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***TP53* Gene Polymorphisms in Cancer Risk: The Modulating Effect of Ageing, Ethnicity and *TP53* Somatic Abnormalities**

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1. Introduction

The multi-talented “guardian of the genome” p53 is fundamental to preventing tumor development through the regulation of important cellular processes such as cell cycle arrest and senescence, DNA replication and repair, apoptosis, metabolism, antioxidant defense, and autophagy, among others. (Chumakov, 2007; Green and Kroemer, 2009; McCarthy, 2011; Olovnikov et al., 2009; Vousden and Prives, 2009; Vousden and Ryan, 2009). p53 protein is encoded by the *TP53* gene (OMIM no. 191170), the structure of which is extremely variable in both healthy and diseased subjects, particularly in cancer, because of multiple germinal and somatic variations (Olivier et al., 2010; Whibley et al., 2009). Currently, approximately 85 polymorphisms and 27580 somatic mutations are known in the *TP53* gene (Petitjean et al., 2007b). In addition, the *TP53* gene, as a classic tumor suppressor, undergoes a loss of heterozygosity (LOH) and hypo- or hypermethylation (Brosh and Rotter, 2009; Sidhu et al., 2005; Soussi, 2007). From all polymorphisms found in the *TP53* gene, three - rs1042522, rs17878362, and rs1625895 - are well studied in terms of functional characterization, distribution in human populations and association with cancer risk. During the last 15 years, the predisposing value of these *TP53* polymorphic variants has been estimated in relation to many human cancers; however, the data are inconsistent.

It is not surprising that cancer risk is a consequence of the interaction between constitutional genetics and environmental exposure. The combination of genetic background (gene-gene interactions) and environmental endo- and exogenous factors varies among individuals of different ethnical groups and might explain the distinct tumor susceptibility. Cancer is an extremely complicated phenotype and, together with the incomplete penetrance of the inherited tumor risk alleles, interaction with environmental risk factors could substantially alter hereditary susceptibility (Perez-Losada et al., 2011). Nutritional aspects, reproductive

factors, and alcohol, smoking, and radiation along with other exposures may considerably influence the genetic background via genotoxic effects or the activation/inhibition of major pathways and modify cancer susceptibility. This statement is especially true of *TP53*, the functionality of which has inducible character and depends on environmental exposure. Additionally, cancer arises as a result of the stepwise accumulation of genetic mutations, chromosomal aberrations and epigenetic alterations (Hanahan and Weinberg, 2011; Marshall, 1991). Thus, *TP53* polymorphisms may define the sequence of mutational events, as previously demonstrated (Denisov et al., 2011; Hrstka et al., 2009; Litviakov et al., 2010; Whibley et al., 2009). Even more importantly, the manifestation of functional roles of *TP53* polymorphisms is tissue- and age-specific, meaning that their effect on p53-controlled processes may vary between cell types and age groups (Azzam et al., 2011; Bonafe et al., 2004; Salvioli et al., 2005). Based on the above reasoning, a simultaneous account of *TP53* polymorphisms and their tissue- and age-specific effects, along with ethnicity-specific genetic background and environmental exposure, may reveal how *TP53* germline variations modify cancer risk. In this review, we focus on the recent findings regarding *TP53* polymorphisms, rs1042522, rs17878362, and rs1625895, their functional role and association with cancer risk, their relationships with environmental exposure and somatic aberrations in tumors, as well as discuss some hypotheses explaining the present contradictions in the biological role of *TP53* variations in cancer.

2. Functional *TP53* polymorphisms and cancer risk

2.1 *TP53* polymorphisms: The functional value

The *TP53* rs1042522 (Ex4+119C>G: C and G alleles) polymorphism displays substitution of C to G in codon 72 of exon 4 of the *TP53* gene, changing the amino acid from proline (Pro) to arginine (Arg) in the proline-rich domain of p53 protein (Harris et al., 1986). p53 forms p53Pro and p52Arg are characterized by molecular differences in protein structure (Table 1); however, the data are contradictory and inconclusive (Naldi et al., 2010; Ozeki et al., 2011; Thomas et al., 1999). In addition, there is no final opinion concerning the influence of *TP53* rs1042522 polymorphism on the p53 mRNA level (Nikbahkt Dastjerdi, 2011; Ribeiro et al., 1997; Siddique et al., 2005; Wang et al., 1999). Further, it is beyond any doubt that p53Pro and p53Arg differ in their capability to regulate p53-dependent cell processes (Table 1). Many thousands of years ago, precisely such p53 functional differentiation was the reason for dramatic changes in the proportion of rs1042522 alleles from equatorial areas to northern latitudes (Beckman et al., 1994; Sjalander et al., 1996). In particular, the rs1042522 C allele is the ancestral form with ~60-95% frequency in African populations, whereas the G allele arose some 30,000 to 50,000 years ago and increased in percentage as populations migrated farther north, where its allele frequency reached 75-85% (Hirshfield et al., 2010; Jeong et al., 2010). The most likely components of evolutionary selection pressure fixing *TP53* alleles into these geographic regions are implantation and reproduction, as well as sunburn resistance (Hirshfield et al., 2010; Hu et al., 2011; Jeong et al., 2010), the antithetic regulation of which has been demonstrated for p53 rs1042522 protein forms (Table 1). Specifically, the rs1042522 G allele exhibits 2-fold higher transcriptional activity toward the *LIF* gene, which encodes a cytokine that is required for optimal implantation and reproduction, compared with the C allele (Feng et al., 2011; Jeong et al., 2010; Kang et al., 2009).

	p53 protein forms						Ref.
	rs1042522		rs17878362		rs1625895		
	G	C	A1	A2	G	A	
p53 protein structure	Identical		Altered topology of G-quadruplexes in intron 3		-	-	(Marcel et al., 2011; Naldi et al., 2010; Ozeki et al., 2011; Thomas et al., 1999)
	Different						
p53 mRNA level	High	Low	High	Low	-	-	(Gemignani et al., 2004; Nikbahkt Dastjerdi, 2011; Ribeiro et al., 1997; Siddique et al., 2005)
	Identical						
Capability to							
transactivation	Low	High	-	-	-	-	(Frank et al., 2011; Thomas et al., 1999)
cell cycle arrest	Low	High	-	-	-	-	(Frank et al., 2011; Pim and Banks, 2004)
senescence induction	Low	High	-	-	-	-	(Frank et al., 2011; Salvioli et al., 2005)
DNA repair	Low	High	High	Low	High	Low	(Siddique and Sabapathy, 2006; Wu et al., 2002)
genomic stability maintenance	Low	High	-	-	High	Low	(Litviakov et al., 2010; Qiu et al., 2008; Schwartz et al., 2011; Siddique and Sabapathy, 2006)
apoptosis activation							
in extrinsic pathway	Low	High	High	Low	High	Low	(Bendesky et al., 2007; Biroş et al., 2002; Bonafe et al., 2002; Dumont et al., 2003; Pim and Banks, 2004; Schneider-Stock et al., 2004b; Siddique and Sabapathy, 2006; Wu et al., 2002)
in intrinsic pathway	High	Low					
suppression of transformed cell growth	High	Low	-	-	-	-	(Thomas et al., 1999)
survival in hypoxia	High	Low	-	-	-	-	(Sansone et al., 2007; Vannini et al., 2008)
induction of cell death in hypoxia	Low	High	-	-	-	-	

