Renin-Angiotensin System: is it Possible to Identify Hypertension Susceptibility Genes?

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It is estimated that from 15% to 20% of Brazilian adult urban population is affected by Hypertension[1,2]. Although no populational study based on nationwide data is available, morbimortality indicators resulting from cerebrovascular disease clearly show the relevance of hypertension for public health in Brazil since it is reported as significant impacting risk factor for the onset of cardiovascular diseases[3]. In 2004, cerebrovascular disease was responsible for 90,930 deaths, having been a major cause of death in Brazil[4].

A number of factors have been identified for the development of hypertension. Some of them are: obesity, insulin resistance, increased alcohol and salt consumption, age, sedentary life, and stress. The epidemiological knowledge of those risk factors is key for the understanding of how impacting each one of them is to determine the hypertension condition. A recently published review study evaluated the prevalence of the most commonly found risk factors for hypertension in Brazil. The study was based on populational studies conducted in the period between 1996 and 2005 (Table 1)[5]. Quite a wide prevalence range could be observed for risk factors, which signals towards the need of more structured epidemiological studies. However, median values presented show high prevalence, thus explaining high mortality rate resulting from cerebrovascular disease.

Hypertension: a complex condition

Environmental and genetic risk factors combined are considered to be intermediate phenotypes, just as obesity and insulin resistance, among others. Therefore, hypertension may be understood as a final phenotype, resulting from a number of intermediate phenotypes. In the light of molecular biology hypertension can be defined as a complex, polygenic, multifactorial condition. Each patient may present different cause factors (environmental and/or genetic) for the trait[6].

Blood pressure (BP) is the result of cardiac debit and peripheral vascular resistance. New systems and mechanisms affecting cardiac debit and peripheral vascular resistance – as well as BP, as a consequence – have contributed for a complex chain of physiopathological inter-relations in the hypertension condition scenario[7]. Changes in sodium renal retention, in the sympathetic nervous system, in the renin-angiotensin system (RAS), in cell membrane, and in hyperinsulinemia, among others, are integral parts of this complex physiopathological chain[8]. The understanding of each of those components as intermediate multiple-gene phenotypes supports the concept of hypertension as a complex condition.

Many studies have been conducted to identify hypertension susceptibility genes (Table 2). The number of genes involved is not yet known; neither is the transmission mode, quantitative effect on BP, the interaction with other genes or with environmental factors[9]. Genetic factors are responsible for one third of all factors involved in hypertension etiopathogeny[9-12]. However, many studies may have underestimated the impact of those genes since

Table 1 - Prevalence of Risk Factors associated to hypertension in Brazil

Risk factors (n, %)*	Lower Prevalence 9%)	Higher Prevalence (%)	Median (%)
Obesity (BMII ≥ 30 kg/m²)	7.9	20.8	12.7
Overweight (BMI ≥ 25 kg/m²)	25.7	51.6	32.6
Dyslipidemia	4.2	42.8	12.7
Diabete Mellitus	2.3	36.2	6.1
Sedentary Life	38.7	80.7	68.5
Alcohol Abuse/Consumption	2.9	45.4	9.3

Key words

Renin-angiotensin system; genes; hypertension / epidemiology; risk of factors.

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Table 2 - Systems/Mechanisms involved in the pathophysiology of hypertension and hypertension susceptibility candidate genes

System/Mechanism involved in hypertension pathophysiology	Gene
Renin-Angiotensin System	Angiotensinogen *(AGT)*
	Renin *(REN)*
	Angiotensin Converting Enzyme *(ACE)*
	Angiotensin II AT1 Receptor *(AGTR1)*
	Angiotensin II AT2 Receptor (AGTR2)
Synpathetic Nervous System	β1 Adrenergic Receptor*(ADRB1C)*
	β2 Adrenergic Receptor(ADRB2C)
Ions Transport	Subunit B3 of protein G *(GNB3)*

behavioral patterns – such as obesity and alcohol abuse – may also be modulated by genetic factors[6]. Response to physical exercise has been demonstrated to vary from individual to individual, thus suggesting that the effects from exercise may – to a great extent – be mediated by genetic variations[13].

