

## **Genetic Polymorphism and Pathogenesis of Benign Prostatic Hyperplasia (BPH)**

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### **Abstract**

There is apparent uncertainty in etiology and pathogenesis of Benign Prostatic Hyperplasia. Though several hypothesis put forwarded, like other multifactorial complex diseases, BPH still lacks an integrated model of pathogenesis and progression. BPH is a common problem of aged men due uncontrollable non-cancerous prostatic growth. A wide variety of genetic factors have been associated with tissue hyperplasia in general. Androgen related genes and metabolism genes are closely associated with growth and function of prostate. Recent emergence of BPH as inflammation-mediated disease also opens new avenues in search for genetic factors of BPH. Knowledge of gene polymorphisms may be an important aid in genetic screening of risk of disease involved and the understanding of complex interactions involved in genesis and progression of BPH. Till to date there is no report of high penetrance genetic marker in BPH. There is immense possibility of evolving a model of low penetrance markers of BPH and with this prospect a more exhaustive search for all BPH associated polymorphism in larger population is needed. This strategy combined with high-throughput expression profiling and linkage studies of genes for establishing a clear picture of pathophysiology and risk factor of a complex disease like BPH. In this study, we have reviewed a variety of genetic polymorphisms in relation to their possible role in benign prostatic hyperplasia. We have included associations identified in molecular epidemiology studies and the consistency of findings reported to date. Suggestions for further research are also offered.

**Keyword:** Polymorphism, Benign Prostatic Hyperplasia, Pathogenesis

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## INTRODUCTION

Benign prostatic hypertrophy (BPH) is the most frequent urological problem of ageing men, manifested as severe obstruction in urinary flow with discomfort and pain. The principal hypothesis for the hypertrophic reaction of prostate tissue is steroid mediated cellular proliferation and inflammatory response to local infection (**Fig 1**). Besides, inefficiency of apoptotic machinery and aberrant stromal-epithelial interactions are also suggested to probably contribute to the abnormal growth of prostate [1]. BPH traditionally managed with minimal prostate surgery with primarily transurethral resection of the prostate (TURP), now additionally have options for administration of  $\alpha$ -adrenoreceptor blockers such as alfuzosin, tamsulosin; and  $5\alpha$ -reductase inhibitors such as finasteride, dutasteride for patient with moderate to severe symptomatic symptoms.

BPH still an enigmatic problem for biologist with very vague understanding of its pathogenesis and mode of early detection due to lack of well-established biochemical or genetic marker. PSA is the most useful marker for monitoring prostate cancer [2] and is also a strong predictor of prostate volume in BPH [3]. However, level of this kallikrein-related serine protease increases at advanced stage of the disease and more helpful in monitoring at later stage for clinical management [4]. Though no major high penetrating genetic markers has been identified in BPH, several reports of association of polymorphism of low penetrance marker indicating possibility of involvement with much wider applicability. There are several reports of heritability of BPH [5] seen as higher risk with race and ethnicity [6] as well as family history [7-10]. With the limited understanding of disease and susceptibility genes, functional polymorphism in genes involving, steroidogenesis, steroid action and metabolizing enzyme, growth factor, inflammation, apoptosis genes could be major target of these studies. Traditionally, non-functional polymorphisms had already set numerous examples in describing risk of a disease. Unfortunately, there are too limited leads in understanding role of these non-functional gene interactions involved in increased disease susceptibility. The sequencing of human genome had caused great expectations for evolving genetic knowledge of many diseases [11]. However, clinical genetics, encountered the reality that single gene diseases show wide heterogeneity and there is substantial penetrance variability of high penetrance markers. Even apparently simple mendelian disorders prove to have widely variable clinical phenotypes [12]. Polygenic disorders even after decade of genome sequencing still lies unanswered. Environment plays a dominant role in many diseases and therefore identifying a subtle genetic component capable of interacting with environment is also important. A clear understanding of one or a set of susceptibility genes could provide improved mechanistic insight, clues to exposure mechanisms or may suggest a target for chemoprevention or other interventions. More importantly, such findings could serve as key to elucidate fundamental questions about BPH.