cell-cell adhesion activation	High	Low	-	-	-	-	(Jeong et al., 2010)
reproduction	High	Low	-	-	-	-	(Feng et al., 2011; Jeong et al., 2010; Kang et al., 2009; Kay et al., 2006)
degradation mediated by							
E6 oncoprotein	High	Low	-	-	-	-	(Storey et al., 1998)
MDM2 ubiquitin ligase	High	Low	-	-	-	-	(Dumont et al., 2003; Ozeki et al., 2011)
	Low	High					
sunburn	High	Low	-	-	-	-	(McGregor et al., 2002; Pezeshki et al., 2006)

Table 1. Structural and functional characteristics of p53 proteins encoded by *TP53* (rs1042522, rs17878362 and rs1625895) polymorphisms.

Moreover, the C allele was found to be increased in women with recurrent implantation failure and individuals undergoing *in vitro* fertilization (IVF), and is a risk factor for implantation failure after IVF (Kang et al., 2009; Kay et al., 2006). Interestingly, the frequency of the G allele has been positively correlated with low winter temperatures (Shi et al., 2009). In this respect, northern populations living in cold climates and having a high percentage of G alleles could be at an advantage due to a reduced risk of implantation failure (Feng et al., 2011; Hu et al., 2011). Additionally, it is critical to note that the geographic distribution of rs1042522 alleles is also linked with the capacity of p53 to regulate pigmentation and sunburn resistance through the activation of tyrosinase, the rate-limiting enzyme for melanin synthesis, and by induction of transcription of the melanogenic cytokine pro-opiomelanocortin (Hirshfield et al., 2010; Khlgatian et al., 2002; Murase et al., 2009). Accordingly, one may reasonably suppose that the p53-dependent stimulation of pigmentation could be a protective mechanism from UV light for light-skinned populations. Previously, a significant positive association between the G allele and susceptibility to sunburn was demonstrated (McGregor et al., 2002; Pezeshki et al., 2006), whereas the C allele was most prevalent in dark-skinned races originating from areas with high ambient UV levels (McGregor et al., 2002).

It should not be forgotten that one of the main functions of *TP53* is the maintenance of genomic stability through the removal of genetically aberrant cells and the suppression of tumor development. Different abilities concerning induction cell cycle arrest, DNA repair, and senescence, the activation of apoptosis and the suppression of transformed cell growth, and survival in hypoxia have been observed for the p53 protein encoded by alleles with *TP53* rs1042522 polymorphism (Table 1). As compared to p53Arg, p53Pro protein (C allele) is the best transactivation molecule (Frank et al., 2011; Thomas et al., 1999) and displays a high capability to block the cell cycle (Frank et al., 2011; Pim and Banks, 2004), induce DNA repair (Siddique and Sabapathy, 2006), remove micronuclei (Siddique and Sabapathy, 2006)

and chromosome aberrations (Litviakov et al., 2010; Schwartz et al., 2011), and stimulate cell senescence (Frank et al., 2011; Salvioli et al., 2005) and cell death in hypoxic environments via activation/inhibition of p53-target genes such as *p21*, *p53R2*, *p48*, *GADD45*, *PAI-1* and the hypoxia response genes. In contrast, p53Arg protein induces apoptosis markedly better and with faster kinetics than p53Pro but mainly through intrinsic pathways and a significant ability to activate the *DR-4*, *NOXA*, *PUMA*, *PIG-3*, and *PERP* genes, localize to the mitochondria and release cytochrome C into the cytosol (Dumont et al., 2003; Jeong et al., 2010; Pim and Banks, 2004; Thomas et al., 1999; Zhu et al., 2010). However, the strongly pronounced apoptotic ability of p53Arg does not protect against the process of carcinogenesis (Zhu et al., 2010). Likewise, p53Arg is more efficient than p53Pro in the suppression of transformed cell growth by the E7 and EJ-ras oncogenes and survival in hypoxia (Thomas et al., 1999; Vannini et al., 2008). Curiously, tumors of the head and neck losing the C and bearing the G allele show a lack of co-expression of Fas/FasL and high expression of Bcl2 proteins, and, as a consequence, markedly reduced apoptosis (Schneider-Stock et al., 2004b). Simply stated, p53Pro protein seems to be the best inducer of apoptosis in the extrinsic pathway. This also results from the fact that p53Pro, but not p53Arg, along with NF- κ B, transactivates caspase 4/11, an important component of the extrinsic pathway in apoptosis induction (Azzam et al., 2011; Frank et al., 2011). Aside from the above-mentioned data, it was recently established that the *TP53* rs1042522 polymorphism impacts the apoptotic function of p53 in a tissue-specific manner. Specifically, p53Pro protein more effectively activates programmed cell death in thymus (Frank et al., 2011), whereas in the small intestine, apoptosis is significantly higher in G-expressing cells (Azzam et al., 2011; Zhu et al., 2010). Interestingly, in the spleen, there was no difference in the induction of apoptosis between rs1042522 variants (Azzam et al., 2011). Taken together, the tumor-suppressing function of p53 is considerably modified by *TP53* rs1042522 polymorphism, while the effect of p53 allelic variants on tumor growth, mainly manifested in apoptosis regulation, depends on the genetic and tissue-specific background.

p53 is a multifaceted and multifunctional molecule with implications in a majority of cell processes. There is growing evidence that p53 is involved in regulation of the epithelial-mesenchymal transition (EMT) and cell phenotype, as well as cell migration and invasion (Muller et al., 2011). Breast and lung cancers with p53 mutations exhibit stem cell-like transcriptional patterns and are depleted in terms of the activity of differentiation genes (Mizuno et al., 2010). Furthermore, a loss of p53 leads to decreased expression of microRNA miR-200c, stimulated expression of EMT and stemness markers, and the development of high tumor grades in a cohort of breast tumors (Chang et al., 2011). Interestingly, p53 mutants with gain of novel function enhanced the efficiency of the reprogramming process compared with p53 deficiency (Sarig et al., 2010). As recently published by Jeong et al. (Jeong et al., 2010), *TP53* rs1042522 polymorphism may modify cell-cell adhesion, particularly through the high capability of p53Arg protein to induce expression of the *PERP* gene (Table 1). Additionally, p53Arg possesses the best ability to activate *CHMP4C*, a member of the EMT family of genes. In comparison with *TP53* rs1042522 polymorphism, rs17878362 and rs1625895 variations are poorly characterized in terms of structural and functional properties. However, the current data are sufficiently convincing of significant influence on p53 activity. The *TP53* rs17878362 polymorphism consists of a 16 bp duplication in intron 3 (PIN3: A1, non-duplicated allele and A2, duplicated allele). In a series of previous studies, it was demonstrated that the presence of the rs17878362 minor allele (A2) results in decreasing p53 mRNA levels, intensity of DNA repair and apoptosis processes (Table 1) (Gemignani et al., 2004; Wu et al.,

