is becoming recognized that the contribution of single variants to the genetic risk of cancer may be very modest.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

ABBREVIATIONS

ALL	=	Acute lymphoblastic leukemia
AML	=	Acute myeloid leukemia
ATM	=	Ataxia-Telangiectasia Mutated
bps	=	Base pairs
BCC	=	Basal cell carcinoma
BRCA1	=	Breast cancer 1 protein
BRCA2	=	Breast cancer 2 protein
BRCT	=	BRCA1 carboxy-terminal domain
DSB	=	DNA double-strand break
FHA	=	Forkhead associated domain
HCC	=	Hepatocellular carcinoma
HL	=	Hodgkin lymphoma
HNSCC	=	Head and neck squamous cell carcinomas
HRR	=	Homologous recombination repair
MRN	=	MRE11/RAD50/NBN complex
NBS	=	Nijmegen Breakage Syndrome
NHEJ	=	Non-homologous end-joining
NHL	=	Non-Hodgkin lymphoma
NPC	=	Nasopharyngeal carcinoma
RCC	=	Renal cell carcinoma
SNP	=	Single nucleotide polymorphism
OR	=	Odd ratio
UV	=	Ultraviolet

REFERENCES

[1] Carney, J.P.; Mase, R.S.; Olivares, H.; Davis, E.M.; Le Beau, M.; Yates, J.R. 3rd; Hays, L.; Morgan, W.F.; Petrini, J.H. The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. *Cell*, **1998**, *93*, 477-486. dx.doi.org/10.1016/S0092-8674(00)81175-7

[2] Varon, R.; Vissinga, C.; Platzer, M.; Cerosaletti, K.M.; Chrzanowska, K.H.; Saar, K.; Beckmann, G.; Seemanová, E.; Cooper, P.R.; Nowak, N.J.; Stumm, M.; Weemaes, C.M.; Gatti, R.A.; Wilson, R.K.; Digweed, M.; Rosenthal, A.; Sperling, K.; Concannon, P.; Reis, A. Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. *Cell*, **1998**, *93*, 467-476. /dx.doi.org/10.1016/S0092-8674(00)81174-5

[3] Gatei, M.; Scott, S.P.; Filippovitch, I.; Soronika, N.; Lavin, M.F.; Weber, B.; Khanna, K.K. Role for ATM in DNA damage-induced phosphorylation of BRCA1. *Cancer Res.*, **2000**, *60*, 3299-3304. PMID:10866324

[4] Lim, D.S.; Kim, S.T.; Xu, B., Maser, R.S.; Lin, J.; Petrini, J.H.; Kastan, M.B. ATM phosphorylates p95/nbs1 in an S-phase checkpoint pathway. *Nature*, **2000**, *404*, 613-617. doi:10.1038/35007091

[5] Wu, X.; Ranganathan, V.; Weisman, D.S.; Heine, W.F.; Ciccone, D.N.; O'Neill, T.B.; Crick, K.E.; Pierce, K.A.; Lane, W.S.; Rathbun, G.; Livingston, D.M.; Weaver, D.T. ATM phosphorylation of Nijmegen breakage syndrome protein is required in a DNA damage response. *Nature*, **2000**, *405*, 477-482. doi:10.1038/35013089;

[6] Zhao, S.; Weng, Y.C.; Yuan, S.S.; Lin, Y.T.; Hsu, H.C.; Lin, S.C.; Gerbino, E.; Song, M.H.; Zdzienicka, M.Z.; Gatti, R.A.; Shay, J.W.; Ziv, Y.; Shiloh, Y.; Lee, E.Y. Functional link between ataxia-telangiectasia and Nijmegen breakage syndrome gene products. *Nature*, **2000**, *405*, 473-477.

[7] Falck, J.; Coates, J.; Jackson, S.P. Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. *Nature*, **2005**, *434*, 605-611. dx.doi.org/10.1038/nature03442

[8] You, Z.; Chahwan, C.; Bailis, J.; Hunter, T.; Russell, P. ATM activation and its recruitment to damaged DNA require binding to the C terminus of Nbs1. *Mol. Cell Biol.*, **2005**, *25*, 5363-5379. 10.1128/MCB.25.13.5363-5379.2005

[9] Becker, E.; Meyer, V.; Madaoui, H.; Guerois, R. Detection of a

tandem BRCT in Nbs1 and Xrs2 with functional implications in the DNA damage response. *Bioinformatics*, **2006**, *22*, 1289-1292. dx.doi.org/10.1093/bioinformatics/btl075

[10] Williams, R.S.; Dodson, G.E.; Limbo, O.; Yamada, Y.; Williams, J.S.; Guenther, G.; Classen, S.; Glover, J.N.; Iwasaki, H.; Russell, P.; Tainer, J.A. Nbs1 flexibly tethers Ctp1 and Mre11-Rad50 to coordinate DNA double-strand break processing and repair. *Cell*, **2009**, *139*, 87-99. /dx.doi.org/10.1093/bioinformatics/btl075

[11] Schiller, C.B.; Lammens, K.; Guerini, I.; Coordes, B.; Feldmann, H.; Schlauderer, F.; Möckel, C.; Schele, A.; Strässer, K.; Jackson, S.P.; Hopfner, K.P. Structure of Mre11-Nbs1complex yields insights into ataxia-telangiectasia-like disease mutations and DNA damage signaling. *Nat. Struct. Mol. Biol.*, **2012**, *19*, 693-700. dx.doi.org/10.1038/nsmb.2323

[12] D'Amours, D.; Jackson, S.P. The Mre11 complex: at the crossroads of DNA repair and checkpoint signalling. *Nat. Rev. Mol. Cell Biol.*, **2002**, *3*, 317-327. //dx.doi.org/10.1038/nrm805

[13] Digweed, M.; Sperling, K. Nijmegen breakage syndrome: clinical manifestation of defective response to DNA double-strand breaks. *DNA Repair (Amst)*, **2004**, *3*, 1207-1217. /dx.doi.org/10.1016/j.dnarep.2004.03.004

[14] Kobayashi, J.; Antoccia, A.; Tauchi, H.; Matsuura, S.; Komatsu, K. NBS1 and its functional role in the DNA damage response. *DNA Repair (Amst)*, **2004**, *3*, 855-861. dx.doi.org/10.1016/j.dnarep.2004.03.023

[15] Iijima, K.; Ohara, M.; Seki, R.; Tauchi, H. Dancing on damaged chromatin: functions of ATM and the RAD50/MRE11/NBS1 complex in cellular responses to DNA damage. *J. Radiat. Res. (Tokyo)*, **2008**, *49*, 451-464. dx.doi.org/10.1269/jrr.08065

[16] Gullotta, F.; De Marinis, E.; Ascenzi, P.; di Masi, A. Targeting the DNA double strand breaks repair for cancer therapy. *Curr. Med. Chem.*, **2010**, *17*, 2017-2048. dx.doi.org/10.2174/092986710791233698

[17] Rupnik, A.; Lowndes, N.F.; Grenon, M. MRN and the race to the break. *Chromosoma*, **2010**, *119*, 115-135 /dx.doi.org/10.1007/s00412-009-0242-4.

[18] Wen, J.; Cerosaletti, K.; Schultz, K.J.; Wright, J.A.; Concannon, P. NBN Phosphorylation regulates the accumulation of MRN and ATM at sites of DNA double-strand breaks. *Oncogene*, **2012**, Nov 12. doi: 10.1038/onc.2012.443.

[19] Shin, D.S.; Chahwan, C.; Huffman, J.L.; Tainer, J.A. Structure and function of the double-strand break repair machinery. *DNA Repair (Amst)*, **2004**, *3*, 863-873. dx.doi.org/10.1016/j.dnarep.2004.03.022

[20] Jeggo, P.A.; Lobrich, M. DNA double-strand breaks: their cellular and clinical impact? *Oncogene*, **2007**, *26*, 7717-7719. dx.doi.org/10.1038/sj.onc.1210868

[21] Mahaney, B.L.; Meek, K.; Lees-Miller, S.P. Repair of ionizing radiation-induced DNA double-strand breaks by non-homologous end-joining. *Biochem. J.*, **2009**, *417*, 639-650. dx.doi.org/10.1042/BJ20080413

[22] Seemanová, E.; Jarolim, P.; Seeman, P., Varon, R.; Digweed, M.; Swift, M.; Sperling, K. Cancer risk of heterozygotes with the NBN founder mutation. *J. Natl. Cancer Inst.*, **2007**, *99*, 1875-1880. dx.doi.org/10.1093/jnci/djm251

[23] di Masi, A.; Antoccia, A. NBS1 Heterozygosity and cancer risk. *Curr. Genomics*, **2008**, *9*, 275-281. dx.doi.org/10.2174/138920208784533610

[24] Dzikiewicz-Krawczyk, A. The importance of making ends meet: mutations in genes and altered expression of proteins of the MRN complex and cancer. *Mutat Res.*, **2008**, *659*, 262-273. //dx.doi.org/10.1016/j.mrrev.2008.05.005

[25] Weemaes, C.M.; Hustinx, T.W.; Scheres, J.M.; van Munster, P.J.; Bakkeren, J.A.; Taalman, R.D. A new chromosomal instability disorder: the Nijmegen breakage syndrome. *Acta Paediatr. Scand.*, **1981**, *70*, 557-564. /dx.doi.org/10.1111/j.1651-2227.1981.tb05740.x

[26] The International Nijmegen Breakage Syndrome Study Group, Nijmegen breakage syndrome. The International Nijmegen Breakage Syndrome Study Group. *Arch. Dis. Child*, **2000**, *82*, 400-406. dx.doi.org/10.1136/adc.82.5.400