The complexity of studying hypertension molecular determinants results not only of the gene-environment interaction, but of the interference of the multiples alleles themselves, which individually may have little influence on final phenotype but when combined may have significantly additional effect[14-16]. Reports on combined RAS-related genotypes and high prevalence of hypertension are available, although no individual effect of each genotype, isolatedly, has been detected[17]. On the other hand, some hypertension genes may be activated at certain points in time along life. So, some individuals who develop hypertension at a later age may have hypertension gene activation as the mechanism responsible. Despite such evidence, longitudinal studies are needed to investigate the association between hypertension and genes at different age ranges[18]. Mutations at different loci in the same gene may also contribute to make the understanding of gene impact on hypertension even harder.

However, the study of genetic polymorphisms involved in hypertension is not only made difficult due to genetic aspects already mentioned. There are limitations related to study methodology. The most commonly used studies have a case-control design and linkage analysis. Case control studies screen non-related individuals, allow larger samples and have higher statistical power, but are more susceptible to false-positives. Linkage analysis recruit individuals within the same family or groups of family members who have a history of hypertesion. As a smaller number of individuals are enrolled in the study, power is reduced[9].

Renin–angiotensin system: one component in the complex chain

One of the components in the complex chain regulating blood pressure is RAS. The role played by RAS in the pathophysiology of hypertension has been extensively studied, as have the genes regulating the expression of proteins involved in that system. RAS interferes in the homeostasis of salt, water and vascular tonus[7]. It is made up by four major proteins: renin (REN), angiotensinogen (AGT), angiotensin converting enzyme (ACE) and angiotensin II receptors (AII). All RAS components have been found in tissues of the heart, brain, kidneys, adrenal glands, blood vessels and reproductive organs. That leads to the identification of local RAS and circulating RAS. An intracellular RAS has been suggested, where components would not be excreted and would act inside the cell[7,20].

Ultimately we know that renin, from renal origin, acts over AGT, formed in the liver - and that is how angiotensin I (AI) is originated. Through ACE angiotensin I is turned into AII, a powerful, direct vasoconstrictor which indirectly interacts with aldosterone secretion, with central nervous system and with sympathetic nervous system. In addition to AII, other angiotensins have specific actions. Among the best characterized are angiotensin III, angiotensin IV and angiotensin 1-7[7].

The regulating actions of AII are mediated by cell surface receptors that are coupled to effectors, phosphorylase C and adenyl cyclase included[21], through G protein. The four pharmacologically distinctive classes of angiotensin receptors are: AT_1, AT_2, AT_4 and AT_{1-7} type 1 seems to be the mediator for AII major pathophysiologic actions. It is through type 1 that RAS acts over BP[7,20]. AT_1 receptors are located in the plasma membrane of target cells for AII: vascular smooth muscle cells, adrenal cells, myocardial cells and brain cells[22].

In most species renin is codified by one gene only. In man, the *REN* gene is located in the 1q32 region. Messenger RNA is translated to an inactive form called pre-prorenin, with 401 aminoacid residues which are later clevaged until active renin is formed. Angiotensinogen is codified by *AGT* gene in chromosome 1q42-43 and can be cleavaged by different enzymes to generate angiotensin I or angiotensin II directly. The ACE is codified by the *ACE*- gene located at chromosome 17q23. In addition to increasing the production of AII, it is also responsible for the degradation of bradicinin – a vasodilating, natriuretic substance[20]. The codifying gene for AT1 (*AGTR1*) receptor is located at chromosome 3q21-25, spreads over 60 Kb and contains 6 exons. The whole codifying region is situated at exon 5[23].

Hypertension and renin-angiotensin system polymorphisms

A number of genes codifying RAS have been involved in the etiopathogeny of hypertension, coronary disease, mitral valve prolapse syndrome, cardiac hypertrophy, obstructive sleep apnea, and Alzheimer, among other conditions.