2002). In addition, there is an opinion that *TP53* rs17878362 polymorphism may alter the topology of G-quadruplexes in intron 3, regulating the alternative splicing of intron 2, thus modulating the patterns of expression of transcripts encoding either p53 or its N-terminally truncated isoform, $\Delta 40p53$ (Marcel et al., 2011). With respect to rs1625895 (IVS6+62A>G: A and G alleles), this polymorphism displays an A>G transversion and, according to literature data, is responsible for changes in the induction of DNA repair and apoptosis and the maintenance of genomic stability (Table 1) (Qiu et al., 2008; Wu et al., 2002). It should be pointed out that *TP53* rs1625895 and rs17878362 polymorphisms are in perfect linkage disequilibrium with rs1042522 (Sjalander et al., 1995; Weston et al., 1997) and, most likely, these intronic variations control the alternative splicing and mRNA level of p53Arg and p53Pro proteins. Consequently, it would be logical to take into account the *TP53* linkage disequilibrium box in disease pathogenesis studies.

2.2 *TP53* polymorphisms: The cancer predisposing value

Owing to the importance of p53 in tumor suppression, *TP53* rs1042522, rs17878362, and rs1625895 polymorphisms altering p53 functionality might affect cancer risk (Whibley et al., 2009). The results of the consortium works and last meta-analyses, demonstrating the predisposing value of *TP53* germline variations in different types of human cancer, are overviewed in Table 2. It should be immediately noticed that in a majority of cancers, the data are inconclusive, and further studies are needed to clarify the associations. In addition, there are certain annoying mistakes in some meta-analyses, which result in entirely noncredible data, and it would be valuable to provide a new, more accurate estimation of association of *TP53* polymorphisms with cancer risk (Economopoulos and Sergeantanis, 2010; Lu et al., 2011a; Lu et al., 2011b; Lu et al., 2011c; Sergeantanis and Economopoulos, 2010a, 2011). However, in spite of the present disagreements and methodological flaws, association tendencies for some cancer localizations are clear (Table 2). Simply stated, the rs1042522 C allele is associated with increased susceptibility to cancers, including of the lung (Dai et al., 2009; Francisco et al., 2010; Li et al., 2009; Yan et al., 2009), head and neck (Francisco et al., 2010), thyroid (Francisco et al., 2010), esophagus (Wang et al., 2010a; Zhao et al., 2010), pancreas (Liu et al., 2011), liver (Chen et al., 2011; Francisco et al., 2010), gallbladder (Liu et al., 2011), nasopharynx (Zhuo et al., 2009b), and cervix (Francisco et al., 2010; Klug et al., 2009). No significant contribution of *TP53* rs1042522 polymorphism to oral cancer has been reported (Zhuo et al., 2009c). A high heterogeneity of results was observed in breast (He et al., 2011; Hu et al., 2010b; Lu et al., 2011b; Ma et al., 2011; Peng et al., 2011; Sergeantanis and Economopoulos, 2010b; The Breast Cancer Association Consortium, 2006; Zhang et al., 2010b; Zhuo et al., 2009a), colon and rectum (Dahabreh et al., 2010; Economopoulos and Sergeantanis, 2010; Economopoulos et al., 2010; Liu et al., 2011; Tang et al., 2010; Wang et al., 2010b) cancers. Though still not quite clear, cancer of the ovary (Schildkraut et al., 2009; Zhang et al., 2008), endometrium (Francisco et al., 2010; Jiang et al., 2010b), stomach (Francisco et al., 2010; Gao et al., 2009; Liu et al., 2011), bladder (Jiang et al., 2010a; Li et al., 2010), prostate (Zhang et al., 2010a; Zhang et al., 2011b; Zhu et al., 2011), and skin (Francisco et al., 2010; Jiang et al., 2011) appear to be affected. As for the rs17878362 polymorphism, a clear association of the A2 allele with a high risk of breast cancer (He et al., 2011; Hu et al., 2010a; Hu et al., 2010b; Zhang et al., 2011a) and a lack of involvement in lung (Hu et al., 2010a), ovary (Schildkraut et al., 2009), colon and rectum (Hu et al., 2010a) cancer susceptibility has been demonstrated. Interestingly, Peng et al. (Peng et al., 2011) did not show a dependence of breast cancer development on rs17878362 germline variation. For the

rs1625895 polymorphism, no association with breast (He et al., 2011; Hu et al., 2010b) or ovary (Schildkraut et al., 2009) cancers has been presented in the available literature. Cancer is a heterogeneous polygenic disorder with a well-established gene environment playing an important role in disease etiology (Hanahan and Weinberg, 2011; Perez-Losada et al., 2011). The significant heterogeneity of the associative value of TP53 polymorphisms, especially rs1042522 variation, among human cancers is most likely explained by specific p53 inducible functionality essentially depending on ethnicity-related genetic background and environmental exposure, tissue and age specificity (Azzam et al., 2011; Chung et al., 2010; Donehower, 2006; Francisco et al., 2010; van Heemst et al., 2005). The complex of lifestyle endo- and exogenous factors of each ethnic group, the proportion of which increases with age, may dramatically modulate the contribution of TP53 polymorphisms to cancer risk through, for example, genotoxic effects and epigenetic modifications of the TP53 gene structure. Exogenous modifiable factors, such as alcohol, smoking and betel or areca quid chewing, and radiation and chemical poisoning, together with endogenous estrogen metabolites and other secreted chemicals, have been found to be involved in DNA damage and epigenetic alterations (De Bont and van Larebeke, 2004; Hsu et al., 2010; Seviour and Lin, 2010). In this case, TP53 functionally different polymorphisms serving as background for origin of TP53 abnormalities, such as mutations and a loss of heterozygosity (LOH), promote neoplastic transformation by switching off p53-dependent control of genomic stability and further accumulation of genetic damage (Denisov et al., 2011). As a classic tumor suppressor, TP53 inactivation seems to underlie Knudson’s “two-hit” model supposing that two mutations or “hits” (point mutation and loss of allele, producing LOH) are required to inactivate genes and cause cancer or promote disease progression (Knudson, 1971); however, there are tumors that are exceptions to this rule (Donehower and Lozano, 2009; Thiagalingam et al., 2002). Nevertheless, the simultaneous presence of mutations and LOH in the TP53 gene is a widespread phenomenon in human cancer, suggesting that one inactivation is not sufficient to completely inactivate p53 (Baker et al., 1990; Nigro et al., 1989).