[27] Chrzanowska, K.H.; Gregorek, H.; Dembowska-Bagińska, B.; Kalina, M.A.; Digweed, M. Nijmegen breakage syndrome (NBS). *Orphanet J. Rare Dis.*, **2012**, *7*, 13. dx.doi.org/10.1186/1750-1172-7-13

[28] Cerosaletti, K.M.; Morrison, V.A.; Sabath, D.E.; Willerford, D.M.; Concannon, P. Mutations and molecular variants of the NBS1 gene in non-Hodgkin lymphoma. *Genes Chromosomes Cancer*, **2002**, *35*, 282-286. /dx.doi.org/10.1002/gcc.10114

[29] Resnick, I.B.; Kondratenko, I.; Pashanov, E.; Maschan, A.A.; Karachunsky, A.; Togoev, O.; Timakov, A.; Polyakov, A.; Tverskaya, S.; Evgrafov, O.; Roumiantsev, A.G. 657del5 mutation in the gene for Nijmegen breakage syndrome (NBS1) in a cohort of Russian children with lymphoid tissue malignancies and controls. *Am. J. Med. Genet. A.*, **2003**, *120*, 174-179. /dx.doi.org/10.1002/gcc.10114

[30] Steffen, J.; Varon, R.; Mosor, M.; Maneva, G.; Maurer, M.; Stumm, M.; Nowakowska, D.; Rubach, M.; Kosakowska, E.; Ruka, W.; Nowecki, Z.; Rutkowski, P.; Demkow, T. Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. *Int. J. Cancer*, **2004**, *111*, 67-71. dx.doi.org/10.1002/ijc.20239

[31] Chrzanowska KH, Piekutowska-Abramczuk D, Popowska E, Gładkowska-Dura, M.; Małdyk, J.; Syczewska, M.; Krajewska-Walasek, M.; Goryluk-Kozakiewicz, B.; Bubała, H.; Gadomski, A.; Gaworczyk, A.; Kazanowska, B.; Kołtan, A.; Kuźmicz, M.; Luszawska-Kutrzeba, T.; Maciejka-Kapuścińska, L.; Stolarska, M.; Stefańska, K.; Sznurkowska, K.; Wakulińska, A.; Wieczorek, M.; Szczepański, T.; Kowalczyk, J. Carrier frequency of mutation 657del5 in the NBS1 gene in a population of Polish pediatric patients with sporadic lymphoid malignancies. *Int. J. Cancer*, **2006**, *118*, 1269-1274. /dx.doi.org/10.1002/ijc.21439

[32] Steffen, J.; Maneva, G.; Poplawska, L.; Varon, R.; Mioduszewska, O.; Sperling, K. Increased risk of gastrointestinal lymphoma in carriers of the 657del5 NBS1 gene mutation. *Int. J. Cancer*, **2006**, *119*, 2970-2973. /dx.doi.org/10.1002/ijc.22280

[33] Chrzanowska, K.; Stumm, M.; Bialecka, M.; Saar, K.; Bernatowska-Matuszkiewicz, E.; Michalkiewicz, J.; Barszcz, S.; Reis, A.; Wegner, R.D. Linkage studies exclude the AT-V gene(s) from the translocation breakpoints in an AT-V patient. *Clin Genet.*, **1997**, *51*, 309-313. DOI: 10.1111/j.1399-0004.1997.tb02479.x

[34] Bakhshi, S.; Cerosaletti, K.M.; Concannon, P.; Bawle, E.V.; Fontanesi, J.; Gatti, R.A.; Bhambhani, K. Medulloblastoma with adverse dx.doi.org/10.1097/00043426-200303000-00013

[35] Distel, L.; Neubauer, S.; Varon, R.; Holter, W.; Grabenbauer, G. Fatal toxicity following radio- and chemotherapy of medulloblastoma in a child with unrecognized Nijmegen breakage syndrome. *Med. Pediatr. Oncol.*, **2003**, *41*, 44-48.

[36] Meyer, S.; Kingston, H.; Taylor, A.M., Byrd, P.J.; Last, J.I.; Brennan, B.M.; Trueman, S.; Kelsey, A.; Taylor, G.M.; Eden, O.B. Rhabdomyosarcoma in Nijmegen breakage syndrome: strong association with perianal primary site. *Cancer Genet. Cytogenet.*, **2004**, *154*, 169-174. /dx.doi.org/10.1016/j.cancergencyto.2004.02.022

[37] Meyer, P.; Stepelmann, H.; Frank, B.; Varon, R.; Burwinkel, B.; Schmitt, C.; Boettger, M.B.; Klaes, R.; Sperling, K.; Hemminki, K.; Kammerer, S. Molecular genetic analysis of NBS1 in German Melanoma patients. *Melanoma Res.*, **2007**, *17*, 109-116. dx.doi.org/10.1097/CMR.0b013e3280dec638

[38] Buslov, K.G.; Iyevleva, A.G.; Chekmariova, E.V.; Suspitsin, E.N.; Togo, A.V.; Kuligina, E.Sh.; Sokolenko, A.P.; Matsko, D.E.; Turkevich, E.A.; Lazareva, Y.R.; Chagunava, O.L.; Bit-Sava, E.M.; Semiglazov, V.F.; Devilee, P.; Cornelisse, C.; Hanson, K.P.; Imyanitov, E.N. NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. *Int. J. Cancer*, **2005**, *114*, 585-589. /dx.doi.org/10.1002/ijc.20765

[39] Górski, B.; Cybulski, C.; Huzarski, T.; Byrski, T.; Gronwald, J.; Jakubowska, A.; Stawicka, M.; Gozdecka-Grodecka, S.; Szwiec, M.; Urbański, K.; Mituś, J.; Marczyk, E.; Dziuba, J.; Wandzel, P.; Surdyka, D.; Haus, O.; Janiszewska, H.; Debniak, T.; Tołoczko-Grabarek, A.; Medrek, K.; Masojć, B.; Mierzejewski, M.; Kowalska, E.; Narod, S.A.; Lubiński, J. Breast cancer predisposing alleles in Poland. *Breast Cancer Res. Treat.*, **2005**, *92*, 19-24. //dx.doi.org/10.1002/ijc.20765

[40] Bogdanova, N.; Feshcenko, S.; Schürmann, P.; Waltes, R.; Wieland, B.; Hillemanns, P.; Rogov, Y.I.; Dammann, O.; Bremer, M.; Karstens, J.H.; Sohn, C.; Varon, R.; Dörk, T. Nijmegen Breakage Syndrome mutations and risk of breast cancer. *Int. J. Cancer*, **2008**, *122*, 802-806 //dx.doi.org/10.1002/ijc.23168

[41] Roznowski, K.; Januszkiewicz-Lewandowska, D.; Mosor, M.; Pernak, M.; Litwiniuk, M.; Nowak, J. I171V germline mutation in the NBS1 gene significantly increases risk of breast cancer. *Breast Cancer Res. Treat.*, **2008**, *110*, 343-348. /dx.doi.org/10.1007/s10549-007-9734-1

[42] Cybulski, C.; Górski, B.; Debniak, T.; J akubowska, A.; Górski, B.; Gronwald, J.; Huzarski, T.; Kashyap, A.; Byrski, T.; Dębniak, T.;

Gołąb, A.; Gliniewicz, B.; Sikorski, A.; Switała, J.; Borkowski, T.; Borkowski, A.; Antczak, A.; Wojnar, L.; Przybyła, J.; Sosnowski, M.; Małkiewicz, B.; Zdrojowy, R.; Sikorska-Radek, P.; Matych, J.; Wilkosz, J.; Różański, W.; Kiś, J.; Bar, K.; Bryniarski, P.; Paradysz, A.; Jersak, K.; Niemirowicz, J.; Słupski, P.; Jarzemski, P.; Skrzypczyk, M.; Dobruch, J.; Domagała, P.; Narod, S.A.; Lubiński, J.; Polish Hereditary Prostate Cancer Consortium. NBS1 is a prostate cancer susceptibility gene. *Cancer Res.*, **2004**, *64*, 1215-1219. dx.doi.org/10.1158/0008-5472.CAN-03-2502

[43] Suspitsin, E.N.; Sherina, N.Y.; Ponomariova, D.N.; Sokolenko, A.P.; Iyevleva, A.G.; Gorodnova, T.V.; Zaitseva, O.A.; Yatsuk, O.S.; Togo, A.V.; Tkachenko, N.N.; Shiyanov, G.A.; Lobeiko, O.S.; Krylova, N.Y.; Matsko, D.E.; Maximov, S.Y.; Urmancheyeva, A.F.; Porhanova, N.V.; Imyanitov, E.N. High frequency of BRCA1, but not CHEK2 or NBS1 (NBN), founder mutations in Russian ovarian cancer patients. *Hered. Cancer Clin. Pract.*, **2009**, *7*, 5. dx.doi.org/10.1186/1897-4287-7-5

[44] Moreno-Pérez, D.; García Martín, F.J.; Vázquez López, R.; Pérez Ruiz, E.; Gonález-Valentín, M.E.; Weil Lara, B.;, Jurado Ortiz, A. Nijmegen breakage syndrome associated with pulmonary lymphoma. *An. Esp. Pediatr.*, **2002**, *57*, 574-577. PMID:12466083

