

## Genetic Polymorphism of NAT2 Gene and its Association with Prostate Cancer

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### ABSTRACT

N-acetyltransferase 2 (NAT2) is one of the phase II metabolizing enzymes that participate in the bioconversion of heterocyclic arylamines into electrophilic nitrenium ions, which are important ultimate carcinogens that are directly implicated in tumor initiation process. Prostate epithelial cells express N-acetyltransferase (NAT) enzymes and recent molecular epidemiological studies have analyzed the relationship between NAT2 in etiology of prostate cancer. A review by Chen (2001) in prostate cancer (PCa) suggests that the frequencies of some polymorphisms in certain genes differ among different racial and ethnic groups. In a case control study in India by Srivastava and Mittal (2005), observed significant association between rapid acetylator genotype NAT2 and PCa in tobacco users (OR = 3.43, 95% CI: 1.68-7.02,  $p < 0.001$ ) when compared with controls. Hamasaki et al (2003) in Japanese men, observed the frequency of the NAT slow acetylator genotype was statistically higher among prostate cancer patients (17.1%) compared with controls (8.6%). Another case control study in Turkey by Kosova et al. (2009), concluded that NAT2\*6A and NAT2\*7A/B gene polymorphism were significantly associated with prostate cancer.

**Key Words:** NAT2 gene, Prostate cancer.

### Introduction

Prostate cancer is the most common cancer affecting men and is a major medical problem. African-American men have the highest rate of prostate cancer in the world (incidence approximately 149 per 100,000 person/year).<sup>1</sup> The etiology of prostate cancer is not well understood, however studies examining genetics, diet and lifestyle are increasingly attracting attention. Cigarette smoking, high fat diet and the consumption of overcooked red meat, increase exposure of aromatic amines and heterocyclic amine,<sup>2,3</sup> both of which are genotoxic chemicals, acquire bioactivation and inactivation by enzymes.<sup>4</sup> If these carcinogens are metabolically active they can initiate carcinogenesis by damaging DNA.<sup>5</sup> Through N-oxidation or O-acetylation by N-acetyltransferase (NAT) enzymes N-hydroxy aromatic and heterocyclic amines are activated to acetoxy intermediary compounds, which can bind to

DNA and produce adducts.<sup>6</sup> It was reported prostate epithelial cells express phase II metabolizing NAT enzymes and recent molecular epidemiological studies have analyzed the relationship between N-acetyltransferase in etiology of prostate cancer.<sup>7,8,9,10</sup>

### Literature Review and Discussion

NAT are encoded by two genes, NAT1 and NAT2 located in chromosome 8p 21.3-23.1.<sup>11</sup> Both genes are highly polymorphic. NAT2 is one of the phase II metabolizing enzymes that participate in the bioconversion of heterocyclic arylamines into electrophilic nitrenium ions, which are important ultimate carcinogens that are directly implicated in tumor initiation process.<sup>12</sup> NAT2 gene is quite polymorphic and there are 29 NAT2 alleles have been identified. Some of these polymorphisms can affect enzyme activity; e.g., 2 or more polymorphisms

result in a slow acetylator phenotype, whereas a heterozygote or wild type genotype results in a rapid or medial acetylator phenotype. Consequently, the acetylation ratio of drugs and carcinogens can change with respect to an individual's acetylator phenotype and predispose them to diseases like cancer.<sup>13</sup>

A review by chen (2001) in prostate cancer suggests that the frequencies of some polymorphisms in certain genes differ among different racial and ethnic groups.<sup>14</sup> The populations of Europe and North America contain from 40-70% of slow acetylators, whereas only 10-30% of slow acetylators were found among the populations of Asian Pacific coast (Japanese, Chinese, Koreans).<sup>15</sup> In Caucasian populations, the NAT2 M1 allele is the most frequent allele (40-50%), in contrast to Asian populations, which exhibit a very low frequency (0-5%).<sup>16,17,18,19</sup>

The first identified and most commonly detected NAT2 alleles in Caucasian populations are the wild type NAT2\*4, as well as the "slow" NAT2\*5 and NAT2\*6 alleles.<sup>(20,21,22)</sup> In contrast, the "slow" NAT2\*5 allele is extremely rare in Oriental populations, difference compensated for by an increased frequency of the "rapid" NAT2\*4 allele.<sup>(23,24)</sup>