Cancers	rs1042522	rs17878362	rs1625895	Ref.
Breast	no	no	-	(Ma et al., 2011; Peng et al., 2011; The Breast Cancer Association Consortium, 2006; Zhuo et al., 2009a)
	C↓, Mediterraneans	A2↑	no	(Hu et al., 2010a; Hu et al., 2010b)
	G↑	-	-	(Lu et al., 2011b; Sergentanis and Economopoulos, 2010b; Zhang et al., 2010b)
	G↑, Indians	A2↑	no	(He et al., 2011)
	no	A2↑	-	(Zhang et al., 2011a)
Lung, head and neck, thyroid	C↑	no	-	(Dai et al., 2009; Francisco et al., 2010; Hu et al., 2010a; Li et al., 2009; Truong et al., 2010; Yan et al., 2009)

Gynecologic				
Ovary	no	no	no	(Schildkraut et al., 2009)
	C↓	-	-	(Zhang et al., 2008)
Cervix	G↑*	-	-	(Klug et al., 2009)
	C↓	-	-	(Francisco et al., 2010)
Endometrium	no	-	-	(Jiang et al., 2010b)
	C↑	-	-	(Francisco et al., 2010)
Digestive tract				
Oral cavity	no	-	-	(Zhuo et al., 2009c)
Stomach	C↑	-	-	(Francisco et al., 2010; Liu et al., 2011)
	C↑, diffuse type, Asians	-	-	(Gao et al., 2009)
	C↓, intestinal type, Caucasians			
Esophagus, pancreas, liver, gallbladder	C↑	-	-	(Chen et al., 2011; Francisco et al., 2010; Liu et al., 2011; Wang et al., 2010a; Zhao et al., 2010)
Colon and rectum	no	no	-	(Economopoulos and Sergentanis, 2010; Hu et al., 2010a; Tang et al., 2010; Wang et al., 2010b)
	C↓, Caucasians (tendency)†	-	-	(Economopoulos et al., 2010)
	C↓*	-	-	(Dahabreh et al., 2010)
	C↑	-	-	(Liu et al., 2011)
Total group without oral cavity	C↑, Asians	-	-	(Liu et al., 2011)
Bladder	G↑, Caucasians	-	-	(Li et al., 2010)
	G↓, Asians	-	-	(Jiang et al., 2010a)
Nasopharynx	G↓, C↑	-	-	(Zhuo et al., 2009b)
Prostate	no	-	-	(Zhu et al., 2011)
	G↑, Caucasians	-	-	(Zhang et al., 2010a)
	C↓‡	-	-	(Zhang et al., 2011b)
Skin	no	-	-	(Jiang et al., 2011)
	C↓	-	-	(Francisco et al., 2010)

↑allele increases cancer risk. ↓allele decreases cancer risk.
*only in non-epidemiological studies and studies, where controls were not in Hardy-Weinberg equilibrium and polymorphism analysis was determined from tumor tissue. †in studies where controls did not deviate from the Hardy-Weinberg equilibrium. ‡in population-based control subjects.

Table 2. The association of *TP53* gene polymorphisms with human cancers (data from the consortium works and the last meta-analyses).

2.3 *TP53* polymorphisms: The background for *TP53* abnormalities

TP53 gene mutations, represented by specific single monoallelic missense aberrations, are “universal” genetic abnormalities in human tumors, with a frequency varying from 10 to close to 100% (Brosh and Rotter, 2009; Olivier et al., 2010; Rivlin et al., 2011). *TP53* mutants display a loss of transactivation capability via conformational changes in p53 protein structure, as well as gain-of-function effects through the activation of multidrug resistance genes (*ABCB1*, *ABCC1*, *ABCG1*, and *MVP*), growth factor receptor genes (*EGFR*, *bFGF*, and *VEGF*), oncogenes (*c-Myc*, *c-Fos*, and *Ras*) or via the inhibition of paralogs p63 and p73, which are responsible for the induction of apoptosis (Brosh and Rotter, 2009; Olivier et al., 2010; Oren and Rotter, 2010). Due to tumor-promoting effects, *TP53* mutations have been shown to contribute to poor prognosis and therapeutic effectiveness in a majority of cancers (Brosh and Rotter, 2009; Olivier et al., 2010; Petitjean et al., 2007a). Despite the high *TP53* mutability, there is data concerning the presence of alternative inactivation pathways through the methylation of CG repeats in the *TP53* gene (Almeida et al., 2009; Amatya et al., 2005; Kang et al., 2001; Sidhu et al., 2005). Although the promoter region of *TP53* does not contain a classic CpG island, the methylation of one or two CG sites may result in significant inhibitory effects in gene expression (Sidhu et al., 2005). As for the LOH in the region of the *TP53* gene (17p13.1) or allelic imbalance (AI) as currently, the abnormality is detected in a majority of tumors leading to cancer progression and poor prognosis (Ellsworth et al., 2005; Frohling and Dohner, 2008; Lee et al., 2006; Tsuda, 2009; Willman and Hromas, 2010).

At present, it is not known which of these inactivation hits occurs first; however, the initial step by way of LOH is expected to create prerequisites for mutations in retained *TP53* alleles through a significant increase in genomic instability caused by the dramatic reduction of p53 functionality. In contrast, point mutations and methylation do not always result in inactivation or alteration of the activity of the corresponding protein. Information concerning the simultaneous occurrence of LOH and mutations in the *TP53* gene is well represented in association with rs1042522 alleles (Table 3). However, it was quite recently shown that rs17878362 and rs1625895 germline variations are also associated with *TP53* somatic abnormalities in tumor cells (Denisov et al., 2011; Marcel et al., 2009), although the data are not numerous enough and require further confirmation. Several studies reported that LOH more often occurs at the C allele than at the G allele in tumor cells of rs1042522 heterozygous cancer patients. This phenomenon is typical for cancers of the breast (Bonafe et al., 2003; Denisov et al., 2009; Denisov et al., 2011; Wegman et al., 2009), lung (Nelson et al., 2005; Papadakis et al., 2002), head and neck (Marin et al., 2000; Mitra et al., 2007), colon and rectum (Schneider-Stock et al., 2004a), renal pelvis, ureter and bladder (Furihata et al., 2002), oral cavity (Hsieh et al., 2005), vulva (Brooks et al., 2000; Marin et al., 2000), liver (Anzola et al., 2003), skin (Marin et al., 2000; McGregor et al., 2002), esophagus (Kawaguchi et al., 2000), and cervix (Pegoraro et al., 2002). However, the early studies on renal, bladder and oral cancer models did not show any differences in the preference of LOH at the rs1042522 alleles (Oka et al., 1991; Tandle et al., 2001). An interesting situation is that two reports involving ovary cancer have demonstrated contradictory results concerning preferential loss of the rs1042522 alleles in tumor (Buller et al., 1997; Wang et al., 2004); however, in a study by Wang et al. (Wang et al., 2004), the differences did not reach statistical significance. In a majority of cancers with a loss of the C allele, *TP53* gene mutations are significantly more frequent displayed in the retained G variant. Interestingly, persons with the GG and GC genotype in blood also have an increased frequency of *TP53* somatic mutations (Table 3).

