REVIEW

Genetic polymorphisms in the drug detoxification genes and susceptibility to Urinary Bladder Cancer (UBC)

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ABSTRACT

The central event in cancer development is loss of genomic integrity which itself probably initiates from the alteration of genomic DNA by exogenous or endogenous carcinogens. All humans are exposed to various environmental and occupational sources of genotoxic compounds and radiations which may act as carcinogens. Genetic factors are thought to play a central role in determining individual susceptibility to carcinogens. Urinary bladder cancer (UBC) is the most common malignancy of the urinary tract. In this review, the literature investigating the relationship between genetic polymorphisms of drug metabolizing genes and the risk of UBC are summarised. We have thoroughly reviewed the DNA polymorphism studies on GSTM1, GSTP1, GSTT1, GSTM3, GSTA1, NAT1, NAT2, SULT, UGT, MPO, COMT, MnSOD, GPX1 and ADH3 genes in relation with UBC. Overall, it appears that genetic polymorphisms in the drug detoxification genes play an important role in determining susceptibility to UBC.

KEYWORDS: Urinary bladder cancer, drug-metabolizing enzyme, carcinogens, genetic polymorphism

Citation: Gautam KA. (2018). Genetic polymorphisms in drug detoxification genes and susceptibility to Urinary Bladder Cancer (UBC). Polymorphism;1: 17-37.

INTRODUCTION

Urinary bladder cancer (UBC) is the most common malignancy of the urinary tract. In 2008, there were an estimated 386,300 new cases of UBC and approximately 150,200 deaths (Ferlay et al., 2008). Transitional cell carcinoma (TCC) comprises about 90% of all primary tumors of the urinary bladder while the remaining 10% of primary bladder tumors are represented by squamous cell carcinoma, adenocarcinoma and small cell carcinoma (Longe, 2005). The incidence of UBC varies 14-fold internationally with higher occurrence in males as compared to females (Jemal et al., 2011). Expectedly, the mortality rates have stabilized in males and decreased in females of United States (Edwards et al., 2010) and Europe (Karim-Kos et al., 2008) due to reduction in smoking prevalence and occupational exposures. Within India, the age standardized incidence rate of UBC is 2.7 for men and 0.6 for women, respectively (Ferlay et al., 2012) and according to the recent report of National Cancer Registry Programme, the highest incidence rate of UBC in men is found in Delhi (6.8%, 2008-2009) (Leading sites of cancer, Bangalore, 2013). In addition, literature suggest that, five year survival rate is very low in the developing countries, such as India (39%) and Thailand (48%) (Sankaranarayanan et al., 2010) as compared to the developed countries, such as the United States (97%) (Altekruse et al., 2010) and Europe (72.4%) (Sant et al., 2009).

The central event in cancer development is loss of genomic integrity which itself probably initiates from the alteration of genomic DNA by exogenous or endogenous carcinogens. All humans are exposed to various environmental and occupational sources of genotoxic compounds and radiations which may act as carcinogens. People are also frequently exposed to carcinogens in everyday life by virtue of their habits such as smoking, drinking alcohol etc (Burger et al., 2013). Consequently, there is an ongoing debate on gene and genotoxin, their interaction, and the degree of their relative impact on life and health. However, most common diseases including cancer involve not only separate action of genetic and environmental causes, but also interactions between the two (Bailey et al., 2003; Vineis et al., 1994; Marcus et al., 2000; Hung et al., 2004). Although any two unrelated people share about 99.9% of their DNA sequences, the remaining 0.1% is important because it contains the genetic variants that influence how people differ in their risk of cancer or their response to carcinogen exposures.

Exposure to genotoxic carcinogen compounds may induce mutations. Small exposure to cancer-initiating chemicals, such as aromatic amines or polycyclic aromatic hydrocarbons (PAHs), if prolonged, may lead to accumulation of mutations in somatic and germ cells and, eventually, to the development of tumors and cancer (Amdur et al., 1991). Genetic factors are thought to play a central role in determining individual susceptibility to carcinogens. Same duration of exposure to any carcinogen will result in different response towards detoxification of that carcinogen in different individuals. The factors that may be responsible for difference in individual's susceptibility include genetic polymorphisms in the genes coding for enzymes those involve in the metabolism of carcinogens (Burger et al., 2013).

GENETIC POLYMORPHISMS AND UBC SUSCEPTIBILITY

The genetic characteristics that determine individual's susceptibility to cancer are altered by the "genetic polymorphisms" – germ line variations in DNA sequences. Genetic polymorphism is the coexistence of various alleles; those exist as stable component of the population, at a locus. Alternative forms of a gene that exit at single locus are known as alleles and are defined as polymorphic if present at an allele frequency higher than 1% in the general population (Strachan et al., 1996). Not every individual exposed to risk factors develops UBC. On the other hand, many individuals develop the disease even without being exposed to any type of

the known risk factors (Cohen et al., 2000). Such discrepancies in cancer development arise due to genetic polymorphisms in genes coding for enzymes involved in different pathways such as carcinogen metabolism, DNA repair, cell cycle regulation, apoptosis, inflammation and epigenetic regulation. Therefore, genetic polymorphisms may contribute to the inter-individual variations in genetic susceptibility to UBC.

Drug-metabolising enzymes activate and detoxify chemical carcinogens to provide the first line of defence (Friedberg et al., 2003). Various investigations relating specific alleles, combinations of alleles, and enzyme regulation by interaction between genetic and environmental factors to increased carcinogenesis have been conducted (Anwar et al., 1996; Franekova et al., 2008; Mueller et al., 2008; Horikawa et al., 2008). Polymorphisms in carcinogen metabolism pathways, partially explain individual susceptibility to cancer and therefore, are postulated to serve as 'susceptibility markers' for the disease.