[45] Pardini, B.; Naccarati, A.; Polakova, V.; Smerhovsky, Z.; Hlavata, I.; Soucek, P.; Novotny, J.; Vodickova, L.; Tomanova, V.; Landi, S.; Vodicka, P. NBN 657del5 heterozygous mutations and colorectal cancer risk in the Czech Republic. *Mutat. Res.*, **2009**, *666*, 64-67. dx.doi.org/10.1016/j.mrfmmm.2009.04.004

[46] Maraschio, P.; Peretti, D.; Lambiase, S.; Lo, C.F.; Caufin, D.; Gargantini, L.; Minoli, L.; Zuffardi, O. A new chromosome instability disorder. *Clin. Genet.*, **1986**, *30*, 353-365. dx.doi.org/10.1111/j.1399-0004.1986.tb01892.x

[47] Tupler, R.; Marseglia, G.L.; Stefanini, M.; Prosperi, E.; Chessa, L.; Nardo, T.; Marchi, A.; Maraschio, P. A variant of the Nijmegen breakage syndrome with unusual cytogenetic features and intermediate cellular radiosensitivity. *J. Med. Genet.*, **1997**, *34*, 196-202. dx.doi.org/10.1136/jmg.34.3.196

[48] Maraschio, P.; Danesino, C.; Antoccia, A.; Ricordy, R.; Tanzarella, C.; Varon, R.; Reis, A.; Besana, D.; Guala, A.; Tiepolo, L. A novel mutation and novel features in Nijmegen breakage syndrome. *J. Med. Genet.*, **2001**, *38*, 113-117. /dx.doi.org/10.1136/jmg.38.2.113

[49] Maraschio, P.; Danesino, C.; Varon, R.; Tiepolo, L. Corpus Callosum Hypoplasia and associated brain anomalies in Njmegen Breakage Syndrome. *J. Med. Genet.*, **2002**, *39*, E25. dx.doi.org/10.1136/jmg.39.5.e25

[50] Nakanishi, K.; Taniguchi, T.; Ranganathan, V.; New, H.V.; Moreau, L.A.; Stotsky, M.; Mathew, C.G.; Kastan, M.B.; Weaver, D.T.; D'Andrea, A.D. Interaction of FANCD2 and NBS1 in the DNA damage response. *Nat. Cell Biol.*, **2002**, *4*, 913-920. /dx.doi.org/10.1038/ncb879

[51] Resnick, I.B.; Kondratenko, I.; Togoev, O.; Vasserman, N.; Shagina, I.; Evgrafov, O.; Tverskaya, S.; Cerosaletti, K.M.; Gatti, R.A.; Concannon, P. Nijmegen breakage syndrome: clinical characteristics and mutation analysis in eight unrelated Russian families. *J. Pediatr.*, **2002**, *140*, 355-361. dx.doi.org/10.1067/mpd.2002.122724

[52] Gennery, A.R.; Slatter, M.A.; Bhattacharya, A.; Barge, D.; Haigh, S.; O'Driscoll, M.; Coleman, R.; Abinun, M.; Flood, T.J.; Cant, A.J.; Jeggo, P.A. dx.doi.org/10.1016/j.clim.2004.03.024

[53] New, H.V.; Cale, C.M.; Tischkowitz, M.; Jones, A.; Telfer, P.; Veys, P.; D'Andrea, A.; Mathew, C.G.; Hann, I. Nijmegen breakage syndrome diagnosed as Fanconi anaemia. *Pediatr. Blood Cancer*, **2005**, 44, 494-499. dx.doi.org/10.1002/pbc.20271

[54] Varon, R.; Reis, A.; Henze, G.; von Einsiedel, H.G.; Sperling, K.; Seeger, K. Mutations in the Nijmegen Breakage Syndrome gene (NBS1) in childhood acute lymphoblastic leukemia (ALL). *Cancer Res.*, **2001**, *61*, 3570-3572.dx.doi.org/10.1016/S0165-4608(01)00409-5

[55] Taylor, G.M.; O'Brien, H.P.; Greaves, M.F.; Ravetto, P.F.; Eden, O.B. Correspondence re: Mutations in the Nijmegen breakage syndrome gene (NBS1) in childhood acute lymphoblastic leukaemia. *Cancer Res.*, **2003**, *63*, 6563-6564. PMID:14559852

[56] Shimada, H.; Shimizu, K.; Mimaki, S.; Sakiyama, T.; Mori, T.; Shimasaki, N.; Yokota, J.; Nakachi, K.; Ohta, T.; Ohki, M. First case of aplastic anemia in a Japanese child with a homozygous missense mutation in the NBS1 gene (I171V) associated with genomic instability. *Hum. Genet.*, **2004**, *115*, 372-376. dx.doi.org/10.1007/s00439-004-1155-1

[57] Hebbring, S.J.; Fredriksson, H.; White, K.A.; Maier, C.; Ewing, C.; McDonnell, S.K.; Jacobsen, S.J.; Cerhan, J.; Schaid, D.J.; Ikonen, T.; Autio, V.; Tammela, T.L.; Herkommer, K.; Paiss, T.; Vogel, W.; Gielzak, M.; Sauvageot, J.; Schleutker, J.; Cooney, K.A.; Isaacs, W.; Thibodeau, S.N. Role of the Nijmegen Breakage Syndrome 1 gene in familial and sporadic prostate cancer. *Cancer Epidemiol. Biomarkers Prev.*, **2006**, *15*, 935-938. dx.doi.org/10.1158/1055-9965.EPI-05-0910

[58] Ziółkowska, I.; Mosor, M.; Wierzbika, M.; Rydzanicz, M.; Pernak-Schwarz, M.; Nowak, J. Increased risk of larynx cancer in heterozygous carriers of the I171V mutation of the NBS1 gene. *Cancer Sci.*, **2007**, *98*, 1701-1705. dx.doi.org/10.1111/j.1349-7006.2007.00594.x

[59] Bogdanova, N.; Schürmann, P.; Waltes, R.; Feshchenko, S.; Zalutsky, I.V.; Bremer, M.; Dörk, T. NBS1 variant I171V and breast cancer risk. *Breast Cancer Res. Treat.*, **2008**, *112*, 75-79. dx.doi.org/10.1007/s10549-007-9820-4

[60] Nowak, J.; Mosor, M.; Ziòłkowska, I.; Wierzbicka, M.; Pernak-Schwarz, M.; Przyborska, M.; Roznowski, K.; Pławski, A.; Słomski, R.; Januszkiewicz, D. Heterozygous carriers of the I171V mutation of the NBS1 gene have a significantly increased risk of solid malignant tumours. *Eur. J. Cancer*, **2008**, *44*, 627-630. /dx.doi.org/10.1016/j.ejca.2008.01.006

[61] Ciara, E.; Piekutowska-Abramczuk, D.; Popowska, E.; Grajkowska, W.; Barszcz, S.; Perek, D.; Dembowska-Bagińska, B.; Perek-Polnik, M.; Kowalewska, E.; Czajńska, A.; Syczewska, M.; Czornak, K.; Krajewska-Walasek, M.; Roszkowski, M.; Chrzanowska, K.H. Heterozygous germ-line mutations in the NBN gene predispose to medulloblastoma in pediatric patients. *Acta Neuropathol.*, **2010**, *119*, 325-334. dx.doi.org/10.1007/s00401-009-0608-y

[62] Piekutowska-Abramczuk, D.; Ciara, E.; Popowska, E.; Grajkowska, W.; Dembowska-Bagińska, B.; Kowalewska, E.; Czajńska, A.; Perek-Polnik, M.; Roszkowski, M.; Syczewska, M.; Krajewska-Walasek, M.; Perek, D.; Chrzanowska, K.H. The frequency of NBN molecular variants in pediatric astrocytic tumors. *J. Neurooncol.*, **2010**, *96*, 161-168 dx.doi.org/10.1007/s11060-009-9958-5

[63] Maser, R.S.; Zinkel, R.; Petrini, J.H. An alternative mode of translation permits production of a variant NBS1 protein from the common Nijmegen breakage syndrome allele. *Nat. Genet.*, **2001**, *27*, 417-421.PMID: 11279524

[64] Yang, L.; Li, Y.; Cheng, M.; Huang, D.; Zheng, J.; Liu, B.; Ling, X.; Li, Q.; Zhang, X.; Ji, W.; Zhou, Y.; Lu, J. A functional polymorphism at microRNA-629-binding site in the 3'-untranslated region of NBS1 gene confers an increased risk of lung cancer in Southern and Eastern Chinese population. *Carcinogenesis*, **2012**, 33, 338-347. PMID: 22114071

[65] Jiang, L.; Liang, J.; Jiang, M.; Yu, X.; Zheng, J.; Liu, H.; Wu, D.; Zhou, Y. Functional polymorphisms in the NBS1 gene and acute lymphoblastic leukemia susceptibility in a Chinese population. *Eur. J. Haematol.*, **2011**, *86*, 199-205. dx.doi.org/10.1111/j.1600-0609.2010.01562.x

[66] Bowden, G.T. Prevention of non-melanoma skin cancer by targeting ultraviolet-B-light signalling. *Nat. Rev. Cancer*, **2004**, *4*, 23-35. //dx.doi.org/10.1038/nrc1253

[67] Tsai, K.Y.; Tsao, H. The genetics of skin cancer. *Am. J. Med. Genet. C. Semin. Med. Genet.*, **2004**, *131C*, 82-92. dx.doi.org/10.1002/ajmg.c.30037

[68] Green, C.L.; Khavari, P.A. Targets for molecular therapy of skin cancer. *Semin. Cancer Biol.*, **2004**, *14*, 63-69. dx.doi.org/10.1016/j.semcancer.2003.11.007