Cancers	Preferential loss		Preferential mutation		Ref.
	G	C	G	C	
Breast	yes	no	no	no	(Kyndi et al., 2006)
	no	yes	-	-	(Bonafe et al., 2003)
	-	-	yes	no	(Langerod et al., 2002)
	no	yes	yes	no	(Wegman et al., 2009)
	no	yes	yes	no	(Denisov et al., 2009; Denisov et al., 2011)
Head and neck	no	yes	yes	no	(Mitra et al., 2007)
	no	yes	yes	no	(Marin et al., 2000)
Renal pelvis, ureter and bladder	no	no	-	-	(Oka et al., 1991)
	no	yes	yes	no	(Furihata et al., 2002)
Oral cavity	no	yes†	yes	no	(Hsieh et al., 2005)
	no	no	-	-	(Tandle et al., 2001)
Colon and rectum	no	yes	yes	no	(Schneider-Stock et al., 2004a)
	-	-	yes	no	(Godai et al., 2009)
Stomach	-	-	no	no	(Belyavskaya et al., 2006)
Vulva	no	yes	yes	no	(Brooks et al., 2000)
	no	yes	yes	no	(Marin et al., 2000)
Skin	no	yes	yes	no	
	-	-	no	yes	(Almquist et al., 2011)
	no	yes	no	no	(McGregor et al., 2002)
Liver (hepatitis C virus)	no	yes	-	-	(Anzola et al., 2003)
Esophagus (HPV)	no	yes	-	-	(Kawaguchi et al., 2000)
Cervix (HPV)	no	yes	-	-	(Pegoraro et al., 2002)
Ovary	no	yes	no	yes	(Buller et al., 1997)
- advanced cancer	yes	no	no	yes	(Wang et al., 2004)
Lung					
- non-small cell cancer	-	-	no	yes	(Hu et al., 2005; Mechanic et al., 2005; Szymanowska et al., 2006)
	-	-	yes	no	(Lind et al., 2007)
	no	yes	yes	no	(Nelson et al., 2005)
- advanced cancer	no	yes	-	-	(Papadakis et al., 2002)
Total group of human cancers at the background of radiation	no	yes	-	-	[own unpublished data]

†C allele is preferentially lost in oral squamous cell carcinomas associated with cigarette smoking and areca quid chewing, while the frequency of G allele loss is increased with alcohol drinking.

Table 3. The preferential loss and mutation of *TP53* rs1042522 alleles in human cancer.

Selective loss of the rs1042522 C allele and retention and mutation of the G variant seems to be a unique phenomenon, of which the molecular mechanism, point of origin and biological significance remain unclear. As opposed to hereditary cancer, the origin of which occurs in Knudson's "two-hit" model, in sporadic tumors, the question of whether the mutation or LOH arises first is not resolved, likely due to the high variability of inactivation modes among target (tumor suppressor) genes in cancer development (Thiagalingam et al., 2002; Wilentz et al., 2001). Thus, one may suppose that the LOH and mutations arise in any alleles and in any order but not simultaneously in the two allelic variants because the chances of this "scenario" are very low. Accordingly, in *TP53* rs1042522 heterozygous carriers, the following groups of cells are theoretically possible: with LOH at both the C and G alleles and mutations in both the C and G alleles (Fig. 1). It is most likely that any variations from monoallelic inactivation hits may provoke neoplastic transformation because a 50% reduction in *TP53* gene dosage, protein expression and activity is sufficient to promote tumorigenesis (Donehower and Lozano, 2009); however, loss of the chromosome region underlying LOH is always more dramatic than point mutation. The selective advantage will be displayed for the two groups of cells lacking the C allele and having a mutation in the G variant because of the uncontrolled proliferation caused by the withdrawal of cell cycle checking and the high survival capacity in hypoxia and conditions of chemotherapy provoked by the preferential activation of hypoxia and multidrug resistance genes by p53Arg and inactivation of p73 protein, an important determinant of cellular sensitivity to anticancer agents (Bergamaschi et al., 2003; Sansone et al., 2007; Siddique and Sabapathy, 2006; Vannini et al., 2008). The dramatically increased genomic instability in these cells will most likely result in the second inactivation hit by mutation of the retained G allele in one clone and loss of the C variant in the other. Thus, any of these variants will lead to formation of a cell clone lacking the C allele and having the mutated G variant, the presence of which has been reported in a majority of human cancers (see above). As opposed to single monoallelic inactivation sufficient for tumorigenesis, biallelic switching of p53 activity may accelerate tumors to invade and metastasize. Taken together, the "two-hit" model of *TP53* somatic abnormalities was suggested to explain the regular occurrence of loss of the rs1042522 C allele and mutation of the G variant in human tumors.

The biological value of *TP53* somatic abnormalities in the rs1042522 polymorphic region is well investigated in relation to tumor onset and progression. Nonetheless, there are difficulties in determining the specific interrelationship between certain rs1042522 inactivation hits and tumor development, perhaps due to tissue-specific manifestation of *TP53* allelic variants (Azzam et al., 2011). In particular, the positive contribution of loss of the C allele to short disease-free and overall survival, as well as tumor spreading, has been established in breast and colorectal cancers (Bonafe et al., 2003; Schneider-Stock et al., 2004a). Interestingly, inactivation of the C allele, already having mutations, has been associated with short survival and a worse outcome in patients with lung, ovarian and colorectal neoplasias (Godai et al., 2009; Nelson et al., 2005; Wang et al., 2004). In contrast, patients lacking the G variant in breast tumors possessed early tumor onset and more recurrence and short disease-free survival (Kyndi et al., 2006; Wegman et al., 2009). In addition, it should be pointed out that preferential loss of the C allele in human tumors may imply a protective effect of this variant regarding cancer development (Denisov et al., 2010; Denisov et al., 2011); however, the current disagreements between meta-analyses (Table 2) and studies reporting rs1042522 allelic loss in tumors (Table 3) allow us to consider this statement as not quite truthful. Likely, further studies are needed to clarify the above-mentioned hypothesis.

