

Overview of The Role of B2-Adrenergic Receptor Variants in Human Hypertension

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Abstract: Essential hypertension is a complex trait with multifactorial origin arising from an interaction between genetic and environmental factors contribute interactively. Consequently, the identification of genes related to hypertension is complicated by the heterogeneity of its causes and the possibility that various genes with moderate impacts, probably acting in a same manner, affect blood pressure and the occurrence of hypertension. Multiple studies have suggested that variation within the β 2-adrenergic receptor (ADRB2) is implicated in blood pressure regulation and the development of hypertension. The evidence for ADRB2 gene association with hypertension is not conclusive. There are conflicting reports on the association of these polymorphisms with hypertension. Several reports have suggested the association of the ADRB2 variants with the prevalence of hypertension and systolic blood pressure (BP) whilst others refuted the association. The role of these findings is reviewed here, and their potential clinical influences in human hypertension.

Keywords: Hypertension – Polymorphism – ADRB2- SNPs.

Introduction

Hypertension is a complex trait, influenced by multiple environmental and genetic factors to ultimately determine blood pressure levels and the occurrence of various diseases [1]. Although numerous reports have provided evidence for the role of genes in the determination of blood pressure levels and hypertension, the identity of the contributing genes remains unclear [2]. Because there are diverse systems known to regulate blood pressure levels, one cannot limit particular genes encoding certain class of proteins could probably be responsible in hypertension regulation. Convincing evidence for the identification of a true functional polymorphism for hypertension should come from diverse sources, mostly from both population and functional studies. The β 2-adrenergic receptor (ADRB2) may represent such a functional candidate gene [3].

The human ADRB2 is a member of the G-protein-coupled adrenergic receptor superfamily with seven trans-membrane domains. Like other members of this receptor family, ADRB2 specifically binds and is stimulated by an endogenous class of ligands known as catecholamines particular epinephrine. The gene encoding this receptor, ADRB2, was firstly cloned by Kobilka et al. in 1987 and is located in chromosome 5q31–q32 region [4].

ADRB2 are widely distributed and play an essential role in regulating pulmonary, vascular, metabolic and cardiac functions [5]. The ADRB2 gene has 9 different single nucleotide polymorphisms (SNPs); in which, four of these polymorphisms involve the change of amino acids at residues 16, 27, 34 and 164. The most polymorphic substitution is the substitution of Glycine for Arginine at codon 16 (Arg16Gly) and the alteration of Glutamic acid for Glutamine at codon 27 (Gln27Glu) [6]. Numerous reports have suggested possible associations between SNPs in the coding region of the ADRB2, mostly for Arg16Gly, Gln27Glu and Threonine

16 Isoleucine (Thr164Ile), but have produced conflicting results [7,8]. This review highlights the genetic variations in ADRB2 and its crucial role with hypertension.

Functional Studies of Adrb2 Variants

The human β_2 -adrenergic receptor is a G-protein-coupled receptor found in many tissue types and is a target for several β_2 -adrenoreceptor agonists and antagonists currently used in the treatment of various diseases. Individual variations in physiological responses, expression and function of the receptor, as well as individual differences in response to drugs that act on these receptors may relate to polymorphic variants of the receptor. In myocardium, β_1 and β_2 adrenergic receptors mediate inotropic and chronotropic responses to endogenous and exogenous adrenergic agents, while in vascular smooth muscle, β_2 -adrenergic receptors mediate vasodilatation in response to adrenergic agonists [9].

The human ADRB2 has seven transmembrane spanning domains, an extracellular N-terminus and an intracellular C-terminus, which is coupled to the stimulatory form of G protein (Gs). Specific amino acids within hydrophobic membrane-spanning regions of the ADRB2 function as targets for catecholamine ligand binding and activate adenylate cyclase activity and cyclic adenosine monophosphate (cAMP) synthesis by intracellular release of activated Gs [10]. cAMP serve as a second messenger in the signal transduction cascade by activating protein kinase A (PKA). The activation of PKA results in the cascade of protein phosphorylations, predominately enzymes, receptors, or channels which may be activated or deactivated upon phosphorylation. Through activation of cAMP-dependent protein kinase A and other signalling pathways, the ADRB2 regulates a number of metabolic and physiologic processes in various organs such as heart, lung and kidney [3].