Several polymorphisms, both functional and non-functional have already been reported to demonstrate positive associations with prostatic growth and surprisingly, BPH still lack a definitive and complete picture of subtle genetic polymorphism that would be useful for early diagnosis. Eventually these polymorphisms will also demand a definite association with any or all the hypothesis of the disease postulated thus far. Existing human genome knowledge with application of high throughput techniques such as mass spectrometry, NMR and microarray analysis is needed for rapid screening and also

validation of genetic associations currently under investigation in larger populations with ethnic variations. Recently, molecular profiling of BPH patient has also been carried out introducing systems biology approach for rapid search of candidate marker gene [13, 14].

### **PATHOGENESIS OF BPH AND POLYMORPHISM**

BPH is a complex disease from etiology and pathogenesis point of view. Clinicians till to date possesses only symptomatic treatment options. Therefore, treatment modality fails many a time with repetitive TURPS. Identifying the genes responsible for complex diseases, such as BPH, has been less successful, possibly in part because, aside from being polygenic, this disease is multi-factorial.

Several genetic strategies have been used over the past two decades in the investigation of BPH and other complex diseases, but with only limited success. The candidate gene strategy has yielded a number of candidates in BPH. In several other diseases, genetic linkage studies have yielded a large number of quantitative trait loci (QTL) harboring many genes, but none of these strategies alone has been successful in restricting the number of candidate genes. This may seem appealing for the investigators to focus attention on combined use of two or more genetic strategies rather than on a defined set of highly likely candidate genes in BPH.

Till to date all the polymorphism association studies conducted in BPH patients are in genes involved in the proposed pathways of pathogenesis. These polymorphisms studies are summarized along with their association in the disease as shown in **Table 1**.

### **POLYMORPHISM IN ANDROGEN RECEPTOR GENE**

The growth of the prostate gland is dependent on circulating androgens and intracellular steroid signaling pathways mediated through the androgen receptor (AR), a ligand-activated nuclear transcription factor. Androgens bind to the AR, stimulating transcription of a cascade of androgen-responsive genes such as prostate-specific antigen (PSA) and genes involved in cell-cycle control [15]. The transactivation of AR that is important for the normal growth and function of the prostate is found in transactivation domain encoded by exon 1 of the AR gene (Xq11-12) which contains polymorphic CAG and GGN (also GGC) repeats encoding polyglutamine and polyglycine tracts, respectively [16]. Several studies have been conducted to evaluate association of this polymorphism with BPH.

Short CAG repeat length with large prostate size was reported in Japan [17]. Giovannucci *et al* also reported association of short CAG repeat length with BPH patients [18]. There were other studies which further supports the hypothesis that the shorter CAG repeat length of the androgen receptor gene is related to prostate enlargement [19] and urologic measures in BPH [20].

Remarkably, several independent studies reported from India and other populations showed a clear non-significant association of CAG repeats with prostate enlargement or BPH [21-24]. These studies indicate CAG repeat polymorphism may not be suitable for assessment of risk of BPH or at least they might have ethnic variations. Similarly, GGC short repeat was also reported for non-significant association with BPH in Indian population [25].

Androgen and aging are considered to be the main determinants of prostate enlargement. Blocking androgen receptor (AR) activity is a common therapeutic course for BPH [26]. This approach however, results in several side effects, and most notably erectile dysfunction [27, 28]. Gene polymorphisms studies include regulation of androgen

and AR expressions, but lacks investigation of these two issues in different unrelated populations. Indeed, population-based differences in the androgen/AR pathway in prostate cancer are already reported [29] and a similar outcome can be surmised in BPH patient of unrelated populations.

### **POLYMORPHISM IN STEROID METABOLISM PATHWAY GENES**

Androgen and other steroid metabolites along with estrogen have long been considered as a major risk factor in pathogenesis of BPH [30-32]. As expected, genetic polymorphism studies of several genes involved in steroid metabolizing pathway has been shown to be associated with increased BPH risk.

The *CYP3A4* variant allele identified men with BPH who are at increased risk of progressing to prostate cancer (odds ratio 6.3, 95% CI 2.3-17.3) [33]. In another study, it was found that incidence rate of prostate cancer was higher in BPH patients having *CYP3A4* variant genotype compared to those with wild type (relative risk (RR)=2.7; 95% CI=0.77-7.66) [34].