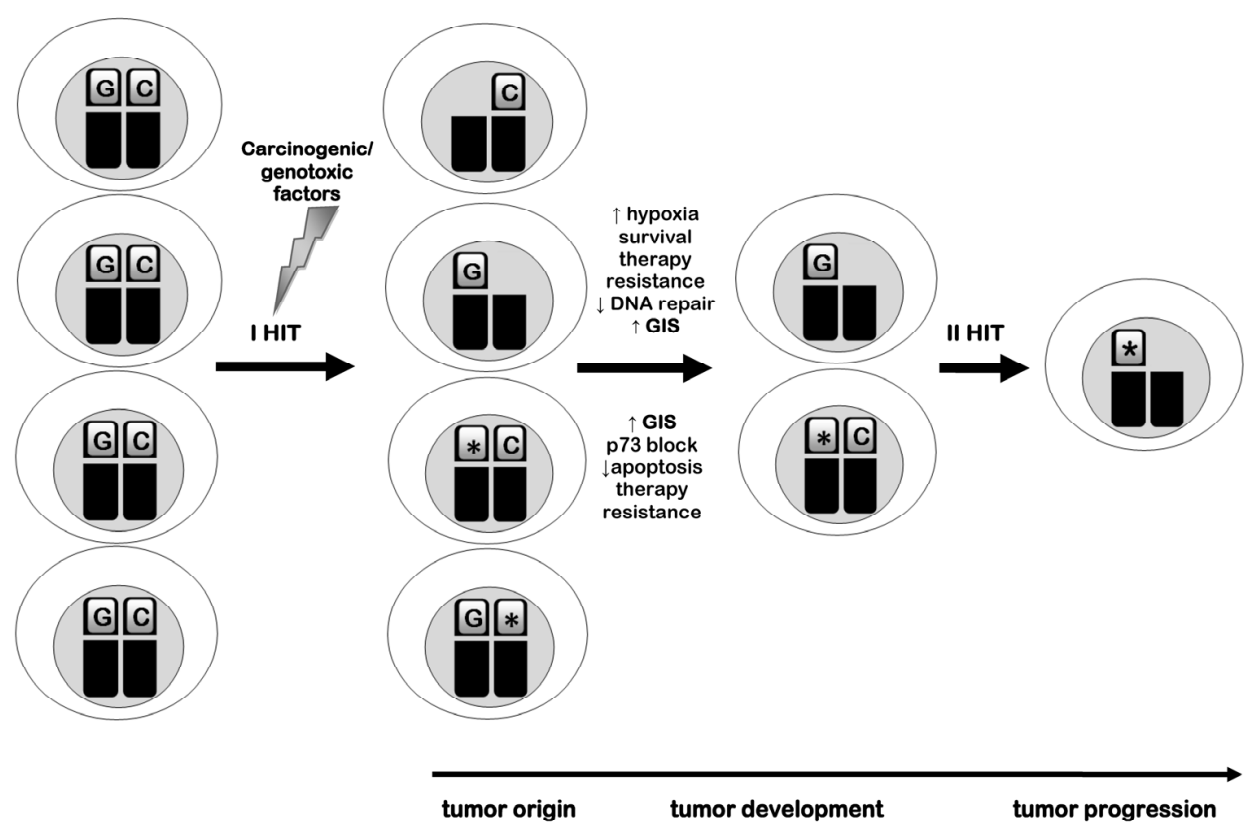


Fig. 1. The “two-hit” model of regular occurrence of *TP53* somatic abnormalities depending on the *TP53* rs1042522 polymorphism and environmental exposure. This model describes rs1042522-specific origin of *TP53* somatic aberrations in cancer tumors. At the first stage, LOH (indicated as a loss of chromosome arm) and/or mutation (indicated as asterisk on the chromosome arm) arise in any rs1042522 allele and in any order resulting in neoplastic transformation. From all tumor clones, only two ones with loss of the C allele and mutation in the G variant will have selective advantage via high survival capacity in hypoxia and therapy conditions, low ability to DNA repair and apoptosis. The dramatically increased genomic instability (GIS) in these cells will cause second inactivation forming the predominant tumor clone with loss of the C allele and mutation in the retained G variant. It is most likely that complete inactivation of p53 will impart invasive and/or metastatic potential to these cells.

In summary, the cancer predisposing effect of the *TP53* rs1042522 polymorphism through environment-induced regular occurrence of *TP53* somatic abnormalities has been reviewed in the present study. The “two-hit” model was suggested to explain the universal phenomenon for a majority of human tumors, consisting of a preferential loss of the C allele and mutation of the G variant. As reviewed herein, functional differentiation between rs1042522 allelic variants and its tissue specificity underlie selective pressure to maintain cells in which the C allele is lost and the G allele is mutated. Moreover, the inactivation of both the C and G allelic variants, resulting in a dramatic reduction in p53 functionality, may serve as an important background for tumorigenesis, as explained by the results of a study series on the association of *TP53* abnormalities in the rs1042522 polymorphic region with

tumor onset and aggressiveness (Bonafe et al., 2003; Godai et al., 2009; Kyndi et al., 2006; Nelson et al., 2005; Schneider-Stock et al., 2004a; Wang et al., 2004; Wegman et al., 2009).