METABOLISM OF DRUG-METABOLISING ENZYMES

In late 18th century, it was hypothesised that xenobiotic compounds are consumed and transformed to water-soluble substances. But this mechanism was defined by RT Williams in 1947. In this metabolism, a lipophilic (pre-carcinogen) parental substance is metabolised to hydrophilic metabolite using enzymes of broad specificity, so that it can be easily excreted out mainly through bile or urine. The enzymes involved in carcinogen metabolism, despite certain overlaps, are traditionally classified as phase I (functionalization) and phase II (conjugation) enzymes (Brockmoller et al., 2000). The phase I detoxification system is a set of mainly cytochrome P450 (CYPs) enzymes; in this functionalization reaction, enzyme add reactive site to a non-water soluble compound via reduction, oxidation or hydrolysis. The resultant of phase I is a water soluble molecule which is more toxic than parental compound and, if not detoxified by phase II enzymes can cause damage to DNA, RNA and proteins (Vermeulen et al., 1996). The metabolites from phase I reactions undergo detoxification by phase II enzymes. In this conjugation reaction, phase II enzymes attach an ionised group like glutathione, acetyl, methyl or sulphate to the activated metabolites from phase I, converting them into less toxic, more water soluble and excretable compounds (Shimada et al., 2006). Phase II enzymes are usually known as drug metabolism or detoxifying enzymes since they detoxify toxic parental compound from phase I and also play important roles in drug metabolism (Amdur et al., 1991). Currently, a phase III- antiporter activity has also been defined to pump out non-metabolized xenobiotic compounds from the cell into the lumen of intestine for phase I activity (Chin et al., 1993).

POLYMORPHISMS IN DRUG-DETOXIFICATION GENES AND UBC RISK

Altered expression and activity of metabolic genes depends on genetic polymorphisms, age, sex, dietary compounds and lifestyle habits of an individual (McIlwain et al., 2006; Shimada et al., 2006). The result of polymorphisms in the drug detoxification genes partly depends on which metabolic phase the gene is concerned with and also on the effectiveness of the other phase (McCarver et al., 2002). The carcinogens known to initiate UBC, like polycyclic aromatic hydrocarbons (PAHs) and aromatic amines are chemically inert and require metabolic activation by drug metabolising enzymes (Strange et al., 1999). Once activated, these carcinogens may also undergo detoxification. Imbalance between activation and detoxification may result in an increased risk of UBC via accumulation of active carcinogens (reactive intermediates) and increased DNA adducts formation (Gu et al., 2005). An induced phase I along with reduced phase II metabolism results in the accumulation of reactive (toxic) metabolites within cells, which are strong carcinogens and may

cause damage to DNA and RNA. A reverse condition helps in detoxification and excretion of xenobiotic compounds but it can also cause damage if parental compound is more toxic than its metabolites and may lead to increased UBC risk (Shimada et al., 2006). Therefore, a dynamic equilibrium between phase I and phase II is necessary for proper activation and detoxification of carcinogens. Molecular epidemiological studies suggest that genetic polymorphisms and associated functional alterations in detoxification enzymes influenced individual's susceptibility to cancer (Brockmoller et al., 1998; Shimada et al., 2006; Siegel et al., 1999; Ross et al., 1996; Engel et al., 2002; Garcia-Closas et al., 2005; Gu et al., 2005). In the following section, studies investigating the association between UBC risk and polymorphisms in the genes encoding major phase II enzymes have been summarized.

The human Glutathione S-transferases (GSTs) are divided into three main families: cytosolic, mitochondrial and membrane-bound microsomal. The cytosolic family of GSTs exists as monomers and are catalytically active in a homo- or heterodimeric state (Mannervik et al., 1988). The cytosolic family is further divided into eight classes: alpha, mu, pi, omega, theta, kappa, sigma and zeta (McIlwain et al., 2006). Appreciable GST activities are seen in bladder epithelium (Simic et al., 2005). GSTs involve in detoxification of toxic compounds (drugs) and environmental pollutants (PAHs) by the conjugation of soluble glutathione to electrophilic centres on a variety of substrates and are important line of defence in protection of cellular components against reactive species (Strange et al., 2000). These enzymes are believed to play a crucial role in the protection of DNA from oxidative damage. Genetic polymorphisms in GST genes contribute to the predisposition, modulating the susceptibility of individuals to urinary bladder cancer development (Brockmoller et al., 2000; Strange et al., 1999).

Glutathione S-transferases M1 (GSTM1) gene, located on chromosome 1p13.3, and encoded enzymes show highest activities with most electrophiles and products of oxidative stress (Hayes et al., 1995). Among GST genes, GSTM1 is the most extensively studied gene for its association with UBC risk. Null-genotype of GSTM1 is present in a high percentage of the human population with major ethnic differences. The observed frequency of GTSM1 null-genotype in normal healthy individuals is approximately 67% in Australians, 50% in Caucasians, 22% in Nigerians and 33% in Indians (Smith et al., 1994; Mishra et al., 2004). A majority of studies reported that GSTM1 null-genotype showed a significant increased risk of UBC (Brockmoller et al., 1996; Hung et al., 2004; Broberg et al., 2005; Garcia-Closas et al., 2005; Kim et al., 2005; Covolo et al., 2008; Shao et al., 2008; Moore et al., 2010; Matic et al., 2014). For example, this significant association was reported in a study conducted in the Caucasian population with large sample size comprising 1138 cases and 1132 controls (Garcia-Closas et al., 2005). A similar study conducted in New England comprising 1188 cases and 1282 controls also reported a significant association between GSTM1 null-genotype and UBC risk (Moore et al., 2010). In addition, Shao et al., 2008 in their study on Chinese (Asian population) subjects, supported the findings that GSTM1 null-genotypes have an association with increased risk of UBC (Shao et al., 2008). However, several opposite results have also been reported. Studies based on American populations did not find statistically significant connection between GSTM1 null-genotype and UBC risk (McGrath M, 2006; Grando et al., 2009). A number of Asian and Caucasian populations based studies showed no association between GSTM1 null-genotype and UBC risk; however, the sample size was relatively small (Okkels et al, 1997; Salagovic J, 1999; Moore LE, 2004; Srivastava et al., 2005; Carreon et al., 2006; Altayli et al., 2009; Zupa et al., 2009; Berber U, 2013; Safarinejad et al., 2013). Nevertheless, a meta-analysis of 17 studies comprising 2,149 cases and 3,646 controls found that the GSTM1 null genotype conferred an increased risk of UBC with an odds ratio of 1.44; CI, 1.23 – 1.68 (Engel et al., 2002). All

the important and relevant findings are summarized in Table 1.

Table 1. Chronologically published reports on GSTM1-null polymorphism and UBC risk.