The association between RAS polymorphisms and hypertension has not been clearly defined, as seen in tables 3, 4 and 5. Some studies have actually shown the association

Table 3 - Some studies investigating the association between angiotensinogen polymorphism M235T and hypertension

Authors	Population (N)	Genotypes n (%)						Association with hypertension
		Normotensives			Hypertensives			
		MM	MT	TT	MM	MT	TT	
Kobashi et al, 2006 [32]	Japan. (481)	18 (4.9)	143 (38.9)	207 (56.3)	2 (1.8)	15 (13.3)	96 (85.0)	Genotype TT was more commonly found in hypertensive pregnant women (OR: 2.3; CI 95%: 1.5–3.5).
Mondry et al, 2005[18]	Germany (1,357)	231 (32.1)	456 (63.3)	33 (4.6)	229 (35.9)	391 (61.4)	17 (2.7)	Genotype ITT was more commonly found in normotensives (OR: 0.52; CI 95%: 0.28–0.96).
Wu et al, 2004[57]	Taiwan (778)	5 (1.5)	89 (27.4)	231 (71.1)	18 (3.8)	115 (25.4)	320 (70.6)	No association found
Agachan et al, 2003[29]	Turkey (174)	23 (31.6)	49 (66.2)	2 (2.7)	32 (32.0)	48 (48.0)	20 (20.0)	Association with genotype TT (X^2= 11.52; p= 0.001).
Paillard et al, 1999[58]	France (114)	35 (30.7)	62 (54.4)	17 (14.9)				No association with AGT plasma levels.
Freitas et al, 2007[59]	Brazil (205)	64 (55.7)	43 (37.4)	7 (6.9)	26 (28.6)	35 (38.5)	30 (33)	Genotypes (MT + TT) were more commonly found between hypertensives (OR: 3.2; CI 95%: 1.71-6.01; p<0.05.
Freitas et al, 2007[60]	Brazil (160)	8 (10)	56 (72.5)	14 (17.5)	7 (8.5)	50 (61.0)	25 (30.5)	No association found (p=0.154).

p - Comparison between cases and controls.

Table 4 - Some studies investigating the association between polymorphism I/D and hypertension

Authors	Population (N)	Genotypes n (%)						Association with hypertension
		Normotensives			Hypertensives			
		DD	DI	II	DD	DI	II	
Mondry et al, 2005[18]	Germany (1,355)	193 (26.8)	356 (49.5)	170 (23.6)	171 (26.9)	315 (49.5)	150 (23.6)	No association found
Agachan et al, 2003[29]	Turkey (194)	36 (42.4)	32 (37.6)	17 (20.0)	49 (45.0)	59 (54.1)	1 (0.9)	Association with genotype TT (X^2 20.66; p= p=0.000).
Castellano et al, 2003[46]	Italy (2,390)	247 (41.0)	272 (46.0)	77 (13.0)	747 (42.0)	812 (45.0)	235 (13.0)	No association found
O'Donnell et al, 1998[37]	USA (3,094)	484 (28.4)	882 (51.8)	336 (19.7)	445 (32.0)	682 (49.0)	265 (19.0)	Genotype DD shows increased risk for hypertension in males, but not in females (OR: 1.59; CI 95%: 1.13-2.23).
Freitas et al, 2007[59]	Brazil (205)	12 (10.5)	52 (45.2)	51 (44.3)	13 (14.3)	46 (50.5)	31 (34.1)	No association found (OR 0.70; CI 95%: 0.28-1.75)
Freitas et al, 2007[60]	Brazil (160)	4 (5.1)	13 (16.7)	61 (78.2)	8 (9.8)	27 (32.9)	47 (57.3)	Association with genotype DD. (p=0.019)

p - Comparison between cases and controls.

between those polymorphisms with hypertension, others have not. Ethnic diversity and sample size considered, similar findings have been related by Sakuma et al[24] in Brazil, and Sayed-Tabatabaei et al[25] in Roterdam, The Netherlands. The same study design (cross-sectional study) was used to describe the association between allele D of ACE I/D polymorphism and hypertension. The first group of researchers used a sample made up of 184 individuals, whereas the second group evaluated 5,321.