2.4 *TP53* polymorphisms: The cancer predisposing effect and aging

p53 is emerging as an important player in the regulation of senescence and longevity with pronounced antagonistic pleiotropy (Campisi, 2005; Donehower, 2006; Vigneron and Vousden, 2010). By suppressing cancers early in life, p53 is clearly a longevity assurance gene. However, there is some evidence that p53 might accelerate aging and reduce longevity late in life (Donehower, 2006). Results have shown that the genotype distribution of *TP53* polymorphisms, mainly the rs1042522 germline variation, in both healthy persons and cancer patients, is also consistent with antagonistic pleiotropy. As early as 1999, Bonafe et al. (Bonafe et al., 1999) demonstrated a slightly increased percentage of rs1042522 C carriers among Italian centenarians. Later, this research team reported that the presence of only major genotypes for rs1042522, rs17878362, and rs1625895, absence of the GSTT1 deletion, and the simultaneous occurrence of the *TP53* genotypes with minor alleles and the GSTT1 deletion, were much more frequent in young subjects than in centenarians (Gaspari et al., 2003). However, our data did not confirm this fact, likely due to the small study sample (Belyavskaya et al., 2005). Based on the observations, it is most likely that the reason for disagreement can be explained by the different genetic backgrounds modifying the age-specific functionality of *TP53* polymorphisms (Belyavskaya et al., 2005). With respect to cancer, an age-specific dependence of cancer risk has been reported for *TP53* polymorphisms (Cherdyntseva et al., 2010; Chung et al., 2010; Gervas et al., 2007; Perel'muter et al., 2008). In this aspect, it is of note that some contradictions in the above-mentioned meta-analyses could be due to age-related effects of *TP53* germline variations. For example, breast cancer is one of a few diseases for which *TP53* rs1042522 polymorphism raises many questions (He et al., 2011; Hu et al., 2010b; Lu et al., 2011b; Ma et al., 2011; Peng et al., 2011; Sergeantanis and Economopoulos, 2010b; The Breast Cancer Association Consortium, 2006; Zhang et al., 2010b; Zhuo et al., 2009a). According to our data, the C allele contributes to high breast cancer risk in the premenopausal period (Cherdyntseva et al., 2011), whereas a combination of rs1042522, rs17878362, and rs1625895 major genotypes often occurs in postmenopausal BC (Perel'muter et al., 2008). Therefore, a more accurate meta-analysis that takes into account age specificity is required to clarify the associations between rs1042522 and breast cancer risk. Interestingly, an age-associated change in the *TP53* genotype distribution was also observed for lung cancer: the elderly (60-79 yr) affected subjects were characterized by an increased frequency of *TP53* major genotypes, whereas a high proportion of heterozygous genotype combinations was frequently detected in mature (40-59 yr) patients (Cherdyntseva et al., 2010; Gervas et al., 2007). These data not only agreed with recent meta-analyses (Dai et al., 2009; Francisco et al., 2010; Li et al., 2009; Yan et al., 2009) but also suggest that age might be an important modifier of the association between *TP53* rs1042522 polymorphism and lung cancer risk. With regard to rs17878362 and rs1625895 germline variations, the alteration in frequency of their genotypes is most likely linked to the regulation of *TP53* gene dosage particularly that which results in an increase in expression of the rs1042522 G allele, as already mentioned previously. Curiously enough, a high percentage of rs1042522 GG genotype was displayed in elderly patients with both breast and lung cancer. It is possible that apoptosis preferentially activated by p53Arg protein can lead to tissue atrophy, organ degeneration and cancer-related aging phenotypes (Campisi, 2005; Rodier et al., 2007). Moreover, it is known that the effect of *TP53* rs1042522

polymorphism becomes evident as the age of individuals increases (Bonafe et al., 2004; Salvioli et al., 2005). In particular, cells isolated from centenarians and sexagenarians, GG carriers, undergo oxidative stress-induced apoptosis to a higher extent than cells obtained from C carriers (Bonafe et al., 2004). Additionally, individuals that live a long time with the C allele display slower cell cycle kinetics and an increased propensity to undergo cell senescence than age-matched persons not expressing the C variant (Salvioli et al., 2005). These findings result from the preferential induction of p21, cyclin-dependent kinase inhibitor 1, and, likely, age-dependent activation of PAI-1, plasminogen activator inhibitor 1, by p53Pro protein (Salvioli et al., 2005; Testa et al., 2009).

Notwithstanding the age-specific effect of *TP53* polymorphisms on cancer risk, interesting findings concerning their influence on longevity have been provided by Van Heemst et al. (van Heemst et al., 2005). Elderly patients, carriers of the CC genotype, display a 41% increased survival despite a 2.54-fold high cancer mortality. Interestingly, some have suggested that the increased longevity of individuals with the CC genotype may be due to a generally increased robustness after a diagnosis of cancer or other life-threatening diseases, perhaps via an age-dependent capability of p53Pro to stimulate the expression of PAI-1 (Bojesen and Nordestgaard, 2008; Orsted et al., 2007; Testa et al., 2009).

p53 is a central node in the molecular network of safeguarding the integrity of the genome. p53 activation can immediately result in alterations in the expression of more than a thousand genes (Kannan et al., 2011). However, the fate of p53 is also under the rigorous control of other molecular players. Quite recently, based on the results of an association study and epistatic interaction analysis, the age- and estrogen receptor-specific interplay between *TP53* and *FGFR2* has been demonstrated in breast cancer (Cherdyntseva et al., 2011). It was found that combinations of *FGFR2* rs1219648 minor and *TP53* rs1042522, rs17878362, and rs1625895 major genotypes were associated with a high risk of BC, particularly in the postmenopausal period. In contrast, combinations of the *FGFR2* and *TP53* major genotypes had a protective effect against BC, especially in premenopausal women. Of note, all observations were ER-dependent. A possible explanation arises from evidence that *FGFR2*, upregulated by estrogens through the rs1219648 (G allele)-formed estrogen receptor site, may result in p53 inactivation via the induction of MDM2 ubiquitin ligase (Cherdyntseva et al., 2011). Importantly, the presence of the minor rs1219648 allele may lead to elevated *FGFR2* expression in tumor cells by itself (Meyer et al., 2008). Another point of view is based on a molecular network consisting of the preferential activation of apoptosis and cancer-related aging phenotype by p53Arg protein and the further induction of *FGFR2* expression leading to the transactivation of cancer genes and increased proliferation. The above-mentioned reasoning allows us once again to conclude that the p53-associated cellular defense system that controls cancer suppression directly depends on age-related features of the human organism, and this phenomenon should be taken into account in future association studies.

2.5 *TP53* polymorphisms: The cancer predisposing effect and ethnicity

The *TP53* polymorphism distribution dramatically changes across the globe (Beckman et al., 1994; Sjalander et al., 1996), indicating selective pressure to fix *TP53* alleles in certain geographic areas. As noted in previous sections of this review, the functionally different p53 polymorphic proteins have the advantage of depending on specific environmental conditions (Hirshfield et al., 2010; Hu et al., 2011; Jeong et al., 2010). In addition,