Study	Ethnicity	Cases/Controls	Results
Brockmoller et al., 1996	European	374/373	Independent risk factor (OR = 1.6; 95%CI, 1.2-2.2)
Okkels et al, 1997	Denmark	254/242	Genotyping of GSTM1 gene showed no association with UBC risk, not even with smokers.
Salagovic et al., 1999	European	76/248	Smokers with null genotype were associated with UBC risk (OR = 2.44; 95%CI, 1.10-5.30)
Toruner et al., 2001	Turkey	121/121	Null-genotype was associated with UBC risk (OR = 1.94; 95%CI, 1.15-3.26)
Hung et al., 2004	Italy	201/214	Null-genotype was associated with UBC risk (OR = 1.69; 95%CI, 1.11-2.56)
Moore et al., 2004	European	106/109	Null genotype was not associated with UBC risk (OR = 1.27; 95%CI, 0.74-2.24)
Broberg et al., 2005	Caucasian	60/152	Null-genotype was significantly associated with UBC risk (OR = 2.2; 95%CI, 1.2-4.2)
Garcia-Closas et al., 2005	Spain	1138/1132	Null genotype was associated with UBC risk (OR = 1.7; 95%CI, 1.4-2.0)
Kim et al., 2005	Korea	153/153	Null genotype was associated with UBC risk (OR = 1.7; 95%CI, 1.09-2.72)
Srivastava et al., 2005	India	106/37	Null-genotype of GSTM1 was not associated with UBC risk (OR = 1.12; 95%CI, 0.72-1.74)
McGrath et al., 2006	Unites States	64/648	Null genotype was not associated with UBC risk (OR = 0.78; 95%CI, 0.46-1.33)
Carreon et al., 2006	China	68/105	No association was found between GSTM1 null genotype and UBC (OR = 1.3; 95%CI, 0.5-3.4)
Covolo et al., 2008	Italy	197/211	Null-genotype was significantly differed between cases and controls (OR = 1.64; 95%CI, 1.15-2.33)
Shao et al., 2008	China	202/272	Null genotype was associated with UBC risk (OR = 1.73; 95%CI, 1.17-2.56). Both smokers (OR = 1.94; 95%CI, 1.11-3.38) and non-smokers were at high risk of UBC (OR = 3.86; 95%CI, 1.28-11.60)
Altayli et al., 2009	Turkey	135/128	Null-genotype was not associated with UBC risk.
Zupa et al., 2009	Italy	23/121	Null-genotype distribution was similar between cases (57%) and controls (56%).
Grando et al., 2009	USA	100/100	Null genotype was not associated with an increased risk of UBC (OR = 1.35; 95%CI, 0.76-2.41)
Moore et al., 2010	New England	1088/1282	Null genotype was associated with an increased risk of UBC (OR = 1.54; 95%CI, 1.05-2.25), results

			were also insignificant when stratified by smoking status
Berber et al., 2013	Turkish	114/114	Null genotype was not associated with UBC risk (OR = 1.20; 95%CI, 0.66-2.21)
Safarinjad et al., 2013	Iran	166/332	GSTM1 null-genotype was not associated with UBC risk (OR = 1.32; 95%CI, 0.82-2.62)
Matic et al., 2014	Belgrade	143/114	GSTM1 null-genotype associated with risk of UBC (OR = 2.1; 95%CI, 1.1-4.2), however active and null genotype with occupational exposure were at significant risk of UBC in cases as compared to controls of unexposed (OR = 5.4; 5%CI, 1.9-15.8) and (OR = 6.0; 95%CI, 2.2-16.5), respectively

Glutathione S-transferases T1 (GSTT1) gene is located on chromosome 22q11.2 and plays a significant role in phase II biotransformation of a number of drugs and industry related chemicals. GSTT1 gene shows polymorphism due to deletion, resulting in a null-genotype and complete absence of the enzyme activity (Bolt et al., 2006; McIlwain et al., 2006). Prevalence of the null-genotype has been found to vary among ethnic groups and about 10-65% of individuals have been reported to possess null-genotype (Nelson et al., 1995). The observed frequency of GSTT1 null-genotype in normal healthy individuals is 18.4% in Indian populations (Mishra et al., 2004). Till date, the findings on GSTT1 null polymorphism are controversial. Several studies also did not find any relationship between GSTT1 null polymorphism and the risk of UBC (Moore LE, 2004; Broberg et al., 2005; Garcia-Closas et al., 2005; Srivastava et al., 2005; McGrath, 2006; Safarinejad et al., 2013; Matic et al., 2014). Nevertheless, contradictory to above findings, several other studies suggested that GSTT1 null-genotype showed an increased risk of UBC (Brockmoller J, 1996; Salagovic J, 1999; Hung RJ, 2004; Sanyal S, 2004; Covolo et al., 2008; Altayli et al., 2009; Grando et al., 2009; Moore LE, 2010; Berber U, 2013). Kim et al., 2005 found a protective effect of GSTT1 null-genotype against UBC (Kim et al., 2005). Interestingly, a study found that the significant risk associated with GSTT1 null-genotype polymorphism was only found in the non-smoker group (Brockmoller J, 1996). Surprisingly, Moore et al., found contradictory results in two studies conducted on Caucasian populations for investigating the role of GSTT1 null-genotype polymorphism in UBC risk, in one study he did not find any association (Moore LE, 2004) while in other study he found a significant result (Moore LE, 2010). This shift from insignificant to significant result may have occurred due to sample size of the study. In a recent meta-analysis, the overall odds ratio for the GSTT1 null-genotype was marginally associated with increased risk. However, stratified data by ethnicity showed that Caucasian populations were at higher risk of UBC, while Asian populations were not. In addition, smoking did not modify the association between GSTT1 null-genotype and UBC risk (Gong et al., 2012). All the importasnt and relevant findings are summarized in Table 2. A significant higher risk of UBC was found when individuals were carrying both GSTM1 and GSTT1 null genotypes (Hung RJ, 2004; Srivastava et al., 2004)