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Table 5 - Some studies investigating the association between polymorphism A1166C of AII AT1 Receptor and hypertension

Authors	Population (N)	Genotypes n (%)						Association with hypertension
		Normotensives			Hypertensives			
		AA	AC	CC	AA	AC	CC	
Kobashi et al, 2006[32]	Japan (459)	281 (89.2)	29 (9.2)	5 (1.5)	122 (84.7)	21 (14.6)	1 (0.7)	Genotypes AC + CC were more commonloy found in hypertensive ♀ than in normotensives (15.3% x 10.8%) p<0.05
Sugimoto et al, 2004[61]	Japan (1,207)	538 (85.3)	89 (14.1)	4 (0.6)	476 (82.6)	100 (17.4)	0 (0)	Genotypes AC + CC were more commonly found between hypertensives (OR: 1.23; CI 95%: 0.92-1.66; p=0.17)
Ono et al, 2003[52]	Japan (3,918)	2,071 (85.3)	335 (13.8)	20 (0.8)	1,259 (84.3)	224 (15.0)	9 (0.6)	No association found
Agachan et al, 2003[29]	Turkey (185)	60 (74.1)	20 (24.7)	1 (1.2)	63 (60.6)	35 (33.7)	6 (5.8)	Genotypes AC + CC were more commonloy found in hypertensives than in normotensives (39.4 x 25.9) p<p=0.054
Castellano et al, 2003[46]	Italy (2,325)	267 (46.0)	258 (45.0)	53 (9.0)	890 (51.0)	726 (42.0)	131 (7.0)	Allele A was more frequently found among hypertensives (p= 0.037)
Bonnardeuax et al, 1994[47]	France (504)	153 (51.3)	121 (40.6)	24 (8.1)	84 (40.8)	95 (46.6)	27 (13.1)	Poor association with allele C (X^2= 6.8; p=<0.01)
Freitas et al, 2007[59]	Brazil (205)	58 (50.4)	45 (30.1)	12 (10.5)	60 (68.6)	29 (32.2)	1 (1.1)	Genotypes AC + CC were more commonly found among hypertensives (OR: 5.13; CI 95%: 1.05-34.1; p<0.05
Freitas et al, 2007[60]	Brazil (159)	55 (70.5)	20 (25.6)	3 (3.8)	46 (56.1)	27 (32.9)	8 (9.8)	No association found (p=0.157)

p - Comparison between cases and controls.

704, exon 2 of gene *AGT*, changes the sequence of protein aminoacids, leading to the replacement of methyonine by treonin at codon 235. TT homozygote individuals have plasma AGT levels 10 to 20% higher than MM homozygotes, thus showing a close association between that polymorphism and AGT plasma levels[18,26,27]. The positive correlation between polymorphism M235T and AGT plasma concentration has been observed in different populations[28-30]. Allele *AGT*235T* shows linkage disequilibrium with a variant in the *AGT*-gene promoting area – a replacement of adenine by guanine in nucleotide 6 (A-6G)[31]. It has been suggested that such mutation - A-6G – interferes in the interaction of transcriptor factors with *AGT* promoter, thus influencing the gene transcription baseline rate. An increase in *AGT* gene expression may increase the production of angiotensin II by RAS, thus resulting the expansion of blood volume, which in turn would increase blood pressure. Polymorphism M235T may be seen as a marker for the coexistence of polymorphism A-6G, which in turn is a marker for polymorphism M235T[32].

The association between gene *AGT* and hypertension was described by Jeunemaitre et al[19] in 1992. The gene seems to be involved in family hypertension as well as some forms of pregnancy-induced hypertension[22,23]. In a study conducted in an ethically diverse population, Pereira et al[34] observed that allele *AGT*235T*, in homozygosis, would pose increased risk of hypertension[34]. Table 3 shows some studies conducted in different populations. In Germany, Mondry et al have demonstrated the decreased risk of hypertension in women with TT genotype[18]. It should be pointed out, also, that in those studies the distribution of *AGT* genotype frequency varied significantly in the different populations under study.

ACE insertion/deletion polymorphism was characterized in 1990[35] and corresponds to the insertion (I) or deletion (D) of 287 base pairs in intron 16 of *ACE-gene*[13]. Studies have suggested that this polymorphism interferes in ACE serum concentration. DD Genotype individuals would have the highest ACE serum concentrations, where those with genotype II would have the lowest[18,25,36]. It is estimated that allele D would contribute with approximately half the variation of ACE plasma levels[37].