manifestation of the cancer predisposing effects of *TP53* polymorphisms may also be altered between the different ethnic groups (Weston et al., 1997). In the literature, there is a significant amount of evidence that *TP53* polymorphisms (rs1042522, rs17878362, and rs1625895) differently influence cancer risk depending on ethnic components. For instance, *TP53* rs1042522 polymorphism has a protective value against breast cancer in inhabitants of the Mediterranean area (Hu et al., 2010b), but a predisposing effect in Indians (He et al., 2011). In addition, Sergeantanis and Economopoulos (Sergeantanis and Economopoulos, 2010b) showed an enhancement of the association between the C allele and cancer, both breast cancer and lung cancer, with increasing latitude. Similar ethnicity-specific contribution of *TP53* rs1042522 germline variation is also typical for other human cancers (Table 2) (Economopoulos et al., 2010; Gao et al., 2009; Jiang et al., 2010a; Li et al., 2010; Liu et al., 2011; Zhang et al., 2010a). Interestingly enough, the allelic expression of human genes, like allele frequency, was found to differ between ethnic groups (Spielman et al., 2007). Siddique et al. showed that the expression of *TP53* rs1042522 alleles is selectively regulated in different ethnic populations: healthy Asian heterozygote individuals preferentially express the C allele, whereas Caucasians express the G allele. Conversely, approximately 75% of Chinese heterozygote patients with breast cancer predominantly express the G allele (Siddique et al., 2005). Although the potential reason for this phenomenon could be preferential loss of the C allele in breast tumors of heterozygous patients, as mentioned above, the data of Siddique et al. may indirectly confirm a predisposing role of the G allele in breast cancer development, as shown in some meta-analyses (He et al., 2011; Lu et al., 2011b; Sergeantanis and Economopoulos, 2010b; Zhang et al., 2010b). In addition, our research team first showed the high risk potential of the G allele and trend toward the protective value of the C variant in relation to breast cancer development in Mongolian ethnic groups (Tuvans, Altaians, Khakases, and Buryats) living in the Siberia region of Russia (Pisareva et al., in press). It is of note that our earlier data demonstrated significantly lower breast cancer incidence in these ethnic groups in comparison with Caucasians living in the same region (Pisareva et al., 2007). Moreover, it is known that Caucasians are approximately 2-fold more prone to breast cancer than Asians (Siddique et al., 2005). As evident from the above, there is a specific selective pressure against high breast cancer incidence in people of Asian ethnicity, and a possible explanation for this might be the functional impact of the *TP53* rs1042522 polymorphism, of which the C allele is overrepresented in these populations. As indicated previously, the *TP53* rs1042522 polymorphism has a significant effect on the origin of *TP53* somatic abnormalities, especially mutations, and, thus, may predispose one to cancer. Race-specific differences in the frequency of *TP53* alterations have been shown between colorectal patients of Afro-American and Caucasian origin, with the prevalence of mutations in the former, which were rs1042522 CC carriers. Surprisingly, the African American CC genotype was associated with a high risk of lymph node metastasis and increased mortality (Katkoori et al., 2009). Although the above evidence is small in number and needs further approval, calculation of the ethnic component is essential to perform accurate and qualitatively correct association studies.

In summary, a disparity between different ethnicities (races) in various cancer incidences and outcomes depends on genetic differences affecting the biology of malignancy. Moreover, recent evidence indicates ethnic differences in toxicity from certain anticancer treatments as well their effectiveness, which apparently contributes to survival (Mahdi et al., 2011; Soo et al., 2011). This might be explained by the diversity in genotype variants, gene

expression levels and epigenetic alterations providing different race/ethnicity-specific functional pathways. p53 is a key player contributing to the defense against cancer and has been shown to be involved in tumor progression and the response to cytostatic drugs via the regulation of metabolism and repair of DNA damage induced by chemotherapy. Therefore, the analysis of *TP53* rs1042522 polymorphism together with other deciding factors may help to understand racial differences in cancer aggressiveness and clinical outcomes, which could increase treatment efficacy.

3. Conclusions

p53 (*TP53* gene) is a key tumor suppressor that balances the need for cell proliferation against the need for cancer suppression, thereby maintaining genomic integrity. Polymorphisms in the *TP53* gene significantly modify p53 functionality, thereby affecting the mechanisms of cancer prevention. Despite the substantial progress in molecular genetics and the understanding of tumorigenesis mechanisms in recent years, the value of *TP53* polymorphisms is not entirely clear in relation to a predisposition to or protection from cancer risk. In the present review, we focused on available information concerning the functional role of *TP53* polymorphisms and data from consortium works and the latest meta-analyses demonstrating their effect on cancer risk. We supposed that the disagreements and ambiguities in these studies are linked to the changeable nature of *TP53* polymorphism manifestation dependent on environmental exposure, mainly age features and ethnic components of the analyzed individuals. In our opinion, the possible variations of the impact of *TP53* polymorphisms on cancer susceptibility, mainly for rs1042522, might be presented as a complex gene-environmental mechanism realized through a regular occurrence of *TP53* somatic abnormalities and selective pressure against certain *TP53* alleles. Overall, the environment-specific character of *TP53* polymorphisms has been reviewed to demonstrate potential cancer risk-modifying factors, which should be taken into account to avoid unclear and ambiguous results in future association studies.

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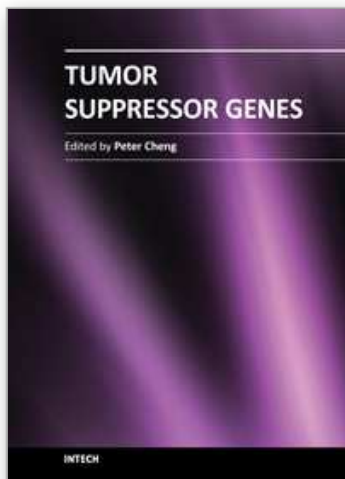
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Tumor Suppressor Genes

Edited by Dr. Yue Cheng

ISBN 978-953-307-879-3

Hard cover, 332 pages

Publisher InTech

Published online 03, February, 2012

Published in print edition February, 2012

Functional evidence obtained from somatic cell fusion studies indicated that a group of genes from normal cells might replace or correct a defective function of cancer cells. Tumorigenesis that could be initiated by two mutations was established by the analysis of hereditary retinoblastoma, which led to the eventual cloning of RB1 gene. The two-hit hypothesis helped isolate many tumor suppressor genes (TSG) since then. More recently, the roles of haploinsufficiency, epigenetic control, and gene dosage effects in some TSGs, such as P53, P16 and PTEN, have been studied extensively. It is now widely recognized that deregulation of growth control is one of the major hallmarks of cancer biological capabilities, and TSGs play critical roles in many cellular activities through signaling transduction networks. This book is an excellent review of current understanding of TSGs, and indicates that the accumulated TSG knowledge has opened a new frontier for cancer therapies.

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Evgeny V. Denisov, Nadezhda V. Cherdyntseva, Nicolay V. Litviakov, Elena A. Malinovskaya, Natalya N. Babyshkina, Valentina A. Belyavskaya and Mikhail I. Voevoda (2012). TP53 Gene Polymorphisms in Cancer Risk: The Modulating Effect of Ageing, Ethnicity and TP53 Somatic Abnormalities, Tumor Suppressor Genes, Dr. Yue Cheng (Ed.), ISBN: 978-953-307-879-3, InTech, Available from:
<http://www.intechopen.com/books/tumor-suppressor-genes/tp53-gene-polymorphisms-in-cancer-risk-the-modulating-effect-of-ageing-ethnicity-and-tp53-somatic-ab>

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