Glutathione S-transferases P1 (GSTP1) gene is located on chromosome 11q13 and shows five non synonymous SNPs. GSTP1 enzyme plays a major role in the inactivation of cigarette smoke carcinogens, such as benzo[a]pyrene diol epoxide and other genotoxic substances (Hayes et al., 1995). An A>G substitution at position 313 (rs1695) in the GSTP1 gene, results in an Ile→Val change at codon 105 (exon 5). This substitution of the less bulkier and

more hydrophobic valine affects the kinetic properties of the enzyme (Ali-Osmam et al., 1997) and results in diminished detoxification capacity in individuals possessing the p.Val105 allele as compared to individuals possessing the p.Ile105 allele (Harries et al., 1997; Srivastava et al., 1999; Watson et al., 1998). In healthy Caucasians, the frequencies of the genotype variants of GSTP1 Ile/Ile, -Ile/Val and -Val/Val are 51.1, 39.4 and 9.1%, respectively (Watson et al., 1998). Several studies did not observe any significant association with UBC risk (Ma et al., 2002; Hung et al., 2004; Garcia-Closas et al., 2005; Covolo et al., 2008; Kopps et al., 2008; Altayli et al., 2009; Grando et al., 2009; Matic et al., 2014). A protective effect of this polymorphism against cancer development has also been documented (Martinez et al., 2006). A study conducted on Caucasian population with relatively very large sample size (1141 cases and 1138 controls) reported no relationship between GSTP1 c.313A>G polymorphism and UBC risk (Garcia-Closas et al., 2005). The other studies conducted on Caucasian populations with relatively small sample size also did not find any association (Hung RJ, 2004; Covolo et al., 2008; Kopps et al., 2008; Altayli et al., 2009 ; Matic et al., 2013). Asian population based studies reported 7.1-7.6 fold higher risk of UBC in individuals who carried Variant (GG) genotype (Mittal et al., 2005; Srivastava et al., 2005; Safarinejad et al., 2013). Surprisingly, a recent meta-analysis considering 16 studies with 4,428 UBC cases and 5,457 controls, showed that there was a significant difference in the distribution of variant genotype (AA+AG vs. GG) between cases and controls in Asian (OR = 1.59; 95%CI, 1.01-2.51) and Caucasian (OR = 1.51; 95%CI, 1.11-2.06) populations (Wu et al., 2013). All the important and relevant findings are summarized in Table 3.

Glutathione S-transferases A1 (GSTA1) gene is located on chromosome 6p12.2. Genetic polymorphisms in GSTA1 are characterized by two variant alleles, GSTA1*A and GSTA1*B and are associated with a significantly decreased protein expression (Coles et al., 2001). GSTA1 polymorphisms are associated with increased risk of breast cancer (Sweeney et al., 2003); however, are not associated with UBC risk (Broberg et al., 2005; Matic et al., 2014)

Glutathione S-transferases M3 (GSTM3) gene is located on chromosome 1p13.3. The GSTM3 locus contains two alleles, A and B. The GSTM3*B allele has a three base pair deletion in intron 6 that results in a recognition motif for transcription factor yin yang1, which subsequently affects GSTM3 expression (Inskip et al., 1995). A study based on GSTM1 and GSTM3 polymorphisms and the risk of UBC observed that rare genotypes increased the chance of UBC while homozygous common genotypes significantly protects against the UBC (Schnakenberg et al., 2000). Matic et al., 2014 did not find any association between GSTM3 polymorphisms and the risk of UBC (Matic et al., 2014).

The human N-acetyltransferases (NATs) are cytosolic enzymes involved in the detoxification and bio-activation of carcinogens via N-, or O-acetylation (Hein et al., 1993). In general, N-acetylation is a detoxification step, and O-acetylation is an activation step of the carcinogens. Aromatic amines are believed to be the most common urothelial carcinogens that are metabolized by NATs. Two distinct NATs, NAT1 and NAT2, have been identified and both are involved in the activation and detoxification of aromatic amines (Hein et al., 2000). NAT1 and NAT2 are products of single, intronless exon containing single 870bp open-reading frame encoding 290 amino acids (Hein et al., 2000). Genes encoding NAT1 and NAT2 are highly polymorphic among human populations and their genetic variations result in rapid or slow acetylator phenotype. Recent studies have suggested that polymorphisms leading to rapid acetylation by NAT1 enzyme and slow acetylation by NAT2 enzyme may be the possible risk factors for UBC (Jian et al., 2005). These polymorphisms may also cause inter-individual variations in biotransformation of aromatic and heterocyclic amine carcinogens. Since aromatic amines, present in cigarette smoke, are a major risk

factor for bladder cancer and are metabolized by NAT enzymes, it is for sure that the polymorphisms of the NAT genes have important roles in predisposing the individuals to bladder cancer (Franekova et al., 2008).

In humans, N-acetyltransferase1 (NAT1) gene is located on the short arm of chromosome 8, more specifically 8p22. NAT1 has a major role in O-acetylation of N-hydroxy aromatic amines in urinary bladder and leads to the activation of aromatic amines (Hein et al., 2002; Hein et al., 2000). The polymorphism of NAT1 gene was first described about two decades ago (Vatsis, 1993). Several studies have investigated the role of NAT1 gene polymorphisms in affecting risk to UBC (Okkels et al., 1997; Taylor et al., 1998; Hsieh et al., 1999; Cascorbi et al., 2001; Jaskula-Sztul et al., 2001; Vaziri et al., 2001; Hung et al., 2004; Gu et al., 2005; Garcia-Closas et al., 2005; Carreon et al., 2006; McGrath et al., 2006; Covolo et al., 2008). Although, overall findings are negative, only two studies found its association with UBC risk; for example, in a study conducted in American population with sample size 230 cases and 203 controls observed an association between NAT1 fast acetylator phenotype and increased risk of UBC (Taylor et al., 1998) while, another study with good sample size comprising 425 cases and 343 controls in a Caucasian population showed a protective effect of NAT1 fast acetylation (NAT1*10) (Cascorbi et al., 2001).

In a meta-analysis on 2668 cases and 3016 controls, no statistically significant association of the NAT1 genotypes with the risk of UBC was observed (Sanderson et al., 2007). This association was further investigated in a recent meta-analysis on 11 case-control studies, including 3311 UBC cases and 3906 controls, finding no significant difference in the NAT1 fast acetylator phenotype between cases and controls. The results were similar when stratified for race: in Caucasian and Asian populations (Wu et al., 2012). In a few studies, a significant increased risk has been described in smokers (Taylor et al., 1998; Hsieh et al., 1999) and in individuals exposed to benzidine (Carreon et al., 2006). Nevertheless, this association was not confirmed by a meta-analysis (Wu et al., 2012). All relevant studies are summarized in Table 4.

The N-acetyltransferase2 (NAT2) polymorphism was discovered over 60 years ago when individual variability in isoniazid neurotoxicity was attributed to genetic variability in N-acetylation (Hughes et al., 1954). The importance increased when it was discovered that many aromatic amines and hydrazine drugs are subjected to the acetylation polymorphism, thus affecting therapeutic efficacy and toxicity (Weber et al., 1985). The NAT2 gene is highly polymorphic and is located on chromosome 8p22. NAT2 is one of the phase II enzymes that have high affinity for *N*-acetylation of most of the aromatic amines that deactivate aromatic amines carcinogens (Hein et al., 1988). Although both, human NAT1 and NAT2 catalyze these detoxification reactions, NAT2 has a three- to four-fold higher affinity than NAT1 for urinary bladder carcinogens such as 4-aminobiphenyl (ABP) and β-naphthylamine (BNA) (Hein et al., 1993). NAT2 gene is polymorphic and the lack of two functional alleles results in decreased enzyme activity, giving the slow acetylation phenotype (Hein et al., 2000). Individuals with any two mutant alleles (out of NAT2*5, NAT2*6 and NAT2*7) were considered as slow acetylators and with NAT2*4 as rapid acetylators (Vatsis et al., 1995).