A study were conducted by Lima Junior et al (2011) in Latin American patients, found there was an association between NAT2T481C (OR=0.47, 95% CI= 0.26-0.84; P=0.01) and NAT2A803G (OR=0.57; 95% CI= 0.33-0.97;P=0.04) polymorphism and PCa protection, conversely the presence of NAT2G857A genotype increased the risk of PCa more than 3 times (OR=3.57; 95% CI=1.39-9.15; P=0.005). They also found slow acetylator NAT2\*7A and NAT2\*6B genotypes occurred in 10.31% of PCa but in none of BPH patients (P=0.0007).<sup>25</sup> However a study among men of African descent by Kidd LCR et al (2011) did not observe strong main or gene combination effects of NAT1 and NAT2 polymorphisms in relation to PCa risk.<sup>26</sup>

A meta-analysis of the NAT1 and NAT2 polymorphisms and prostate cancer by Gong C et al (2010) revealed, a statistically significant association between NAT2 polymorphism and prostate cancer appeared in Asians, but not in Caucasians. But they concluded that, the NAT1 and NAT2 phenotypes detoxify carcinogen and their intermediates are unlikely to be cause of PCa development.<sup>26</sup>

A case control study in Turkey by Kosova et al. (2009) with 150 unrelated healthy men and 110 unrelated patients with prostate cancer show prostate cancer patients had a higher frequency of mutant NAT2 \*6A and heterozygous NAT2\*7A/B genotypes when compared with the control. They concluded that Nat2\* 6A and NAT2 \*7A/B gene polymorphism were significantly associated with prostate cancer in Turkish population.<sup>13</sup>

Another study of NAT2 and nucleotide excision repair (NER) genetic variant and prostate cancer susceptibility in African American by Hooker et al. (2007) showed possible relationship between polymorphism in NAT2 and NER gene and prostate cancer risk in African American is twice than that of European American.<sup>27</sup>

In another case control study in India by Srivastava and Mittal (2005) over a period of 28 months that included 130 patients and 140 controls, they observed a trend of association of NAT2 (OR=1.452, CI95%, 0.5-1.87, p=0.136) gene in prostate cancer risk but which was statistically nonsignificant. However significant association was observed between rapid acetylator genotype NAT2 and PCa in tobacco users (OR = 3.43, 95% CI: 1.68-7.02, p< 0.001) when compared with controls. The data suggest that NAT2 genotype may play an important role in detecting the risk of developing prostate cancers particularly in tobacco users.<sup>12</sup> The meta analysis conducted by Huncharek and colleagues (2010), pooled findings from numerous studies, revealed consistent evidence that both the chance of developing PCa and dying from PCa increases with smoking.<sup>28</sup>

Again Ratnasinghe et al<sup>10</sup> reported that rapid NAT2 phenotype was a risk factor for prostate cancer. Fukutome et al<sup>9</sup> observed that there was an increased NAT1\*10 homozygote in PCa cases and Hein et al<sup>29</sup> also found that this genotype was a risk for PCa. In contrast, Wadelius et al<sup>30</sup> and Norrish et al<sup>31</sup> reported no association between NAT2 and PCa.

Hamasaki et al (2003)<sup>32</sup> in Japanese men, observed the frequency of the NAT slow acetylator genotype was statistically higher among prostate cancer patients (17.1%) compared with controls (8.6%) and exhibited a 2.2 fold increased risk of prostate cancer (OR=2.21; 95% CI, 1.04-4.69; P=0.0289). However smokers with the slow acetylator genotype exhibited a statistically increased risk of prostate cancer (OR=3.87; 95% CI, 1.48-9.66; P=0.0041). Similarly Costa et al (2005) studied in a Southern European population and observed a statistically significant association of slow acetylator genotype, NAT2\*6/NAT2\*6 with prostate cancer protection (P=0.017, OR=0.31, 95% CI 0.11-0.84).<sup>5</sup>

Although the acetylator status of NAT2 in prostate cancers was investigated in several studies, the results were conflicting as to whether the slow or rapid acetylator status did constitute a risk factor. These inconsistencies may be due to variation in NAT2 allele distribution between interethnic populations<sup>6</sup>, as well as to exposure to environmental factors. Another fact is that the NAT2 gene is quite polymorphic and not all polymorphisms were analyzed at the same time in these studies. Only the most frequently observed polymorphisms were studied.

### Conclusion

Since there have been a number of published reports on the association of NAT2 acetylation phenotypes and prostate cancer risk but the results revealing conflicting and there was no such research work, done in Bangladesh. So a study of genetic polymorphism of NAT2 gene and its association with prostate cancer should be evaluated in Bangladeshi population, which will lead to early diagnosis and better management and prevention of prostatic cancer patients.

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