Steroid 5-reductase type II (*SRD5A2*) is also suggested to be associated with BPH and prostate cancer, but the data are not unequivocal. One study demonstrated significant association between LL genotype of V89L polymorphisms in *SRD5A2* and prostate volume in BPH [35]. In contrast, a study in 606 men of 4 ethnic groups from California, reported no significant association between A49T, V89L and (TA)<sub>n</sub> polymorphism and BPH in its overall study population [36]. This study however, reported a significantly increased risk of BPH with the number of L alleles in Hispanic population. Another study with two silent polymorphisms in *SRD5A1* (codon positions 30 and 116) and two polymorphisms in *SRD5A2* (V189L and C to T transition in intron 1) reported that not *SRD5A2* polymorphisms but polymorphisms in *SRD5A1* is associated with severity of BPH [37]. The process by which these silent single-nucleotide polymorphisms (SNPs) of *SRD5A1* influence BPH phenotypes is still unknown. In addition, polymorphism in *HSD3B1*, *CYP19* and *AKR1C3* genes may be associated with an enlarged prostate in older men [38].

Catechol estrogens, a class of carcinogenic metabolites of estrogen plays significant role in malignant transformation of prostate [39] and catechol-*O*-methyltransferase (*COMT*) is the enzyme responsible for neutralizing the genotoxic effects of these metabolites [40]. A variant form of this enzyme has been shown to reduce its activity by up to 4-fold and thus it was hypothesized that polymorphisms of *COMT* gene can be a risk factor for BPH. Up till now, only one study of *COMT* gene polymorphism at codon 62, codon 72, and codon 158 with BPH has been investigated, but failed to find any association [41]. Since the study was restricted to Japanese population, it is still not certain whether *COMT* polymorphism will be unrelated to BPH risk in other populations too.

The A1 allele of the *CYP17* polymorphism is associated with an increased risk of prostate cancer and BPH, with a gene dosage effect. However, the *CYP17* genotype does not seem to influence the disease status in prostate cancer [42]. In another study in Chinese population, it was found that although moderate associations of the A1/A1 and A1/A2 genotypes, there is absence of overall statistically significant associations of *CYP17* polymorphisms with BPH [43]. There was also no evidence for an association between prostate cancer risk and the *CYP17* gene polymorphism in Turkish population [44].

Considering the extent of steroid metabolism pathway gene polymorphism in BPH patients, it requires investigation in larger cohorts of discrete populations. Steroid metabolism pathway genes certainly seem promising as a candidate marker for assessing risk of BPH.

### **POLYMORPHISM CYTOKINE GENES**

Cytokines has immense role in many complex diseases both in immune disorders as well as in several other diseases that are not primarily considered as immune disorder. Inflammatory processes are strongly influenced by the balance between the effects of pro-inflammatory and anti-inflammatory cytokines. In a recent review, Kramer *et al.* has compiled the crucial role of inflammatory processes in BPH considering it as a major factor in disease progression [45]. Several major players in chronic inflammatory process have been suggested for their role in BPH [46] as seen in other diseases [47].

Cytokine genes are highly polymorphic and nature of the polymorphisms determines stability and function of the variants affecting the inflammation response. Genetic polymorphisms that alter cytokine gene expression or protein function could have an important impact on inflammatory pathways and thus in development and progression of disease with inflammatory component [47-49].

Only few genetic polymorphism association studies have been carried out that shed new light on the possible role of low penetrating subtle polymorphism in BPH. Transforming growth factor-beta 1 (TGF- $\beta$ 1) is one of them that plays an important role in the cell cycle regulation and arrests the cell cycle at G1 phase, consequently inhibiting the growth of many kinds of epithelium including prostatic epithelium [50].

Li et al 2003 reported that the codon 10 polymorphism in *TGF- $\beta$ 1* may have a significant influence on the development of BPH, indicating the importance of the TGF pathway in the development of prostatic diseases [51]. Mullan *et al.* reported significant association of BPH with *TGF- $\beta$ 1*, tumor necrosis factor-alpha and epidermal growth factor receptor polymorphisms [52], suggesting involvement of these factors in the pathogenesis of BPH. The authors also reported a positive association of CA repeats of the epidermal growth factor receptor gene with BPH patients [52].

IL1-RN is an important anti-inflammatory cytokine that modulate the inflammation response by binding to IL-1 receptors, and as a consequence inhibits the action of proinflammatory cytokines IL-1 $\alpha$  and IL-1 $\beta$ . Considerable attention has been focused on polymorphism in the gene for the IL-1 receptor. Manchanda *et al.* reported a considerable population variation in the distribution of some of the polymorphisms in *IL-1* gene [53]. A more recent study suggested that *IL-1RN* gene polymorphism is directly implicated in the susceptibility but not in the clinical course of BPH [54].