Table 2. Chronologically published reports on GSTT1-null polymorphism and UBC risk.

Study	Ethnicity	Cases/Controls	Results
Brockmoller et al., 1996	Caucasian	374/373	Associated with cancer risk in non-smokers (OR = 2.6; 95%CI, 1.1-6.0)
Salagovic et al., 1999	Caucasian	76/248	Null genotype associated with UCB risk (OR = 1.9; 95%CI, 1.03-3.42)
Toruner et al., 2001	Turkey	121/121	Null-genotype was not associated with UBC risk
Hung et al., 2004	Italy	201/214	Null-genotype was associated with UBC risk (OR = 1.74; 95%CI, 1.02-2.95)
Moore et al., 2004	European	106/109	Null genotype was not associated with UBC risk (OR = 1.54; 95%CI, 0.71-3.41)
Sanyal et al., 2004	European	309/246	Null genotype was significantly associated with UBC risk (OR = 2.54; 95%CI, 1.32-4.98)
Broberg et al., 2005	Caucasian	61/154	Null-genotype was not associated with UBC risk (OR = 0.85; 95%CI, 0.33-2.2)
Garcia-Closas et al., 2005	Spain	1132/1121	Null-genotype was not associated with UBC risk (OR = 1.0; 95%CI, 0.8-1.3)
Kim et al., 2005	Korea	153/153	Null genotype showed a protective affect against UBC risk (OR = 0.63; 95%CI, 0.39-0.99)
Srivastava et al., 2005	India	106/37	Null-genotype of GSTT1 was not associated with UBC risk (OR = 1.45; 95%CI, 0.89-2.37)
McGrath et al., 2006	Unites States	64/640	Null-genotype was not associated with UBC risk (OR = 1.57; 95%CI, 0.82-3.02)
Covolo et al., 2008	Italy	197/211	Null-genotype significantly differed between cases and controls (OR = 1.74; 95%CI, 1.11-2.74)
Altayli et al., 2009	Turkey	135/128	Null-genotype of GSTT1 was significantly associated with UBC risk (OR = 3.94; 95%CI, 1.70-9.38)
Grando et al., 2009	USA	100/100	Null genotype was significantly associated with an increased risk of UBC (OR = 1.77; 95%CI, 1.01-3.12)
Moore et al., 2010	New England	1088/1282	Null-genotype was unrelated to UBC risk (OR = 1.10; 95%CI, 0.82-1.486), results were also insignificant when stratified by smoking status
Berber et al., 2013	Turkish	114/114	Null genotype associated with UCB risk (OR = 3.06; 95%CI, 1.39-6.74)
Safarinjad et al., 2013	Iran	166/332	GSTM1 null-genotype was not associated with UBC risk (OR = 1.18; 95%CI, 0.79-1.67)
Matic et al., 2014	Belgrade	143/114	Not associated with risk of UBC (OR = 1.0; 95%CI, 0.5-2.2), however active genotype with occupational exposure were at significant risk of UBC in cases as compared to controls (OR = 4.3; 5%CI, 1.7-10.6)

Table 3. Chronological published reports on GSTP1 c.313 A>G polymorphism and UBC risk.

Study	Ethnicity	Cases/Controls	Results
Ma et al., 2003	China	23/210	Variant genotype GA+GG was associated with risk of UBC (OR = 1.95; 5%CI, 0.70-5.46). However, subject exposed to benzidine was at higher risk of UBC with variant genotype in cases than controls (OR = 1.19; 5%CI, 1.10-1.29)
Hung et al., 2004	Italy	201/214	No associated with UBC risk (OR = 1.04; 95%CI, 0.53-2.04)
Broberg et al., 2005	Caucasian	61/155	Variant genotypes GA and AA were not associated with UBC risk (OR = 1.1; 95%CI, 0.58-2.2 or OR = 2.3; 95%CI, 0.87-6.1), respectively.
Garcia-Closas et al., 2005	Spain	1141/1138	No association with UBC risk (OR = 1.2; 95%CI, 0.9-1.5)
Mittal et al., 2005	India	106/162	Variant genotypes AG (OR = 2.69; 95%CI, 1.57-4.59) and GG (OR = 7.68; 95%CI, 2.77-21.26) were significantly associated with UBC risk. the risk increased in combination with tobacco users (OR = 24.06; 95%CI, 4.80-120-42)
Srivastava et al., 2005	India	106/370	Variant genotype GG was significantly differed between cases and controls (OR = 7.12; 95%CI, 3.14-16.16)
Covolo et al., 2008	Italy	197/211	Distribution of variant genotype was not significantly differed between cases and controls
Kopps et al., 2008	Caucasian	143/196	Variant genotype (AG+GG) frequency was similar between cases (54%) and controls (58%)
Altayli et al., 2009	Turkey	135/128	No association was found
Grando et al., 2009	USA	100/100	Variant genotype was not associated with an increased risk of UBC (OR = 0.75; 95%CI, 0.41-1.38)
Safarinjad et al., 2013	Iran	166/332	Variant genotype GG was significantly associated with UBC risk (OR = 4.32; 95%CI, 2.64-6.34)
Matic et al., 2014	Belgrade	143/114	No association with UBC risk (OR = 0.9; 95%CI, 0.4-1.7), however variant genotypes (AG+GG) with occupational exposure were at significant risk in cases as compared to controls (OR = 2.8; 5%CI, 1.0-8.0)

Table 4. Chronological published reports on NAT1 polymorphisms and UBC risk.