[69] de Gruijl, F.R.; van Kranen, H.J.; Mullenders, L.H. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. *J. Photochem. Photobiol. B*, **2001**, *63*, 19-27. dx.doi.org/10.1016/S1011-1344(01)00199-3

[70] Lovatt, T.J.; Lear, J.T.; Bastrilles, J.; Wong, C.; Griffiths, C.E.; Samarasinghe, V.; Roebuck, J.; Ramachandran, S.; Smith, A.G.; Jones, P.W.; Fryer, A.A.; Strange, R.C. Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. *J. Am. Acad. Dermatol.*, **2005**, *52*, 468-473. dx.doi.org/10.1016/j.jaad.2004.08.060

[71] Mohrenweiser, H.W.; Xi, T.; Vazquez-Matias, J.; Jones, I.M. Identification of 127 amino acid substitution variants in screening 37 DNA repair genes in humans. *Cancer Epidemiol. Biomarkers*

Prev., **2002**, *11*, 1054-1064. PMID: 12376507

[72] Festa, F.; Kumar, R.; Sanyal, S.; Unden, B.; Nordfors, L.; Lindholm, B.; Snellman, E.; Schalling, M.; Forsti, A.; Hemminki, K. Basal cell carcinoma and variants in genes coding for immune response, DNA repair, folate and iron metabolism. *Mutat. Res.*, **2005**, *574*, 105-111. dx.doi.org/10.1016/j.mrfmmm.2005.01.026

[73] Thirumaran, R.K.; Bermejo, J.L.; Rudnai, P.; Gurzau, E.; Koppova, K.; Goessler, W.; Vahter, M.; Leonardi, G.S.; Clemens, F.; Fletcher, T.; Hemminki, K.; Kumar, R. Single nucleotide polymorphisms in DNA repair genes and basal cell carcinoma of skin. *Carcinogenesis*, **2006**, *27*, 1676-1681. /dx.doi.org/10.1093/carcin/bgi381

[74] Knowles, M.A. The genetics of transitional cell carcinoma: progress and potential clinical application. *BJU Int.*, **1999**, *84*, 412-427. DOI: 10.1046/j.1464-410x.1999.00217.x

[75] Ferlay, J.; Bray, F.; Pisani, P.; Parkin, D.M. *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide*. IARC CancerBase No. 5. version 2.0. IARC Press: Lyon, **2004**.

[76] Parkin, D.M. The global burden of urinary bladder cancer. *Scand. J. Urol. Nephrol. Suppl.*, **2008**, *218*, 12-20. doi:10.1080/03008880802285032)

[77] Ploeg, M.; Aben, K.K.H.; Kiemeney, L.A. The present and future burden of urinary bladder cancer in the world. *World J. Urol.*, **2009**, *27*, 289-293.dx.doi.org/10.1007/s00345-009-0383-3

[78] Cohen, S.M.; Shirai, T.; Steineck, G. Epidemiology and etiology of premalignant and malignant urothelial changes. *Scand. J. Urol. Nephrol. Suppl.*, **2000**, *205*, 105-115 PMID:11144890

[79] Berggren, P.; Steineck, G.; Adolfsson, J.; Hansson, J.; Jansson, O.; Larsson, P.; Sandstedt, B.; Wijkstrom, H.; Hemminki, K. p53 mutations in urinary bladder cancer. *Br. J. Cancer*, **2001**, *84*, 1505-1511. dx.doi.org/10.1054/bjoc.2001.1823

[80] Kunze, E.; Chang-Claude, J.; Frentzel-Beyrne, R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*, **1992**, *69*, 1776-1790. dx.doi.org/10.1002/1097-0142(19920401)69:7<1776::AID-CNCR2820690721>3.0.CO;2-P

[81] Friedberg, E.C. DNA damage and repair. *Nature*, **2003**, *421*, 436-440. dx.doi.org/10.1038/nature01408

[82] Sanyal, S.; Festa, F.; Sakano, S.; Zhang, Z.; Steineck, G.; Norming, U.; Wijkström, H.; Larsson, P.; Kumar, R.; Hemminki, K. Polymorphisms in DNA repair and metabolic genes in bladder cancer. *Carcinogenesis*, **2003**, *25*, 729-734. dx.doi.org/10.1093/carcin/bgh058

[83] Stern, M.C.; Umbach, D.M.; van Gils, C.H.; Lunn, R.M.; Taylor, J.A. DNA repair gene XRCC1 polymorphisms, smoking and bladder cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **2001**, *10*, 125-131. PMID:11219769

[84] Stern, M.C.; Johnson, L.R.; Bell, D.A.; Taylor, J.A. XPD codon 751 polymorphism, metabolism genes, smoking and bladder cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **2002a**, *11*, 1004-1011. PMID:12376500

[85] Stern, M.C.; Umbach, D.M.; Lunn, R.M.; Taylor, J.A. DNA repair gene XRCC3 codon 241 polymorphism, its interaction with smoking and XRCC1 polymorphisms and bladder cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **2002**, *11*, 939-943. PMID: 12223443

[86] Wang, L.; Habuchi, T.; Takahashi, T.; Mitsumori, K.; Kamoto, T.; Kakehi, Y.; Kakinuma, H.; Sato, K.; Nakamura, A.; Ogawa, O.; Kato, T. Cyclin D1 gene polymorphism is associated with an increased risk of urinary bladder cancer. *Carcinogenesis*, **2002**, *23*, 257-264. dx.doi.org/10.1093/carcin/23.2.257

[87] Cortessis, V.K.; Siegmund, K.; Xue, S.; Ross, R.K.; Yu, M.C. A case-control study of cyclin D1 CCND1 870A/G polymorphism and bladder cancer. *Carcinogenesis*, **2003**, *24*, 1645-1650. dx.doi.org/10.1093/carcin/bgg128

[88] Figueroa, J.D.; Malats, N.; Rothman, N.; Real, F.X.; Silverman, D.; Kogevinas, M.; Chanock, S.; Yeager, M.; Welch, R.; Dosemeci, M.; Tardón, A.; Serra, C.; Carrato, A.; García-Closas, R.; Castaño-Vinyals, G.; García-Closas, M. Evaluation of genetic variation in the double-strand break repair pathway and bladder cancer risk. *Carcinogenesis*, **2007**, *28*, 1788-1793. dx.doi.org/10.1093/carcin/bgm132

[89] Figueroa, J.D.; Malats, N.; Real, F.X.; Silverman, D.; Kogevinas, M.; Chanock, S.; Welch, R.; Dosemeci, M.; Tardón, A.; Serra, C.; Carrato, A.; García-Closas, R.; Castaño-Vinyals, G.; Rothman, N.; García-Closas, M. Genetic variation in the base excision repair pathway and bladder cancer risk. *Hum. Genet.*, **2007**, *121*, 233-242. dx.doi.org/10.1007/s00439-006-0294-y

[90] Choudhury, A.; Elliott, F.; Iles, M.M.; Churchman, M.; Bristow, R.G.; Bishop, D.T.; Kiltie, A.E. Analysis of variants in DNA damage signalling genes in bladder cancer. *BMC Med. Genet.*, **2008**, *9*, 69. dx.doi.org/10.1186/1471-2350-9-69

[91] Grotenhuis, A.J.; Vermeulen, S.H.; Kiemeney, L.A. Germline genetic markers for urinary bladder cancer risk, prognosis and treatment response. *Future Oncol.*, **2010**, *6*, 1433-1460. dx.doi.org/10.2217/fon.10.109

[92] Golka, K.; Selinski, S.; Lehmann, M.L.; Blaszkewicz, M.; Marchan, R.; Ickstadt, K.; Schwender, H.; Bolt, H.M.; Hengstler, J.G. Genetic variants in urinary bladder cancer: collective power of the "wimp SNPs". *Arch. Toxicol.*, **2011**, *85*, 539-554. dx.doi.org/10.1007/s00204-011-0676-3

[93] Chang, D.W., Gu, J., Wu, X. Germline prognostic markers for urinary bladder cancer: obstacles and opportunities. *Urol. Oncol.*, **2012**, *30*, 524-532. dx.doi.org/10.1016/j.urolonc.2012.04.003

[94] Dapic, V.; Carvalho, M.A.; Monteiro, A.N. Breast cancer susceptibility and the DNA damage response. *Cancer Control.*, **2005**, *12*, 127-136. PMID:15855896

[95] Silva, S.N.; Tomar, M.; Paulo, C.; Gomes, B.C.; Azevedo, A.P.; Teixeira, V.; Pina, J.E.; Rueff, J; Gaspar, J.F. Breast cancer risk and common single nucleotide polymorphisms in homologous recombination DNA repair pathway genes XRCC2, XRCC3, NBS1 and RAD51. *Cancer Epidemiol.*, **2010**, *34*, 85-92. dx.doi.org/10.1016/j.canep.2009.11.002

[96] Ralhan, R.; Kaur, J.; Kreienberg, R.; Wiesmuller, L. Links between DNA double strand break repair and breast cancer: accumulating evidence from both familial and nonfamilial cases. *Cancer Lett.*, **2007**, *248*, 1-17. dx.doi.org/10.1016/j.canlet.2006.06.004

[97] Antoniou, A.C.; Pharoah, P.D.; McMullan, G.; Day, N.E.; Ponder, B.A.; Easton, D. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. *Genet. Epidemiol.*, **2001**, *21*, 1-18. dx.doi.org/10.1002/gepi.1014

[98] Thompson, L.H. Recognition, signaling, and repair of DNA double-strand breaks produced by ionizing radiation in mammalian cells: the molecular choreography. *Mutat Res.*, **2012**, *751*, 158-246. dx.doi.org/10.1016/j.mrrev.2012.06.002