The CA repeat polymorphism of 19-allele of *IGF-I* appears to increase the risk of prostate cancer and BPH with a gene dosage effect in the Japanese population [55]. Interestingly, there is widespread consensus and extensive role of growth factors have been elucidated in prostatic growth, but very limited attempts to address growth factor gene polymorphism in BPH patient has been made.

The role of cytokine gene polymorphism on BPH seems to be complex. Cytokines being crucial regulator of cellular function, their polymorphism in BPH may lead to very interesting aspect of not only assessing risk of BPH but also to unwind the intricate nature of pathogenesis and progression of the disease. These results also highlight the

critical need to further elucidate the impact of cytokines and their sequence variants on susceptibility and risk of BPH.

### **POLYMORPHISM OF NITRIC OXIDE GENES**

Recent studies have described the NO involvement in many biological processes including carcinogenesis [56-59]. From different studies it appears that NO levels increase with cancer and inflammation, and this may have a bimodal behavior during cancer development. NO is synthesized by at least three isoenzymes of NOS (NO synthase), iNOS (inducible NOS), nNOS (neuronal NOS) and eNOS (endothelial NOS), located on different chromosomes and expressed in different cell lines. The endothelial nitric oxide synthase (eNOS) has an important role in vascular development and in the carcinogenesis process. The gene encoding eNOS is located on chromosome 7q35-36, which comprises 26 exons spanning 21kb [60]. Various genetic polymorphisms of *eNOS* have been described previously [61]. There is only one study conducted by Marangoni *et al.* till now that correlate the association of Glu-298-Asp polymorphism of endothelial nitric oxide synthase with BPH [62]. However, more studies will be needed for confirming lack of association of these gene polymorphisms with risk of BPH.

### **POLYMORPHISM IN VITAMIN-D RECEPTOR GENE**

Vitamin D is a steroid hormone that in recent times has generated much enthusiasm because of its expanding role beyond the realms of classical calcium metabolism. Vitamin D is known to mediate growth and proliferation of diverse population of cell expressing vitamin D receptor (VDR). The *VDR* gene has several known allelic variants and a mononucleotide repeat polymorphism [63-65]. *VDR* polymorphisms have been associated with bone diseases [66], renal disease [67], tuberculosis [68], cardiovascular diseases [69] and cancer [70-72].

Genetic polymorphism of *VDR* gene has also been extensively investigated in prostate cancer with substantial co-relation in assessment of risk. Activation of VDR may influence androgen receptor activation leading to the development of BPH and thus polymorphism of *VDR* has also been investigated in BPH. Habuchi *et al.* estimated risk of BPH with *VDR* gene polymorphism for the first time and reported a positive association [73]. *VDR* genotypes have been associated with the risk prostatic enlargement in BPH in Japanese men [74] and its importance of *VDR* genotypes in determining the risk of prostatic enlargement in BPH has also been reported [75]. In contrast, several other studies reported lack of association between the *VDR* gene polymorphism and the risk of BPH [34, 76, 77],

The interpretation of polymorphic variations in the *VDR* gene is severely hindered by the fact that only few polymorphisms in this large gene have been studied so far. Most of these are anonymous restriction fragment length polymorphisms (RFLP), with unknown functional effects. Besides, considerable attention needs to be given on ethnic variation in the distribution of some of the polymorphisms in *VDR* gene [78]. All these issues need to be addressed for understanding the nature of association of VDR with the risk of BPH.

### **POLYMORPHISM IN HOMEBOX GENE**

The gene *NKX3.1* is a prostate-specific homeobox gene that influences differentiation and growth suppression of prostatic epithelial cells during development. Prostate homeobox gene *NKX3.1* has polymorphic sites at nucleotide 154 (C154T) that reveals a significant association with development of BPH [79]. This signifies that risk of

BPH is initiated at the time of development and differentiation of organ itself and investigation of polymorphisms of unexplored genes that are involved in prostate development may reveal candidate genes with significant association with the risk of BPH. Particularly, investigation of genes related to developmental defect resulting in aberrant stromal-epithelial interactions may lead to some interesting genetic aspects of pathogenesis of BPH.