Study	Ethnicity	Cases/Controls	Results
Okkels et al., 1997	Denmark	254/242	Genotyping of NAT1 showed no association with UBC risk, not even in smokers.
Taylor et al., 1998	USA	230/203	NAT1 fast acetylator allele was significantly associated with UBC risk (OR = 1.67; 95%CI, 1.13-2.46) and with smoking status (OR = 0.83; 95%CI, 0.26-1.40)
Hsieh et al., 1999	Taiwan	74/184	Allele frequencies were similar between cases and controls (p = 0.92), however subjects with habit of cigarette smoking and NAT1*10 had an increased risk of UBC (OR = 2.34; 95%CI, 1.03-5.31)
Cascorbi et al., 2001	Caucasian	425/343	Fast acetylator NAT1*10 allele was less frequent in cases (OR = 0.65; 95%CI, 0.46-0.91) than in controls
Jaskula-Sztul et al., 2001	Poland	56/320	No association was found between NAT1 polymorphism and UBC risk in cases (OR = 1.2; 95%CI, 0.7-2.0)
Vaziri et al., 2001	USA	53/96	NAT1 allele frequencies were similar between cases and controls (p = 0.23)
Hung et al., 2004	Italy	201/214	Frequency of NAT1 fast acetylator allele was not associated with increased risk of UBC (OR = 0.83; 5%CI, 0.55-1.26)
Garcia-Closas et al., 2005	Spain	965/942	NAT1 fast acetylator was not associated with UBC risk (OR = 1.2; 5%CI, 0.8-1.8) when compared with slow acetylator between cases and controls
Gu et al., 2005	USA	507/513	NAT1*10 allele was not associated with UBC risk (OR = 0.95; 95%CI, 0.73-1.25)
Carreon et al., 2006	China	28/58	Genotype frequencies of NAT1 were insignificant between cases and controls (OR = 2.2; 95%CI, 0.8-7.0) however, a significant association was found with benzidine exposure (OR = 4.4; 95%CI, 1.8-10.8)
McGrath et al., 2006	Unites States	64/648	No association was observed between NAT1 genotype and risk of UBC risk (OR = 0.77; 5%CI, 0.41-1.44)
Covolo et al., 2008	Italy	197/211	Distribution of NAT1 genotype was not significantly differed between cases and controls

NAT2 polymorphisms and their relationship with UBC have been extensively studied. Majority of the studies reported the connection of the NAT2 slow acetylation polymorphisms with higher risk of UBC

(Inatomi H, 1999; Schnakenberg E, et al, 2000; Cascorbi , et al. 2001; Vineis , et al. 2001; Hung et al., 2004; Garcia-Closas et al., 2005; Gu et al., 2005; Covolo et al., 2008). For example, in a case-control study, investigating the role of NAT2 polymorphisms in a large Caucasian population in 1134 cases and 1130 controls, has observed an increased risk of UBC (Garcia-Closas et al., 2005). Studies based on American population with large sample size found a relationship between NAT2 slow acetylation and UBC risk (Gu et al., 2005). Similarly, an association study conducted on Japanese (Asian population) subjects found significant results; however, the sample size was very small (Inatomi H, 1999). In contrast to the above, studies with large sample size and based on Caucasian, American and New England populations did not find any positive association of NAT2 polymorphisms with UBC risk (Brockmoller et al, 1996; Okkels et al, 1997; Taylor et al., 1998; Moore et al., 2010). A meta-analysis included six studies on 1530 cases and 1731 controls of Caucasian population and found significant association between NAT1 polymorphisms and UBC risk (Vineis et al, 2001). In another meta-analysis including 21 published case-control studies, pooled odds ratio using random-effects model showed significant association with UBC risk (Johns, 2001). A meta-analysis published with 22 studies including 2496 cases and 3340 controls found that slow acetylators had a 40% increased risk as compared to rapid acetylators phenotypes (Marcus et al., 2000). In addition, in a recent meta-analysis on Asian population also suggested an association of NAT2 polymorphisms with susceptibility to UBC (Carreon et al., 2006). Marcus et al., (2000) observed in the meta-analysis that the association of NAT2 gene polymorphisms and UBC risk differs by geographical region as it was in Europe (OR = 1.4; 95%CI, 1.2-1.6); Asia (OR = 2.1; 95%CI, 1.2-3.8), and USA (OR = 0.9; 95%CI, 0.7-1.3) (Marcus et al., 2000). Several studies also suggested a significant role of smoking and NAT2 polymorphisms in the risk of UBC (Brockmoller et al, 1996; Okkels et al, 1997; Taylor et al., 1998; Hsieh et al, 1999; Inatomi et al., 1999 Garcia-Closas., 2005; Gu et al., 2005; Moore et al., 2010). Over 50% of most non-Asian population is slow acetylator phenotypes who experience higher incidences of toxicity from various aromatic amine and hydrazine drugs (Weber, 1985). All the important and relevant findings are summarized in Table 5.

The joint effect of NAT1 and NAT2 genotypes has also been investigated in some studies. Taylor et al. 1998, observed that UBC risk from smoking exposure is high in those who inherit NAT2 slow alleles in combination with one or two copies of the NAT1*10 allele (Taylor et al. 1998). Hung et al. 2004, observed a significant increased risk when NAT1 slow and NAT2 slow genotypes were combined (Hung et al. 2004). In a recent meta-analysis, the authors found a joint effect of NAT1 rapid genotypes, NAT2 slow genotypes and smoking as factors that increase cancer risk (Sanderson et al., 2007).

Another phase II enzyme actively involved in carcinogen metabolism is soluble sulfotransferases (SULT). The gene coding for this enzyme is located on the short arm of chromosome 16p11.2. SULT1A1 is highly expressed by SULT gene that is mainly involved in phenolic xenobiotic compound elimination from the body. Genetic polymorphism in SULT1A1 results in an Arg→His change at codon 213 associated with a decreased activity and lower stability of enzyme. Individuals having variant His allele showed a statistically significant role in conferring UBC risk (Zheng et al., 2003; Hung et al., 2004).

UDP-glucuronosyltransferase (UGT) gene is located on the long arm of chromosome 4q13. UGTs plays an important role in the detoxification and elimination of endogenous and exogenous carcinogenic compounds and this reaction is primarily catalyzed by the UGT1A and UGT2B enzymes (Hu et al., 2016). UGT genetic polymorphisms reduce the capability to glucuronidate the carcinogens and therefore are

associated with an increased risk of UBC. Lin et al. 2005, observed in a cohort study that benzidine-exposed workers carry more frequently His268Tyr polymorphism of UGT2B7 and associated with an increased risk of UBC (Lin et al. 2005).

Table 5. Chronological published reports on NAT2 polymorphisms and UBC risk.