The ADRB2 gene (MIM number: ID+109690, gene locus:5q32-34), which consists of a intronless block of 1,242 base pairs [4], has 9 single nucleotide polymorphism (SNPs) in the coding region of the ADRB2 gene and eight SNPs in the 5' upstream region of the ADRB2 gene identified. Five variants in the coding region are silent (synonymous) SNPs, because altering the nucleotide base does not change the amino acid sequence of the ADRB2. The other four variants are non-synonymous SNPs and result in changes in amino acids at residues 16, 27, 34 and 164 in the receptor protein. The most polymorphic substitution is the substitution of Glycine for Arginine at codon 16 (Arg16Gly) and the substitution of Glutamic acid for Glutamine at codon 27 (Gln27Glu). While variation of Valine to Methionine at codon 34 (Val34Met) and Threonine to Isoleucine at codon 164 (Thr164Ile) are rare mutations [6,11]. The frequency of Gly16 is greater than that of Arg16, which is considered the normal allele, while the frequency of Glu27 is less than that of normal allele Gln27 (51% and 7% respectively) [12]. Moreover, two polymorphic sites within the promoter region of the gene have also been demonstrated, a T to C substitution at residue -47 and a T to C substitution at residue -20 [13]. In addition, five SNPs within codons 84, 175, 351, 366, and 413 do not change the amino acid sequence of the protein [6]. Previous studies have associated these variants with differences in the prevalence, severity and response to drugs used in disorders like hypertension, heart failure, coronary disease and sudden cardiac death [14]. A number of reports revealed that both the Arg16Gly and Gln27Glu variants may play a role in receptor down regulation. In studies among asthmatic patients, Arg16Gly substitution exaggerates agonist-mediated receptor down-regulation in response to β_2 agonists. [15]. Conversely, the substitution of Gln to Glu at codon 27 shows resistance to down regulation, which confers to this variant resistance to the desensitization and increased response to the β_2 agonists [16]. The differences observed in rates of down regulation between the two SNPs forms of the receptor protein at codons 16 and 27 were mostly due to differential rates of protein degradation [17]. In another experiments, the Isoleucine substitution of the Threonine in residue 164 causes that receptor to have decreased basal and agonist-stimulated adenylyl cyclase activities and therefore, decreased affinity for β_2 agonists [18].

The Human Adrb2 Variation and Hypertension

Initial population based studies of the functional polymorphisms within the ADRB2 gene focused primarily on their role in asthma, and variation within this gene has been associated with the occurrence of both nocturnal and non-nocturnal asthma [19]. Few years later, however, the role of the ADRB2 gene in human hypertension has been the subject of extensive research, and many reports have suggested association between SNPs in the ADRB2 gene and hypertension in a number of different populations, although genetic evidence of its impact on hypertension has been conflicting. Hypertension is the most essential risk factor for stroke, myocardial infarction and heart failure, as well as the one with the highest incidence in the population, affects almost 4.8 million of Malaysian individuals [20]. Numerous studies have identified genetic factors that impact blood pressure and metabolic responses to β -adrenergic antagonists, thiazide diuretics, and renin-angiotensin system blockers. Given functional relevance of ADRB2 SNPs on expression and properties of the ADRB2, the