### **POLYMORPHISMS IN THE $\alpha$ 1A -ADRENOCEPTOR GENE**

The role of  $\alpha$ 1-adrenergic receptors ( $\alpha$ 1-adrenoceptors) in BPH has recently been expanded; these receptors seem not only to increase the tone of prostatic smooth muscle but also modify prostatic growth [80-82] and contribute to LUTS by affecting the bladder and the spinal cord. Three  $\alpha$ 1-adrenoceptor subtypes have been identified so far, i.e. subtypes  $\alpha$ 1a,  $\alpha$ 1b and  $\alpha$ 1d [83].  $\alpha$ 1 adrenoceptors, which are predominantly situated in the prostatic smooth muscle [84], presumably have a direct effect on voiding symptoms.  $\alpha$ 1d-adrenoceptors, which are mainly located in the bladder wall and spinal cord, may contribute to storage symptoms [85].

$\alpha$ -1 adrenoceptor gene contains polymorphic sites at positions 1035 (T→G), 1175 (G→A), 1475 (C→T), 1677 (A→G), and 1831 (A→T) [86] and at Arg-492-Cys [87]. All investigations conducted so far fails to exhibit any significant association with BPH.

Since  $\alpha$ 1-adrenergic receptor component of symptomatic BPH patient is most essential as activation of this pathway of dynamic obstruction causes much of the pain and discomforts, polymorphism of genes in this pathway therefore, may help in understanding non-responsiveness to  $\alpha$ -adrenergic blockers and most importantly increased risk of the severity of BPH.

### **FUTURE DIRECTIONS**

#### **UNDERSTANDING PATHOGENESIS OF BPH**

BPH is a vaguely understood disease in the sense that it lacks well-established etiology and disease progression model. Though numerous risk factors have been attributed to the disease, it is not yet known how multifactorial interactions lead to the disease. Large-scale studies that test for multiple genetic markers are likely to find some associations with BPH to be statistically significant, due to multiple comparisons and because the genetic markers may be in linkage disequilibrium. However, findings from these studies require careful evaluation towards gaining insight into functional pathways. The major advances in genetics during the last decade will allow us to apply reverse logic to our efforts whereby we use genes to identify pathways for analysis rather than pathways leading us to genes. Future studies that examine associations among several genetic polymorphisms should take into account of known risk factors for BPH, such as diet and other environmental exposures, as well as possible biological pathways.

#### **GENETIC SCREENING AND MONITORING OF BPH**

BPH lacks screening markers and clinical practice involves symptomatic and anatomic diagnosis and treatment. Genotypes, alone or combination may be useful in identifying people at high risk of BPH who would benefit from preventative measures to reduce their future risk. Such identification will also lead to new stratification of candidates for BPH screening and preventive approaches. Additional population-based studies of incidences of BPH, with adequate sample sizes and in racially diverse populations, are needed to be

looked at in order to understand possible associations with several genetic polymorphisms and risk factors for BPH (exogenous androgens, reproductive factors, diet, alcohol intake, cigarette smoking, and other environmental exposures), while taking possible causal pathways into account. Marked population differences in BPH incidence have also been reported which may arise from genetic, environmental, or social influences. To date, molecular epidemiology studies of BPH have rarely looked at a variety of potential gene-environment interactions or explored associations and interactions with more than one genetic polymorphism. However, the initiation and progression of BPH most likely result from a complex series of genetic events along with environmental influences and further studies are needed to identify potential causes for the distinction between latent and symptomatic BPH.

## **CONCLUSIONS**

BPH is a complex disease with very limited understanding of genetic pathways involved in its initiation and progression. Genetic studies have immense role in not only elucidating these subtle pathways but also preventing the disease by examining risk factors. Though most of the studies carried out so far, have yielded significant associations of gene polymorphism with the disease, unfortunately there are very limited numbers of studies of genetic polymorphism in BPH. Studies indicating positive associations of androgen-mediated and steroid metabolism pathways with the risk of BPH are not unexpected. Significant association of various cytokines emphasizes that there is need to investigate more subtle genes in combination with risk factors. However, conclusive determination of BPH risk factor with the polymorphism of cytokine and VDR genes require further studies. Interestingly,  $\alpha$ -1 adrenoceptor genes that are responsible for painful smooth muscle tone in symptomatic BPH has been shown not to be associated with risk of BPH in all the studies reported so far, suggesting that adrenergic component of BPH is secondary and not necessarily associated with risk of BPH. The current understanding of gene polymorphism studies in BPH provides reasonable evidence on power and promise of these studies in assessing the risk of BPH with a more mechanistic correlation to biological pathways. Pharmacogenomics of BPH is still a less explored area and such studies in different ethnic populations with large cohorts may contribute immensely to our existing knowledge.