Study	Ethnicity	Cases/Controls	Results
Brockmoller et al, 1996	European	374/373	NAT2 deficiency associated with cancer risk in heavy-smokers (OR = 2.7; 95%CI, 1.0-7.4)
Okkels et al, 1997	Denmark	254/242	NAT2 genotype frequencies in cases (60.5% slow, 35.2% intermediate, and 4.3% fast) and controls (55.8% slow, 37.6% intermediate, and 6.6% fast) were almost similar (p = 0.39) and no association was found between NAT2 genotype and UBC risk (OR = 1.22; 5%CI, 0.92-1.62).
Taylor et al., 1998	USA	230/203	NAT2 genotype did not influence UBC risk, however, in combination with smoking UBC risk increased (OR = 1.5; 95%CI, 1.4-1.7)
Hsieh et al, 1999	Taiwan	74/184	Allele frequencies of NAT2 were similar between case and control (p = 0.70), however, subjects with habit of cigarette smoking and NAT2 slow acetylator had an increased risk of UBC (OR = 2.34; 95%CI, 1.03-5.31)
Inatomi et al., 1999	Japanese	84/146	Slow genotypes were associated with UBC risk (OR = 4.23; 95%CI, 1.76-10.81), further the risk increased in smokers when compared with rapid and non-smokers (OR = 7.80; 95%CI, 1.66-57.87)
Schnakenberg et al., 2000	Caucasian	157/223	Slow acetylation was observed significantly more frequently in bladder cancer cases than controls (OR = 1.63; 95%CI, 1.03-2.58)
Cascorbi et al., 2001	Caucasian	425/343	NAT2 slow acetylation was marginally associated with UBC risk (OR = 1.36; 95%CI, 0.99-1.86) however, in combination with occupational exposure risk of UBC increased (OR = 5.96; 95%CI, 2.96-12.0)
Vaziri et al., 2001	USA	53/96	Frequency of NAT2 slow acetylator was similar between cases and control (OR = 0.98; 95%CI, 0.49-1.96), while NAT2*5A allele was more common in cases than controls (p = 0.02).
Jaskula-Sztul et al., 2001	Poland	56/320	No association was found between NAT2 polymorphism and UBC risk in cases (OR = 1.3; 95%CI, 0.7-1.9)
Hung et al., 2004	Italy	201/214	NAT2 slow acetylator was associated with marginally increased risk of UBC (OR = 1.50; 5%CI, 0.99-2.27)
Mittal et al., 2004	India	101/110	Frequencies of NAT2 slow or fast acetylator genotypes were not significant either in pooled analysis (OR =

			1.18; 95% CI, 0.69 - 2.03) or in tobacco users with UBC compared to controls (OR = 0.83; 5%CI, 0.32-2.12)
Srivastava et al., 2004	India	106/110	NAT2 genotypes were not associated with UBC risk (OR = 1.18; 95%CI, 0.69-2.03) alone or in combination with tobacco users (OR = 0.84; 95%CI, 0.33-2.12) when compared in cases and controls
Garcia-Closas et al., 2005	Spain	1134/1130	NAT2 slow acetylator was associated with UBC risk (OR = 1.4; 5%CI, 1.2-1.7) when compared with rapid/intermediate acetylator between cases and controls. The relationship was again significant in smokers (OR = 2.9; 5%CI, 2.0-4.2)
Gu et al., 2005	USA	507/513	NAT2 slow acetylator genotypes were associated with UBC risk (OR = 1.31; 95%CI, 1.01-1.70), elevated risk appeared in heavy smokers (OR = 2.11; 95%CI, 1.33-3.35) than never smokers (OR = 1.23; 95%CI, 0.79-1.90)
Carreon et al., 2006	China	68/107	Adjusted confounders like smoking and benzidine exposure showed a protective association between slow NAT2 genotype and UBC risk (OR = 0.3; 95%CI, 0.1-1.0)
McGrathet al., 2006	Unites States	64/648	Overall results were insignificant (OR = 1.33; 95%CI, 0.77-2.31) however, an increased risk was observed in females ever smokers with NAT slow genotype but result was insignificant.
Covolo et al., 2008	Italy	197/211	Subjects carrying NAT2 slow genotype significantly differed between cases and controls (OR = 1.61; 95%CI, 1.12-2.28)
Ouerhani S, 2009	Africa	90/110	No difference between rapid and fast acetylator between cases and controls (p = 0.19)
Zupa et al., 2009	Italy	23/121	The frequency of low acetylator phenotype did not significantly differ between cases (57%) and controls (41%).
Moore LE, 2010	New England	1088/1282	Variant genotypes of NAT2 were not associated with the risk of UBC. However, subjects with slow acetylation and heavy smoking were had elevated UBC risk when compared with rapid acetylation and non smokers (OR = 3.16; 5%CI, 1.22-8.19)
Pramio et al., 2012	Brazil	84/84	SNP c.857G>A showed a protective effect against UBC risk (OR = 0.44; 5%CI, 0.24-0.81), while SNP c.590G>A didn't (OR = 1.06; 95%CI, 0.55-2.04)
Pesch et al., 2013	Caucasian	607/695	NAT2 slow acetylation was not associated with UBC risk (OR = 1.02; 95%CI, 0.81-1.29), also was not differed in cases and controls with heavy smokers (OR = 1.17; 95%CI, 0.63-2.17)

Myeloperoxidase (MPO) gene is located on the long arm of chromosome 17q23.3 and involves in the activation of procarcinogen found in tobacco smoke, such as benzo[a]pyrene (Kadlubar et al., 1992). A single base transition G-463A of MPO promoter was identified at the SP1 binding site. The variant A allele is associated with reduced mRNA expression as a result of reduced binding of SP1 (Piedrafita et al., 1996).

Catechol-omethyltransferase (COMT) gene is located on the long arm of chromosome 22q11.21 and is involved in the protection of DNA from oxidative damage by methylation of various endogenous and exogenous substances, preventing quinine formation and redox cycling (Zhu BT, 2002). A G-to-A allele transition, which results in a Val→Met change at codon 108, results in a lower COMT enzyme activity. The Met/Met genotype of COMT has a quarter of the wild type activity, and the heterozygote has the intermediate activity (Lotta et al., 1995).