[99] Stratton, M.R.; Rahman, N. The emerging landscape of breast cancer susceptibility. *Nat. Genet.*, **2008**, *40*, 17-22. dx.doi.org/10.1038/ng.2007.53

[100] Kuschel, B.; Auranen, A.; McBride, S.; Novik, K.L.; Antoniou, A.; Lipscombe, J.M.; Day, N.E.; Easton, D.F.; Ponder, B.A.; Pharoah, P.D.; Dunning, A. Variants in DNA double-strand break repair genes and breast cancer susceptibility. *Hum. Mol. Genet.*, **2002**, *11*, 1399-1407. dx.doi.org/10.1093/hmg/11.12.1399

[101] Millikan, R.C.; Player, J.S.; Decotret, A.R.; Tse, C.K.; Keku, T. Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **2005**, *14*, 2326-2334. /dx.doi.org/10.1158/1055-9965.EPI-05-0186

[102] Försti, A.; Angelini, S.; Festa, F.; Sanyal, S.; Zhang, Z.; Grzybowska, E.; Pamula, J.; Pekala, W.; Zientek, H.; Hemminki, K.; Kumar, R. Single nucleotide polymorphisms in breast cancer. *Oncol Rep.*, **2004**, *11*, 917-922. PMID 15010895

[103] Zhang, L.; Zhang, Z.; Yan, W. Single nucleotide polymorphisms for DNA repair genes in breast cancer patients. *Clin. Chim. Acta*, **2005**, *359*, 150-155. dx.doi.org/10.1016/j.cccn.2005.03.047

[104] Smith, T.R.; Levine, E.A.; Freimanis, R.I.; Akman, S.A.; Allen, G.O.; Hoang, K.N.; Liu-Mares, W.; Hu, J.J. Polygenic model of DNA repair genetic polymorphisms in human breast cancer risk. *Carcinogenesis*, **2008**, *29*, 2132-2138. dx.doi.org/10.1093/carcin/bgn193

[105] Desjardins, S.; Beauparlant, J.C.; Labrie, Y.; Ouellette, G.; Durocher, F. INHERIT BRCAs. Variations in the NBN/NBS1 gene and the risk of breast cancer in non-BRCA1/2 French Canadian families with high risk of breast cancer. *BMC Cancer*, **2009**, *9*, 181. /dx.doi.org/10.1186/1471-2407-9-181

[106] Hsu, H.M.; Wang, H.C.; Chen, S.T.; Hsu, G.C.; Shen, C.Y.; Yu, J.C. Breast cancer risk is associated with the genes encoding the DNA double-strand break repair Mre11/Rad50/Nbs1 complex. *Cancer Epidemiol. Biomarkers Prev.*, **2007**, *16*, 2024-2032 dx.doi.org/10.1158/1055-9965.EPI-07-0116

[107] Lu, J.; Wei, Q.; Bondy, M.L.; Li, D.; Brewster, A.; Shete, S.; Yu, T.K.; Sahin, A.; Meric-Bernstam, F.; Hunt, K.K.; Singletary, S.E.;

Ross, M.I.; Wang, L.E. Polymorphisms and haplotypes of the NBS1 gene are associated with risk of sporadic breast cancer in non-Hispanic white women <or=55 years. *Carcinogenesis*, **2006**, *27*, 2209-2216 /dx.doi.org/10.1093/carcin/bgl077

[108] Calvert, P.M.; Frucht, H. The genetics of colorectal cancer. *Ann. Intern. Med.*, **2002**, *137*, 603-612.

[109] Parkin, D.M.; Bray, F.; Ferlay, J.; Pisani, P. Global cancer statistics, 2002, CA. *Cancer J. Clin.*, **2005**, *55*, 74-108. /dx.doi.org/10.3322/canjclin.55.2.74

[110] Boyle, P.; Ferlay, J. Cancer incidence and mortality in Europe, 2004. *Ann. Oncol.*, **2005**, *16*, 481-488. dx.doi.org/10.1093/annonc/mdi015

[111] Pardini, B.; Naccarati, A.; Novotny, J.; Smerhovsky, Z.; Vodickova, L.; Polakova, V.; Hanova, M.; Slyskova, J.; Tulupova, E.; Kumar, R.; Bortlik, M.; Barale, R.; Hemminki, K.; Vodicka, P. DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech Republic. *Mutat. Res.*, **2008**, 638, 146-153. dx.doi.org/10.1016/j.mrfmmm.2007.09.008

[112] De la Chapelle. A. Genetic predisposition to colorectal cancer. *Nat. Rev. Cancer*, **2004**, *4*, 769-780. /dx.doi.org/10.1038/nrc1453

[113] Giovannucci, E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.*, **2001**, *10*, 725-731.

[114] Terry, P.; Giovannucci, E.; Michels, K.B.; Bergkvist, L.; Hansen, H.; Holmberg, L.; Wolk, A. Fruit, vegetables, dietary fiber, and risk of colorectal cancer, *J. Natl. Cancer Inst.*, **2001**, *93*, 525-533. dx.doi.org/10.1093/jnci/93.7.525

[115] Jemal, A.; Seigel, R.; Ward, E.; Murray, T.; Xu, J.; Thun, M.J. Cancer statistics, 2007. *CA Cancer J. Clin.*, **2007**, *57*, 43-66. /dx.doi.org/10.3322/canjclin.57.1.43

[116] Ziółkowska-Suchanek, I.; Mosor, M.; Wierzbicka, M.; Fichna, M.; Rydzanicz, M.; Nowak, J. Association of polymorphisms and haplotypes of the NBN gene with laryngeal cancer and multiple primary tumors of the head and neck. *Head Neck*, **2012**, *34*, 376-383. dx.doi.org/10.1002/hed.21741

[117] Carvalho, A.L.; Nishimoto, I.N.; Califano, J.A.; Kowalski, L.P. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int. J. Cancer*, **2005**, *114*, 806-808. dx.doi.org/10.1002/ijc.20740

[118] Jemal, A.; Seigel, R.; Ward, E.; Murray, T.; Xu, J.; Smigal, C.; Thun, M.J. Cancer statistics, 2006. *CA Cancer J. Clin.*, **2006**, *56*, 106-130 /dx.doi.org/10.3322/canjclin.56.2.106

[119] Lin, C.L.; Lo, W.F.; Lee, T.H.; Ren, Y.; Hwang, S.L.; Cheng, Y.F.; Chen, C.L.; Chang, Y.S.; Lee, S.P.; Rickinson, A.B.; Tam, P.K. Immunization with Epstein–Barr Virus (EBV) peptide-pulsed dendritic cells induces functional CD8þ T-cell immunity and may lead to tumor regression in patients with EBV-positive nasopharyngeal carcinoma. *Cancer Res.*, **2002**, *62*, 6952-6958 PMID: 12460912

[120] Chen, C.J.; Liang, K.Y.; Chang, Y.S., Wang, Y.F.; Hsieh, T.; Hsu, M.M.; Chen, J.Y.; Liu, M.Y. Multiple risk factors of nasopharyngeal carcinoma: Epstein–Barr virus, malarial infection, cigarette smoking and familial tendency. *Anticancer Res.*, **1990**, *10*, 547-553. PMID: 2161639

[121] Gulley, M.L. Molecular diagnosis of Epstein–Barr virus-related diseases. *J. Mol. Diagn.*, **2001**, *3*, 1-10. dx.doi.org/10.1016/S1525-1578(10)60642-3

[122] Pattle, S.B.; Farrell, P.J. The role of Epstein–Barr virus in cancer. *Expert Opin. Biol. Ther.*, **2006**, *6*, 1193-1205. dx.doi.org/10.1517/14712598.6.11.1193

[123] Zeng, Z.; Zhou, Y.; Zhang, W.; Li, X.; Xiong, W.; Liu, H.; Fan, S.; Qian, J.; Wang, L.; Li, Z.; Shen, S.; Li, G. Family-based association analysis validates chromosome 3p21 as a putative nasopharyngeal carcinoma susceptibility locus. *Genet. Med.*, **2006**, *8*, 156-160. /dx.doi.org/10.1097/01.gim.0000196821.87655.d0

[124] Zeng, Z.Y.; Zhou, Y.H.; Zhang, W.L.; Xiong, W.; Fan, S.Q.; Li, X.L.; Luo, X.M.; Wu, M.H.; Yang, Y.X.; Huang, C.; Cao, L.; Tang, K.; Qian, J.; Shen, S.R.; Li, G.Y. Gene expression profiling of nasopharyngeal carcinoma reveals the abnormally regulated Wnt signaling pathway. *Hum. Pathol.*, **2007**, *38*, 120-133. dx.doi.org/10.1016/j.humpath.2006.06.023

[125] Zheng, H.; Li, L.L.; Hu, D.S.; Deng, X.Y.; Cao, Y. Role of Epstein–Barr virus encoded latent membrane protein 1 in the carcinogenesis of nasopharyngeal carcinoma. *Cell Mol. Immunol.*, **2007**, *4*, 185-196. /dx.doi.org/10.1016/j.humpath.2006.06.023

[126] Zheng, J.; Zhang, C.; Jiang, L.; You, Y.; Liu, Y.; Lu, J.; Zhou, Y. Functional NBS1 polymorphism is associated with occurrence and advanced disease status of nasopharyngeal carcinoma. *Mol. Carcinog.*, **2011**, *50*, 689-696. dx.doi.org/10.1002/mc.20803