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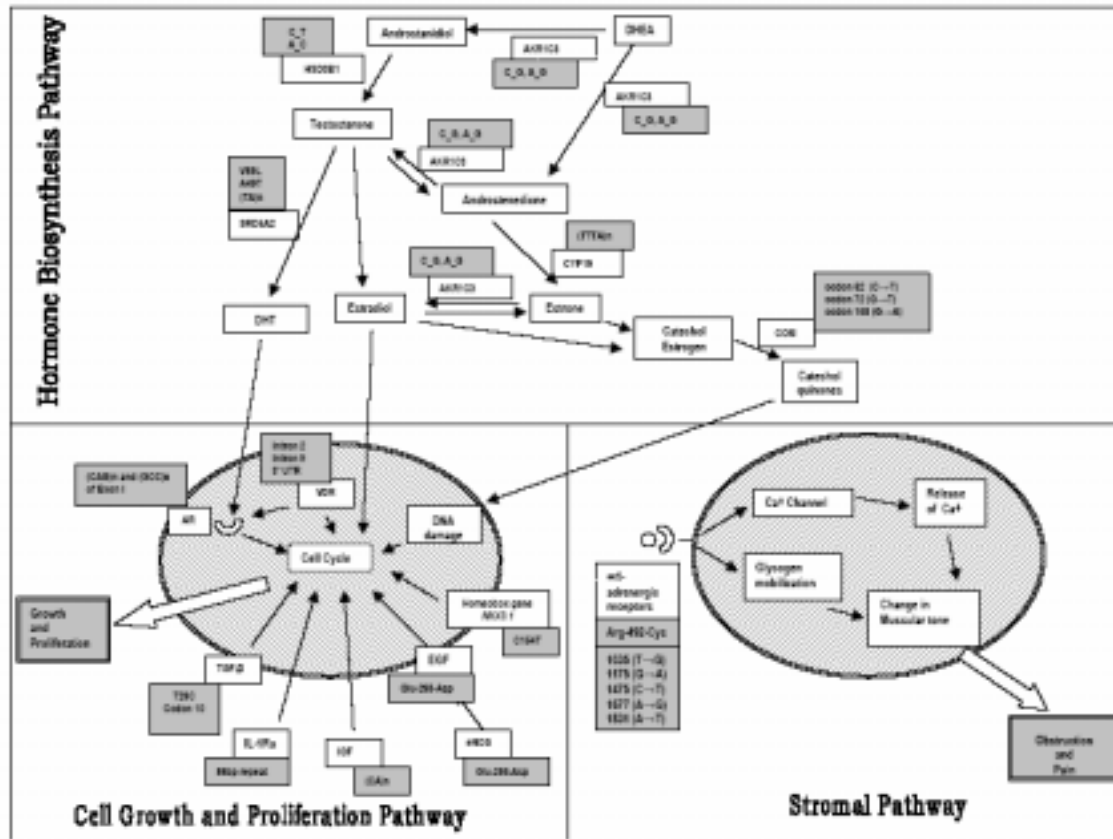
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Table 1: Polymorphism Investigated for Association with BPH

Mechanistic Role in Pathogenesis	Target Gene	Polymorphic Site	Outcome	Citation
Mediates growth of prostatic tissue through different growth factor	Androgen receptor	$\leq 21$ to $\geq 23$ of (CAG) <sub>n</sub>	Significant association	Mitsumori <i>et al</i> 1999 [17]
		$\leq 19$ of (CAG) <sub>n</sub>	Significant association	Giovannucci <i>et al</i> 1999 [18]
		$\leq 20$ of (CAG) <sub>n</sub>	Significant association	Shibata <i>et al</i> 2001[19]
		(CAG) <sub>n</sub>	Significant association	Klotsman <i>et al</i> 2004 [37]
		$\leq 21$ of (CAG) <sub>n</sub> and $< 16$ of (GGC) <sub>n</sub>	Significant association	Roberts <i>et al</i> 2004 [20]
		$\leq 19$ of (CAG) <sub>n</sub>	Significant association	Krishnaswamy <i>et al</i> 2006 [24,25]
		(CAG) <sub>n</sub>	Non-significant association	Bousema <i>et al</i> 2000 [76]
		$< 19$ of (CAG) <sub>n</sub>	Non-significant association	<b>Schatzl <i>et al</i> 2002 [88]</b>
		$\leq 18$ of (CAG) <sub>n</sub>	Significant association	Mononen <i>et al</i> 2002 [89]