The association between ACE I/D polymorphism and hypertension[10,24] has been reported, with high morbidity rate for hypertensives and diabetics, although studies conducted with Caucasian populations have not detected a more impacting effect of that gene in hypertensives[18,38-42]. A study where Blood Pressure Ambulatory Monitoring (ABPM) was used, BP and pressure load were related to ACE

I/D polymorphism[43]. It has been speculated, as well, that this polymorphism modifies hypotensive response of ACE inhibitors, since the residual activity of the enzyme has been detected in hypertensives on that medication[44]. Espinel et al[35] have detected higher prevalence of DD genotype in malign hypertension patients[35]. O'Donnell et al[37] have demonstrated a statistically significant increase in diastolic blood pressure (DBP) adjusted by age in male patients with *ACE*D* in a dose-dependent fashion[37]. Other studies evaluating the association between ACE polymorphism I/D and hypertension can be found in Table 4.

Polymorphism A1166C of AII AT1 receptor corresponds to the replacement of adenine by cytosine at locus 1166 of non-translated region 3' of gene *AGTR1*. Variants in human *AGTR1* gene may affect blood pressure. Some authors have found the association between allele *AGTR1*1166C* and the predisposition for hypertension[45-49]. Castellano et al have reported that allele *AGTR1*1166A* was more commonly found among hypertensives[46]. Jones et al[50] have observed that polymorphism A1166C poses individuals an independent risk for HAS[50]. Other studies, however, have not demonstrated any association[51-54]. Table 5 shows that AA was the most commonly found genotype in the populations under study.

How to explain conflicting findings

The many times conflicting results from studies conducted may be partially explained by the relatively small size of samples, especially in the association studies[25], that is to say, the power is inadequate to detect modest contributions of individual genetic factors for complex traits such as hypertension[37]. The case-control design used in many association studies on candidate genes is efficient to evaluate the association hypothesis, but the methodology is subject to biased results if the screening of cases and controls is not randomized[37]. A recent meta-analysis involving studies with candidate genes showed that large samples are necessary to show the effects of genes involved in complex traits[55].

Another factor that may contribute with conflicting results may be related to the ethnic groups under study. The frequencies of different markers may vary according to population structure and ethnicity[6,32]. Therefore, due to genetic differences among individuals or to life style, one factor identified as hypertension risk factor in one given population may not be significant in another populational group[9,18,32,37].

The interaction gene-environment may also be responsible for some of the contradictions among studies. Environmental or behavioral factors, such as physical exercise and cigarette smoking, may interfere in the expression of a certain gene, and therefore affect final phenotype. Evidence has shown that nicotine increases the expression of a number of genes in the endothelium, ACE-gene included[25]. Montgomery et al[56] have demonstrated that DD homozygote individuals only reported left ventricular hypertrophy when compared to homozygotes II individuas if submitted to the interference of some hypertrophic factor, such as exercise[56]. Sayed-Tabatabaei et al[25] have demonstrated that through multiple regression models ACE I/D polymorphism and cigarette smoking were the only indicators of ACE plasma level activity, thus explaining, in combination, 28% of enzyme variation levels[25].

The interaction gene-gene may also be used to explain some of those diverging results. O'Donnell et al[37] have observed that growth hormone gene is associated to DBP. Based on such finding, they have considered that other genes – in addition to growth hormone gene – could be in linkage disequilibrium with ACE-gene[37].

Final considerations

Just as it is relevant to be aware of the epidemiology of classic risk factors for hypertension and evaluate the impact of each risk on morbimortality related to hypertension, the awareness of risk factors based on genetic polymorphism is equally crucial. Although the latter are not actually modifiable, health actions focusing populations that are genetically more susceptible may act as invaluable impact in reducing hypertension prevalence. Normotensive individuals with RAS polymorphism associated to hypertension might benefit from pharmacological or non-pharmacological treatment procedures with the purpose of preventing the development of hypertension. Early blocking of RAS through drugs presently available, such as ACE inhibiors and $AT_{1,}$ receptors blockers, may be an alternative choice. Additionally, the advances of pharmacogenomic, and therapeutic measures aiming at modifying genes expression, for instance, may be a real scenario in the future.

Considering that hypertension is a multifactorial, polygenic condition, it is no easy task to characterize hypertension susceptibility genes. Evidence available to this point in time shows that the most challenging difficulty may be to find out the extent of the role played by those genes in the hypertension condition when considering gene-gene and gene-environment interactions. However, the advance of genetically applied technology as well as the growing number of studies on molecular epidemiology are strong signs that the objective will be met.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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