[127] Perz, J.F.; Armstrong, G.L.; Farrington, L.A.; Hutin, Y.J.; Bell, B.P. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J. Hepatol.*, **2006**, *45*, 529-538. dx.doi.org/10.1016/j.jhep.2006.05.013

[128] El-Serag, H.B.; Davila, J.A.; Petersen, N.J.; McGlynn, K.A. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann. Intern. Med.*, **2003**, *139*, 817-823. dx.doi.org/10.7326/0003-4819-139-10-200311180-00009

[129] Shiraha, H.; Yamamoto, K.; Namba, M. Human hepatocyte carcinogenesis (review). *Int. J. Oncol.*, **2013**, *42*, 1133-1138. doi: 10.3892/ijo.2013.1829

[130] Davis, G.L.; Alter, M.J.; El-Serag, H.; Poynard, T.; Jennings, L.W. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*, **2010**, *138*, 513-521. doi: 10.1053/j.gastro.2009.09.067

[131] Mazzaferro, V.; Regalia, E.; Doci, R.; Andreola, S.; Pulvirenti, A.; Bozzetti, F.; Montalto, F.; Ammatuna, M.; Morabito, A.; Gennari, L. Liver transplantation for the treatment small hepatocellular carcinomas in patients with cirrhosis. *N. Engl. J. Med.*, **1996**, *334*, 693-700. dx.doi.org/10.1056/NEJM199603143341104

[132] Huang, M.D.; Chen, X.F.; Xu, G.; Wu, Q.Q.; Zhang, J.H.; Chen, G.F.; Cai, Y.; Qi, F.Z. Genetic variation in the NBS1 gene is associated with hepatic cancer risk in a Chinese population. *DNA Cell Biol.*, **2012**, *31*,678-82. dx.doi.org/10.1089/dna.2011.1421

[133] Richardson, R.B. Promotional etiology for common childhood acute lymphoblastic leukemia: the infective lymphoid recovery hypothesis. *Leuk. Res.*, **2011**, *35*, 1425-1431. dx.doi.org/10.1016/j.leukres.2011.07.023

[134] Sherborne, A.L.; Hemminki, K.; Kumar, R.; Bartram, C.R.; Stanulla, M.; Schrappe, M.; Petridou, E.; Semsei, A.F.; Szalai, C.; Sinnett, D.; Krajinovic, M.; Healy, J.; Lanciotti, M.; Dufour, C.; Indaco, S.; El-Ghouroury, E.A.; Sawangpanich, R.; Hongeng, S.; Pakakasama, S.; Gonzalez-Neira, A.; Ugarte, E.L.; Leal, V.P.; Espinoza, J.P.; Kamel, A.M.; Ebid, G.T.; Radwan, E.R.; Yalin, S.; Yalin, E.; Berkoz, M.; Simpson, J.; Roman, E.; Lightfoot, T.; Hosking, F.J.; Vijayakrishnan, J.; Greaves, M.; Houlston, R.S. Rationale for an international consortium to study inherited genetic susceptibility to childhood acute lymphoblastic leukemia. *Haematologica*, **2011**, *96*, 1049-1054. dx.doi.org/10.3324/haematol.2011.040121

[135] Loh, M.L.; Mullighan, C.G. Advances in the genetics of high-risk childhood B-progenitor acute lymphoblastic leukemia and juvenile myelomonocytic leukemia: implications for therapy. *Clin Cancer Res.*, **2012**, *18*, 2754-2767. dx.doi.org/10.1158/1078-0432.CCR-11-1936

[136] Rubnitz, J.E.; Inaba, H. Childhood acute myeloid leukaemia. *Br. J. Haematol.*, **2012**, *159*, 259-276. dx.doi.org/10.1111/bjh.12040

[137] Puumala, S.E.; Ross, J.A.; Aplenc, R.; Spector, L.G. Epidemiology of childhood acute myeloid leukemia. *Pediatr. Blood Cancer*, **2013**, *60*, 728-733 dx.doi.org/10.1002/pbc.24464.

[138] Beyermann, B.; Agthe, A.G.; Adams, H.P.; Seeger, K.; Linderkamp, C.; Goetze, G.; Ludwig, W.D.; Henze, G. Clinical features and outcome of children marrow relapse of acute lymphoblastic leukemia expressing BCR-ABL fusion transcripts. BFM Relapse Study Group. *Blood*, **1996**, *87*, 1532-1538. PMID: 8608244

[139] Seeger, K.; Adams, H.P.; Buchwald, D.; Beyermann, B.; Kremens, B.; Niemeyer, C.; Ritter, J.; Schwabe, D.; Harms, D.; Schrappe, M.; Henze, G. TEL-AML1 fusion transcript in relapsed childhood acute lymphoblastic leukemia. The Berlin-Frankfurt-Munster Study Group. *Blood*, **1998**, *91*, 1716-1722. PMID:9473238

[140] Offit, K. *Introduction to Cancer Genetics and Risk Assessment.* In: *American Society of Hematology, Education Program Book, New Orleans: American Society of Hematology*, **1999**; pp. 9-17.

[141] Richardson, C.; Jasin, M. Frequent chromosomal translocations induced by DNA double-strand breaks. *Nature*, **2000**, *405*, 697-700. PMID: 10864328

[142] Elliott, B.; Jasin, M. Double-strand breaks and translocations in cancer. *Cell Mol. Life Sci.*, **2002**, *59*, 373-385. DOI:10.1007/s00018-002-8429-3

[143] Agarwal, S.; Tafel, A.A.; Kanaar, R. DNA double-strand break repair and chromosome translocations. *DNA Repair (Amst)*, **2006**, *5*, 1075-1081. dx.doi.org/10.1016/j.dnarep.2006.05.029

[144] Chokkalingam, A.P.; Bartley, K.; Wiemels, J.L.; Metayer, C.; Barcellos, L.F.; Hansen, H.M.; Aldrich, M.C.; Guha, N.; Urayama, K.Y.; Scélo, G.; Chang, J.S.; Month, S.R.; Wiencke, J.K.; Buffler, P.A. Haplotypes of DNA repair and cell cycle control genes, X-ray exposure, and risk of childhood acute lymphoblastic leukemia. *Cancer Causes Control*, **2011**, *22*, 1721-1730. dx.doi.org/10.1007/s10552-011-9848-y

[145] Schuetz, J.M.; MaCarthur, A.C.; Leach, S.; Lai, A.S.; Gallagher, R.P.; Connors, J.M.; Gascoyne, R.D.; Spinelli, J.J.; Brooks-Wilson, A.R. Genetic variation in the NBS1, MRE11, RAD50 and BLM genes and susceptibility to non-Hodgkin lymphoma. *BMC Med. Genet.*, **2009**, *10*, 117. dx.doi.org/10.1186/1471-2350-10-117

[146] Monroy, C.M.; Cortes, A.C.; Lopez, M.; Rourke, E.; Etzel, C.J.; Younes, A.; Strom, S.S.; El-Zein, R. Hodgkin lymphoma risk: role of genetic polymorphisms and gene-gene interactions in DNA repair pathways. *Mol. Carcinog.*, **2011**, *50*, 825-834. dx.doi.org/10.1002/mc.20747

[147] Stiller, C.A.; Parkin, D.M. Geographic and ethnic variations in the incidence of childhood cancer. *British Medical Bulletin*, **1996**, *52*, 682-703. dx.doi.org/10.1093/oxfordjournals.bmb.a011577

[148] Mosor, M.; Ziółkowska, I.; Januszkiewicz-Lewandowska, D.; Nowakm J. Polymorphisms and haplotypes of the NBS1 gene in childhood acute leukaemia. *Eur. J. Cancer*, **2008**, *44*, 2226-2232. dx.doi.org/10.1016/j.ejca.2008.06.026

[149] Li, N.; Xu, Y.; Zheng, J.; Jiang, L.; You, Y.; Wu, H.; Li, W.; Wu, D.; Zhou, Y. NBS1 rs1805794G>C polymorphism is associated with decreased risk of acute myeloid leukemia in a Chinese population. *Mol. Biol. Rep.*, **2013**, *40*, 3749-3756. dx.doi.org/10.1007/s11033-012-2451-9

[150] Goricar, K.; Erculj, N.; Zadel, M.; Dolzan, V. Genetic polymorphisms in homologous recombination repair genes in healthy Slovenian population and their influence on DNA damage. *Radiol. Oncol.*, **2012**, *46*, 46-53. doi: 10.2478/v10019-012-0001-7

[151] Herbst, R.S.; Heymach, J.V.; Lippman, S.M. Lung cancer. *N. Engl. J. Med.*, **2008**, *359*, 1367-1380. dx.doi.org/10.1056/NEJMra0802714

[152] El-Basmy, A.; Al-Mohannadi, S.; Al-Awadi, A. Some epidemiological measures of cancer in kuwait: national cancer registry data from 2000–2009. *Asian Pac. J. Cancer Prev.*, **2012**, *13*, 3113-3118. dx.doi.org/10.7314/APJCP.2012.13.7.3113

[153] Pennathur, A.; Luketich, J.D. Multimodal treatment with surgical resection for stage IIIB non-small-cell lung cancer. *Lancet Oncol.*, **2009**, *10*, 742-743. dx.doi.org/10.1016/S1470-2045(09)70205-0

[154] De Ruysscher, D.; Faivre-Finn, C.; Nestle, U.; Hurkmans, C.W.; Le Péchoux, C.; Price, A.; Senan, S. European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. *J. Clin. Oncol.*, **2010**, *28*, 5301-5310. dx.doi.org/10.1200/JCO.2010.30.3271