Manganese superoxide dismutase (MnSOD) is located on the long arm of chromosome 6q25.3 and it catalyzes the dismutation of anion superoxide into hydrogen peroxide and oxygen (Hu et al., 2016). The activity of MnSOD can be induced in the presence of excessive free radical and cigarette smoke; therefore, it plays a key role in protecting cells from oxidative stress (McCord JM, 2002; Rosenblum et al., 1996) A C>T substitution in MnSOD results in Ala→Val change at codon 9 that has been associated with protein structure change leading to defective mitochondrial localization of the protein (Shimoda-Matsubayashi et al., 1996). Hung et al. (2004) described the association between UBC risk and genetic polymorphisms in MPO, COMT and MnSOD (Hung et al., 2004). Their data observed that MPO G-463A homozygous variant was associated with an approximately 70% significantly reduced risk UBC. MnSOD Val/Val genotype significantly increased the risk of UBC about 2-fold; and no effect was observed for COMT Val108Met polymorphism (Hung et al., 2004).

Glutathione peroxidase1 (GPX1) gene is located on the short arm of chromosome 3p21.31 and is a selenium-dependent enzyme. GPX1 is involved in the detoxification of hydrogen peroxide and a wide range of organic peroxides with reduced glutathione (Chada et al., 1989). The polymorphic substitution results in a Pro198Leu change, the variant Leu allele has been shown to be less responsive than the Pro allele during stimulation of the GPX1 enzyme by *in vitro* selenium supplementation (Hu, 2003). Ichimura et al. (2004) studied the association between UBC risk and GPX1 polymorphisms and found that the GPX1 Pro/Leu genotype might significantly increase the risk of UBC and that the increased risk may be modified by the Val16Ala polymorphism of MnSOD (Ichimura et al. 2004).

In addition to chemical carcinogens, some studies proposed the idea of alcohol consumption as a possible risk factor for UBC (Brownson et al., 1987; Zeegers et al., 1999). Zeegers et al. (1999) performed a meta-analysis of 16 epidemiological studies and observed a slightly increased risk of OBC from alcohol consumption for men (Zeegers et al., 1999).

Alcohol dehydrogenase type3 (ADH3) gene is located on the long arm of chromosome 4q23 and catalyzes the oxidation of ethanol to acetaldehyde (van Dilk et al., 2001). Genetic variants result in altered kinetic properties of enzyme. Gamma1 and gamma2 are two different alleles of ADH3. A study suggested that moderate drinkers with the "high-risk" (gamma1 gamma1) genotype appeared to have a 3-fold higher risk of UBC as compared to moderate drinkers with a "low-risk"(gamma1 gamma2 or gamma2 gamma2) genotype (van Dilk et al., 2001).

GENETIC POLYMORPHISMS AND UBC PROGRESSION

Besides modulating the susceptibility, genetic differences may also account for prognosis and outcomes of cancer such as tumor histopathology, cancer stage, tumor development and tendency toward invasiveness. Several studies have

investigated the association between genetic polymorphisms of carcinogen metabolism pathways genes and aggressiveness of UBC (Aktas et al., 2001; Sobti et al., 2005, Castillejo et al., 2009).

Polymorphisms in carcinogen metabolism genes like NAT2, GSTM1, GSTT1 and GSTP1, are also associated with higher stage of tumor (Marcus et al., 2000; Ryk et al., 2005; Kim et al., 2005; Sobti et al., 2005). The GSTM1-null polymorphism has been found to be significantly higher in invasive UBC (Aktas et al., 2001). GSTM1 and GSTT1 null polymorphisms were showed to be more prevalent in a higher grade (grade IV) of UBC (Sobti et al., 2005). However, a contradictory result was found in Korean subjects, suggesting low-stage UBC were more common with GSTM1 null genotypes (Jeong et al., 2003). This suggests that increased metabolism of urinary excretion by GSTM1 might promote cancer progression in UBC patients (Kim et al., 2005). The presence of the Val allele of the GSTP1 Ile105Val SNP was significantly associated with higher stage of tumors (Tis and T2+) (Ryk et al., 2005). Few investigators studied NAT2 slow genotype and its association with UBC and found that patients with NAT2 slow genotype were more likely to have a high-grade tumor (G3) or have an advanced stage tumor (pT2-pT4) (Inatomi et al., 1999; Marcus et al., 2000; Mommsen et al., 1986). The GPX1 Pro198Leu SNP showed that the Pro/Leu genotype was significantly associated with advanced tumor stage compared with the Pro/Pro genotype, suggesting that GPX1 genotype may further affect the disease status of UBC (Ichimura et al., 2004).

CONCLUSION AND FUTURE PERSPECTIVE

As summarized above, several molecular epidemiological experimental studies have dictated linkage of genetic polymorphism of drug detoxification gene with an increased urinary bladder cancer incidence and prognosis. Analysis of data from the previous studies found that familial risk increased with a history of bladder cancer among first-degree relatives (RR=1.35; 95% CI: 0.97-1.79 and RR=2.29; 95% CI: 1.46-3.29), among males and females, respectively. Crawford et al., 2008, found a significantly increased risk of bladder cancer among first-degree relatives of individuals who have bladder cancer, with an earlier age of disease onset; and the risk was even higher if they were smokers (Crawford et al., 2008). Genetic slow acetylator NAT2 variant and GSTM1-null genotypes are the recognized inherited genetic risk factors for UBC. These genetic risk factors are associated with UBC development but confer additional risk upon exposure to carcinogens such as tobacco products. However, these reported significant odds ratios for individual variants (NAT2 and GSTM1) are typically less than 2. The reason for these contradictory results may be small sample size, ethnic heterogeneity, multiple testing, poor matching of case and control groups, exposure documentation and publication bias. Therefore, it is clear that UBC has a clear and significant contribution from genetic factors; however, the data are fragmented and conflicting, as a result the exact contribution of drug detoxification gene polymorphisms to the etiology of UBC still remains unclear.

Since carcinogenesis is a multi-factorial disease, both environmental as well as genetic factors are involved in its occurrence. Environmental factors interact with genes responsible for metabolism of carcinogens and cause genetic instability; this interaction places one individual at a higher risk of UBC than another. It is questionable that any single genetic polymorphism (SNP) would have a dramatic consequence on the risk of any cancer. Although the result of any SNP provides valuable information; however, it has limited role in predicting the risk of cancer in the general population. Therefore, a pathway-based genotyping approach, which evaluates the combined effects of a panel of genetic polymorphisms that act in the same or different pathways, may have better risk prediction ability than individual polymorphisms.

Acknowledgements

KA Gautam would like to thank the University Grants Commission (UGC), Govt. of India, for financial assistance (F.16-1936(SC)/2010(SA-III)).

Conflict of interest statement

The author has declared that no competing or conflict of interests exists. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

KAG conceived, wrote and revised the manuscript.

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