Steroid metabolism resulting in susceptibility to steroid mediated growth and proliferation of prostate	Steroid 5-reductase		49 (A→T), 89 (V→L) and (TA) <sub>n</sub> dinucleotide repeats	Non-significant association Significant	Shibata <i>et al</i> 2001 [19] Klotsman <i>et al</i> 2004 [37] Salam <i>et al</i> 2005 [36] Roberts <i>et al</i> 2005 [35]
	Cyp3A4		5'-UTR (T→C)	Significant association	Tayeb <i>et al</i> 2002 [33,34] Roberts <i>et al</i> 2006 [38]
	Catechol-O methyltransferase		Codon 62 (C→T), Codon 72 (G→T), and Codon 158 (G→A)	Non-significant association	Tanaka <i>et al</i> 2006 [41]
	Endothelial nitric oxide		298 (E→D)	Significant association	Marangoni <i>et al</i> 2006 [62]
Growth and proliferation of prostate	Vitamin-D receptor		Intron 8 <i>BsmI</i> (10,438,141 C→T) Intron 8 <i>Apa I</i> (10,382,143 C→A) Exon 9 <i>TaqI</i> (10,382,063 A→G)	Non-significant association	Chaimuangraj <i>et al</i> 2006 [76]
			<i>TaqI</i> in Exon 9 (10,382,063 A→G)	Significant association	Tayeb <i>et al</i> 2004 [75]
				Significant association	Habuchi <i>et al</i> 2000 [73]
				Non-significant association	Bousema <i>et al</i> 2000 [76]
				Significant association	Hamasaki <i>et al</i> 2002 [74]
	Cytokines	Epidermal growth factor	CA repeat	Significant association	Mullan <i>et al</i> 2006 [52]
		Insulin-like growth factor-I	CA repeat (15-22)	Significant	Tsuchiya <i>et al</i> 2005[55]
TGF beta		Codon 10 (L→P)	Significant association	Li <i>et al</i> 2004 [51]	
Growth and Differentiation of Prostatic epithelia	Prostate homeobox		Nucleotide 154 (C→T) of the <i>NKX3.1</i> gene	Significant association	Ortner <i>et al</i> 2006 [79]
Modulate smooth muscle tone	Alpha-1 adrenoceptor		1035 (T→G), 1175 (G→A), 1475 (C→T), 1677 (A→G), and 1831 (A→T)	Non-significant association	Mochtar <i>et al</i> 2006 [86]
			492(R→C)	Non-significant association	Shibata <i>et al</i> 1996 [87] Klotsman <i>et al</i> 2004 [37]



**Fig 1: Gene Polymorphisms in Putative Pathways Associated with BPH.** The figure depicts polymorphisms in the three major components suggested to be involved in initiation, progression and severity of benign prostatic hyperplasia. The target genes and their polymorphic sites that have been investigated so far for associations with risk of BPH are shown in dashed boxes and dashed box with gray colour respectively. Abbreviations used are, **AKR1C3**- Aldoketoreductase type 1C3 (includes 3-alpha-Hydroxysteroid dehydrogenase type II /DD, 17b-Hydroxysteroid dehydrogenase type V), **SRD5A2**-5-alpha reductase type A, **HSD3B1**-3-beta-Hydroxysteroid dehydrogenase type II, **DHEA**-Dihydroepiandrosterone, **DHT**-Dihydrotestosterone, **COMT**-Catechol-O-methyltransferase, **AR**-Androgen receptor, **TGF beta**- Transforming Growth Factor beta, **EGF**- Epidermal Growth Factor, **VEGF**- Vascular Endothelial Growth Factor, **eNOS**-endothelial nitric oxide synthetase, **VDR**- Vitamin D receptor.