[155] Fidias, P.; Novello, S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. *J. Clin. Oncol.*, **2010**, *28*, 5116-5123. dx.doi.org/10.1200/JCO.2010.30.7074

[156] Goldstraw, P.; Ball, D.; Jett, J.R.; Le Chevalier, T.; Lim, E.; Nicholson, A.G.; Shepherd, F.A. Non-small-cell lung cancer. *Lancet*, **2011**, *378*, 1727-1740. dx.doi.org/10.1016/S0140-6736(10)62101-0

[157] van Meerbeeck, J.P.; Fennell, D.A.; De Ruysscher, D.K. Small cell lung cancer. *Lancet*, **2011**, *378*, 1741-1755. dx.doi.org/10.1016/S0140-6736(11)60165-7

[158] Brennan, P.; Hainaut, P.; Boffetta, P. Genetics of lung-cancer susceptibility. *Lancet Oncol.*, **2011**, *12*, 399-408. dx.doi.org/10.1016/S1470-2045(10)70126-1

[159] Dong, L.M.; Potter, J.D.; White, E.; Ulrich, C.M.; Cardon, L.R.; Peters, U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA*, **2008**, *299*, 2423-2436. dx.doi.org/10.1001/jama.299.20.2423

[160] Park, S.L.; Bastani, D.; Goldstein, B.Y.; Chang, S.C.; Cozen, W.; Cai, L.; Cordon-Cardo, C.; Ding, B.; Greenland, S.; He, N.; Hussain, S.K.; Jiang, Q.; Lee, Y.C.; Liu, S.; Lu, M.L.; Mack, T.M.; Mao, J.T.; Morgenstern, H.; Mu, L.N.; Oh, S.S.; Pantuck, A.; Papp, J.C.; Rao, J.; Reuter, V.E.; Tashkin, D.P.; Wang, H.; You, N.C.; Yu, S.Z.; Zhao, J.K.; Zhang, Z.F. Associations between NBS1 polymorphisms, haplotypes and smoking-related cancers. *Carcinogenesis*, **2010**, *31*, 1264-1271. dx.doi.org/10.1093/carcin/bgq096

[161] Medina, P.P.; Ahrendt, S.A.; Pollan, M.; Fernandez, P.; Sidransky, D.; Sanchez-Cespedes, M. Screening of homologous recombination gene polymorphisms in lung cancer patients reveals an association of the NBS1-185Gln variant and p53 gene mutations. *Cancer Epidemiol. Biomarkers Prev.*, **2003**, *12*, 699-704. PMID:12917199

[162] Cho, S.; Kim, M.J.; Choi, Y.Y.; Yoo, S.S.; Lee, W.K.; Lee, E.J.; Jang, E.J.; Bae, E.Y.; Jin, G.; Jeon, H.S.; Lee, S.Y.; Cha, S.I.; Park, T.I.; Kim, C.H.; Park, J.Y. Associations between polymorphisms in DNA repair genes and TP53 mutations in non-small cell lung cancer. *Lung Cancer*, **2011**, *73*, 25-31. dx.doi.org/10.1016/j.lungcan.2010.10.023

[163] Kumar, R.; Tekkok, I.H.; Jones, R.A. Intracranial tumours in the first 18 months of life. *Childs Nerv. Syst.*, **1990**, *6*, 371-374. dx.doi.org/10.1007/BF00302220

[164] Lantos, P.L.; Louis, D.N.; Rosenblum, M.K.; Kleihues, P. *Tumours of the nervous system*. In: *Greenfield's neuropathology*, 7th ed.; Graham, D.I.; Lantos, P.L.; Eds.; Arnold: London, **2002**; pp. 767-1052.

[165] Louis, D.N.; Ohgaki, H.; Wiestler, O.D.; Cavenee, W.K.; Ed. *WHO classification of tumours of the central nervous system.* IARC: Lyon, **2007**. ISBN-13 9789283224303

[166] Eberhart, C.G.; Cavenee, W.K.; Pietsch, T. *Naevoid basal cell carcinoma syndrome*. In: *WHO classification of tumours of the central nervous system*.; Louis, D.N.; Ohgaki, H.; Wiestler, O.D.; Cavenee,W.K.; Eds.; IARC: Lyon, **2007**; pp. 232-233. ISBN-13 9789283224303

[167] Cavenee, W.K.; Burger, P.C.; Leung, S.Y.; VanMeir, E.G. *Turcot syndrome*. In: *WHO classification of tumours of the central nervous system*.; Louis, D.N.; Ohgaki, H.; Wiestler, O.D.; Cavenee,W.K.; Eds.; IARC: Lyon, **2007**; pp. 229-231. ISBN-13 9789283224303

[168] Huang, J.; Grotzer, M.A.; Watanabe, T.; Hewer, E.; Pietsch, T.; Rutkowski, S.; Ohgaki, H. Mutations in the Nijmegen breakage syndrome gene in medulloblastomas. *Clin. Cancer Res.*, **2008**, *14*, 4053-4058. dx.doi.org/10.1158/1078-0432.CCR-08-0098

[169] Hayward, N.K. Genetics of melanoma predisposition. *Oncogene*, **2003**, *22*, 3053-3062. dx.doi.org/10.1038/sj.onc.1206445

[170] Lafuente, A.; Molina, R.; Palou, J.; Castel, T.; Moral, A.; Trias, M. Phenotype of glutathione S-transferase Mu (GSTM1) and susceptibility to malignant melanoma. MMM group. Multidisciplinary Malignant Melanoma Group. *Br. J. Cancer*, **1995**, *72*, 324-326. dx.doi.org/10.1038/bjc.1995.332

[171] Strange, R.C.; Ellison, T.; Ichii-Jones, F.; Bath, J.; Hoban, P.; Lear, J.T.; Smith, A.G.; Hutchinson, P.E.; Osborne, J.; Bowers, B.; Jones, P.W.; Fryer, A.A. Cytochrome P450 CYP2D6 genotypes: association with hair colour, Breslow thickness and melanocyte stimulating hormone receptor alleles in patients with malignant melanoma. *Pharmacogenetics*, **1999**, *9*, 269-276. /dx.doi.org/10.1097/00008571-199906000-00001

[172] Hutchinson, P.E.; Osborne, J.E.; Lear, J.T.; Smith, A.G.; Bowers, P.W.; Morris, P.N.; Jones, P.W.; York, C.; Strange, R.C.; Fryer, A.A. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin. Cancer Res.*, **2000**, *6*, 498-504. PMID:10690530

[173] Box, N.F.; Duffy, D.L.; Chen, W.; Stark, M.; Martin, N.G.; Sturm, R.A.; Hayward, N.K. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. *Am. J. Hum. Genet.*, **2001**, *69*, 765-773. dx.doi.org/10.1086/323412

[174] Shahbazi, M.; Pravica, V.; Nasreen, N.; Fakhoury, H.; Fryer, A.A.; Strange, R.C., Hutchinson, P.E.; Osborne, J.E.; Lear, J.T.; Smith, A.G.; Hutchinson, I.V. Association between functional polymorphism in EGF gene and malignant melanoma. *Lancet*, **2002**, *359*, 397-401. dx.doi.org/10.1016/S0140-6736(02)07600-6

[175] Meyer, P.; Sergi, C.; Garbe, C. Polymorphisms of the BRAF gene predispose males to malignant melanoma. *J. Carcinog.*, **2003**, *2*, 7. DOI: 10.1186/1477-3163-2-7

[176] Halsall, J.A.; Osborne, J.E.; Potter, L.; Pringle, J.H.; Hutchinson, P.E. A novel polymorphism in the 1A promoter region of the vitamin D receptor is associated with altered susceptibility and prognosis in malignant melanoma. *Br. J. Cancer*, **2004**, *91*, 765-770. PMID:15238985

[177] James, M.R.; Roth, R.B.; Shi, M.M.; Kammerer, S.; Nelson, M.R.; Stark, M.S.; Dumenil, T.; Montgomery, G.W.; Hayward, N.K.; Martin, N.G.; Braun, A.; Duffy, D.L. BRAF polymorphisms and risk of melanocytic neoplasia. *J. Invest. Dermatol.*, **2005**, *125*, 1252-1258. /dx.doi.org/10.1111/j.0022-202X.2005.23937.x

[178] Seemanová, E.; Sperling, K.; Neitzel, H.; Varon, R.; Hadac, J.; Butova, O.; Schröck, E.; Seeman, P.; Digweed, M. Nijmegen breakage syndrome (NBS) with neurological abnormalities and without chromosomal instability. *J. Med. Genet.*, **2005**, *43*, 218-

224. /dx.doi.org/10.1136/jmg.2005.035287

[179] DiSaia, P.J.; Creasman, W.T. *Clinical gynecologic oncology*. 6th ed.; Mosby Inc.: St. Louis, **2002**; p 289. ISBN 032301089X

[180] Fathalla, M.F. Incessant ovulation-a factor in ovarian neoplasia? *Lancet*, **1971**, *298*, 163. doi:10.1016/S0140-6736(71)92335-X

[181] Godwin, A.K.; Testa, J.R.; Handel, L.M.; Liu, Z.; Vanderveer, L.A.; Tracey, P.A.; Hamilton, T.C. Spontaneous transformation of rat ovarian surface epithelial cells: association with cytogenetic changes and implications of repeated ovulation in the etiology of ovarian cancer. *J. Natl. Cancer Inst.*, **1992**, *84*, 592-601. dx.doi.org/10.1093/jnci/84.8.592