possible association of these variants with hypertension has been extensively studied [21]. Svetkey and his colleagues in 1996, firstly reported an association between SNPs in the ADRB2 gene and hypertension in both white and African-American patients, suggesting that the ADRB2 locus is a candidate gene for hypertension [22]. Subsequently, Kotanko et al. reported an association between the Arg16Gly variant and hypertension in sample of African-Caribbean men and women. Based on their finding, Gly16 of ADRB2 gene was increased among hypertensive African Caribbeans relatives to their normotensive groups. They hypothesized that variation in the ADRB2 gene may predispose to essential hypertension by enhancing agonist-mediated receptor down regulation activity, and thus represent an additional candidate for the genetic basis of this complex trait. In their study, the frequency of the Gly16 allele was significantly greater among hypertensive patients in compare to normal groups (0.85 Vs 0.66, respectively: $P < 0.0001$) [23]. A study by Jindra et al. reported a positive association between Arg16Gly polymorphism of the ADRB2 gene and predisposition to primary hypertension and increased plasma noradrenaline concentration in offspring from normotensive and hypertensive parents in northern European. [24]. In a haplotype analysis of Swedish hypertensive patients, Arg16Gly/ Gln27Gln were associated with higher systolic blood pressure (SBP) measurements. SBP was elevated in patients with Arg16Gly/Gln27Gln haplotypes and reduced in patients with Arg16Gly/Gln27Glu as compared with the other haplotypes [25]. Moreover, previous findings showed that the Arg16 allele was associated with higher SBP levels in German twins [26]. Another study investigated sib-pairs from 55 pedigrees and around 2500 additional individuals from 589 families, revealed that the risk for hypertension was higher in individual carrying the Gly16 and Glu27 alleles [27].

In contrast to the previously mentioned results [22-27], some reports suggested that there was no considerable implication of the ADRB2 with hypertension. Iaccarino et al. studied the impact of the ADRB2 variants on cardiac and vascular target organ damage in a population of untreated primary hypertensive patients after evaluation of clinical and biochemical data. This study revealed that Arg16Gly, Glu27Gln, and Thr164Ile SNPs had no notable effect of on blood pressure and heart rate, although Arg16 influenced the age of the onset of hypertension [7]. Moreover, reports on Chinese and Japanese individual studies have also revealed that Arg16Gly and Glu27Gln alleles were not associated with hypertension [28,29]. In a study done by Hindorf et al. on over 5000 Black and Caucasian American participants, there were no significant effect of the Arg16Gly and Glu27Glu variants on BP control and hypertension [30]. Similarly, The Gly16Arg and Glu27Glu variants were not significantly associated with the prevalence of hypertension in a relatively recent study on Malaysian individuals [12]. Further, no significant association between Thr164Ile polymorphism and hypertension was found in a linkage study with 638 participants from 212 Polish pedigrees with clustering of hypertension [31].

The confusion on the exact role of these polymorphisms with the occurrence of hypertension and elevation of systolic blood pressure could probably be solved by the most recent extensive population study done by Gao et al. 2014 on over 4000 participants where they found no significant association between the Arg16Gly polymorphism and hypertension. However, as the study was done on Chinese hypertensive subjects, the association could not be generalized to the other ethnic groups [32]. Although the evidence for ADRB2 gene association with hypertension is not conclusive, studies have suggested that the functional alteration of the sympathetic system contributes to hypertension in spontaneously hypertensive rats [33,34]. The lack of uniformity among these studies probably due to ethnic differences in study subjects or may be due to the loss of power resulting from the reduction in sample size. Taking into account that ADRB2 is a crucial target of various drugs and endogenous agents, interethnic variations in this gene may explain differences in drug response and disease susceptibility [35].

Concluding Remarks

The overall evidence suggests that variants in the coding region of the ADRB2 are not associated with hypertension in a clinically significant manner in many ethnic groups, either probably due to their effect is too weak and/or may be because the polymorphism is too rare to have notable effects on the general population. The most recent study by Gao et al [32] raises the possibility that SNPs in the promoter region of the ADRB2 are not associated with hypertension. In general context, these data highlight the significance of considering ethnicity in genotype–phenotype relationship studies because the possibility that such these associations are more notable in some ethnic groups in compare to others. Epigenetic and gene–environment interactions might cause such differences [36], however it is possibly that genetic influences of SNPs are commonly similar across races with substantially differing in allele frequencies [37].

Abbreviations

ADRB2: Beta-2-adrenergic receptor; cAMP: Cyclic adenosine monophosphate; SNPs: Single nucleotide polymorphisms; PKA: protein kinase A; SBP: systolic blood pressure measurements.

Conflict of Interest: The authors declare that they have no conflict of interest.

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