[182] Auranen, A.; Song, H.; Waterfall, C.; Dicioccio, R.A.; Kuschel, B.; Kjaer, S.K.; Hogdall, E.; Hogdall, C.; Stratton, J.; Whittemore, A.S.; Easton, D.F.; Ponder, B.A.; Novik, K.L.; Dunning, A.M.; Gayther, S.; Pharoah, P.D. Polymorphisms in DNA repair genes and epithelial ovarian cancer risk. *Int. J. Cancer*, **2005**, *117*, 611-618. /dx.doi.org/10.1002/ijc.21047

[183] Jemal, A.; Murray T, Ward E, Samuels, A.; Tiwari, R.C.; Ghafoor, A.; Feuer, E.J.; Thun, M.J. Cancer statistics, 2005. *CA Cancer J. Clin.*, **2005**, *55*, 10-30. dx.doi.org/10.3322/canjclin.55.1.10

[184] Nelson, W.G.; De Marzo, A.M.; DeWeese, T.L.; Isaacs, W.B. The role of inflammation in the pathogenesis of prostate cancer [discussion S11 – 2]. *J. Urol.*, **2004**, *172*, S6-S11. dx.doi.org/10.1097/01.ju.0000142058.99614.ff

[185] Schaid, D.J. The complex genetic epidemiology of prostate cancer. *Hum. Mol. Genet.*, **2004**, *13*, R103-R121. doi: 10.1093/hmg/ddh072

[186] Silva, J.; Teixeira, A.L.; Lobo, F.; Maurício, J.; Medeiros, R. DNA repair system and prostate cancer progression: the role of NBS1 polymorphism (rs1805794). *DNA Cell Biol.*, **2012**, *31*, 1182-1186. dx.doi.org/10.1089/dna.2011.1562

[187] Lipworth, L.; Tarone, R.E.; McLaughlin, J.K. The epidemiology of renal cell carcinoma. *J. Urol.*, **2006**, *176*, 2353-2358. dx.doi.org/10.1016/j.juro.2006.07.130

[188] Christmann, M.; Tomicic, M.T.; Roos, W.P.; Kaina, B. Mechanisms of human DNA repair: an update. *Toxicology*, **2003**, *193*, 3-34. dx.doi.org/10.1016/S0300-483X(03)00287-7

[189] Hirata, H.; Hinoda, Y.; Matsuyama, H.; Tanaka, Y.; Okayama, N.; Suehiro, Y.; Zhao, H.; Urakami, S.; Kawamoto, K.; Kawakami, T.; Igawa, M.; Naito, K.; Dahiya, R. Polymorphisms of DNA repair genes are associated with renal cell carcinoma. *Biochem. Biophys. Res. Commun.*, **2006**, *342*, 1058-1062. dx.doi.org/10.1016/j.bbrc.2006.02.030

[190] Margulis, V.; Lin, J.; Yang, H.; Wang, W.; Wood, C.G.; Wu, X. Genetic susceptibility to renal cell carcinoma: the role of DNA double-strand break repair pathway. *Cancer Epidemiol. Biomarkers Prev.*, **2008**, *17*, 2366-2373. dx.doi.org/10.1158/1055-9965.EPI-08-0259

[191] Bastos, H.N.; Antão, M.R.; Silva, S.N.; Azevedo, A.P., Manita, I.; Teixeira, V.; Pina, J.E.; Gil, O.M.; Ferreira, T.C.; Limbert, E.; Rueff, J.; Gaspar, J.F. Association of polymorphisms in genes of the homologous recombination DNA repair pathway and thyroid cancer risk. *Thyroid*, **2009**, *19*, 1067-1075. dx.doi.org/10.1089/thy.2009.0099

[192] Ron, E.; Lubin, J.H.; Shore, R.E.; Mabuchi, K.; Modan, B.; Pottern, L.M.; Schneider, A.B.; Tucker, M.A.; Boice, J.D. Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat. Res.*, **1995**, *141*, 259-277.

[193] Lund, E.; Galanti, M.R. Incidence of thyroid cancer in Scandinavia following fallout from atomic bomb testing: an analysis of birth cohorts. *Cancer Causes Control.*, **1999**, *10*, 181-187. PMID: 10454063

[194] Schlumberger, M.; Cailleux, A.F.; Suarez, H.G.; Vathaire, F. Irradiation and second cancers: the thyroid as a case in point. *Acad. Sci. Paris Sci. de la vie*, **1999**, *32*, 205-213. dx.doi.org/10.1016/S0764-4469(99)80045-6

[195] Kirsch-Volders, M.; Mateuca, R.A.; Roelants, M.; Tremp, A.; Zeiger, E.; Bonassi, S.; Holland, N.; Chang, W.P.; Aka, P.V.; Deboeck, M.; Godderis, L.; Haufroid, V.; Ishikawa, H.; Laffon, B.; Marcos, R.; Migliore, L.; Norppa, H.; Teixeira, J.P.; Zijno, A.; Fenech, M. The effects of GSTM1 and GSTT1 polymorphisms on micronucleus frequencies in human lymphocytes *in vivo*. *Cancer Epidemiol. Biomark Prev.*, **2006**, *15*, 1038-1042. /dx.doi.org/10.1158/1055-9965.EPI-05-0487

[196] Lu, M.; Lu, J.; Yang, X.; Yang, M.; Tan, H.; Yun, B.; Shi, L. Association between the NBS1 E185Q polymorphism and cancer risk: a meta-analysis. *BMC Cancer*, **2009**, *9*, 124. dx.doi.org/10.1186/1471-2407-9-124

[197] Wang, Z.; Cui, D.; Lu, W. NBS1 8360G > C polymorphism is associated with breast cancer risk: a meta-analysis. *Breast Cancer Res. Treat.*, **2010**, *123*, 557-561. dx.doi.org/10.1007/s10549-010-0772-8

[198] Wang, L.; Cheng, J.; Gao, J.; Wang, J.; Liu, X.; Xiong, L. Association between the NBS1 Glu185Gln polymorphism and lung cancer risk: a systemic review and meta-analysis. *Mol. Biol. Rep.*, **2013**, *3*, 2711-2715. dx.doi.org/10.1007/s11033-012-2358-5

[199] Zienolddiny, S.; Campa, D.; Lind, H.; Ryberg, D.; Skaug, V.; Stangeland, L.; Phillips, D.H.; Canzian, F.; Haugen, A. Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. *Carcinogenesis*, **2006**, *27*, 560-567. dx.doi.org/10.1093/carcin/bgi232

[200] Ryk, C.; Kumar, R.; Thirumaran, R.K.; Hou SM. Polymorphisms in the DNA repair genes XRCC1, APEX1, XRCC3 and NBS1, and the risk for lung cancer in never- and ever-smokers. *Lung Cancer*, **2006**, *54*, 285-292. dx.doi.org/10.1016/j.lungcan.2006.08.004

[201] Stern, M.C.; Lin, J.; Figueroa, J.D.; Kelsey, K.T.; Kiltie, A.E.; Yuan, J.M.; Matullo, G.; Fletcher, T.; Benhamou, S.; Taylor, J.A.; Placidi, D.; Zhang, Z.F.; Steineck, G.; Rothman, N.; Kogevinas, M.; Silverman, D.; Malats, N.; Chanock, S.; Wu, X.; Karagas, M.R.; Andrew, A.S.; Nelson, H.H.; Bishop, D.T.; Sak, S.C.; Choudhury, A.; Barrett, J.H.; Elliot, F.; Corral, R.; Joshi, A.D.; Gago-Dominguez, M.; Cortessis, V.K.; Xiang, Y.B.; Gao, Y.T.; Vineis, P.; Sacerdote, C.; Guarrera, S.; Polidoro, S.; Allione, A.; Gurzau, E.; Koppova, K.; Kumar, R.; Rudnai, P.; Porru, S.; Carta, A.; Campagna, M.; Arici, C.; Park, S.S.; Garcia-Closas, M.; International Consortium of Bladder Cancer. Polymorphisms in DNA repair genes, smoking, and bladder cancer risk: findings from the international consortium of bladder cancer. *Cancer Res.*, **2009**, *69*, 6857-6864. dx.doi.org/10.1158/0008-5472.CAN-09-1091

[202] Ioannidis, J.P.; Boffetta, P.; Little, J.;, O'Brien, T.R.; Uitterlinden, A.G.; Vineis, P.; Balding, D.J.; Chokkalingam, A.; Dolan, S.M.; Flanders, W.D.; Higgins, J.P.; McCarthy, M.I.; McDermott, D.H.; Page, G.P.; Rebbeck, T.R.; Seminara, D.; Khoury, M.J. Assessment of cumulative evidence on genetic associations: interim guidelines. *Int. J. Epidemiol.*, **2008**, *37*, 120-32. dx.doi.org/10.1093/ije/dym159

[203] Vineis, P.; Manuguerra, M.; Kavvoura, F.K.; Guarrera, S.; Allione, A.; Rosa, F.; Di Gregorio, A.; Polidoro, S.; Saletta, F.; Ioannidis, J.P.; Matullo, G. A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. *J. Natl. Cancer Inst.*, **2009**, *101*, 24-36. dx.doi.org/10.1093/jnci/djn437

[204] Ricceri, F.; Matullo, G.; Vineis, P. Is there evidence of involvement of DNA repair polymorphisms in human cancer? *Mutat. Res.*, **2012**, *736*, 117-121. dx.doi.org/10.1016/j.mrfmmm.2011.07.013

[205] Wang, Y.; Cortez, D.; Yazdi, P.; Neff, N.; Elledge, S.J.; Qin, J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. *Genes Dev.*, **2000**, *14*, 927-939. PMID:10783165