Published in final edited form as:

J Hypertens. 2009 June ; 27(6): 1129–1133. doi:10.1097/HJH.0b013e32832bb832.

Opportunities and limitations of genetic analysis of hypertensive rat strains

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Genetic influences contribute upto 30–50% to blood pressure variability in human essential hypertension [1]. Intense efforts have been dedicated to unraveling the role of genes in this disease, following two parallel and interacting tracks. Studies on human populations have mostly focused on the candidate gene linkage approach, associating single nucleotide polymorphic (SNP) markers with the hypertensive phenotype. In spite of some promising observations [2], most attempts to replicate association studies have not been encouraging [3]. There are calls for application of stricter quality criteria for genetic studies, including better definition of phenotype characteristics, increased attention to environmental factors, sharing and combining data resources and more emphasis on whole genome-linkage scans in the context of collaborative multidisciplinary approaches [4–17]. Recently, however, there has been impressive progress in designing studies, understanding the mechanisms of disease and genotyping technology [17].

The second parallel track is the development and study of rodent experimental models of disease. Genetically hypertensive rat strains have been developed over the past 60 years. The models were obtained from initial random rat populations by brother–sister mating selecting for a high blood pressure phenotype. The better characterized genetically hypertensive strains are the spontaneously hypertensive rat (SHR) [18], stroke-prone SHR (SPSHR) [19], Dahl salt-sensitive [20], Milan hypertensive (MHS) [21], New Zealand genetically hypertensive [22], Sabra hypertensive (SBH) [23] and the Lyon hypertensive rats [24]. Comparisons are generally made with inbred normotensive strains derived from the original rat population and sharing most of the genetic background with the corresponding hypertensive strain. The most common normotensive strains are the Dahl salt-resistant, Wistar–Kyoto (WKY), Milan normotensive (MNS), genetically normotensive, Sabra normotensive (SBN) and Lyon normotensive and Lyon low blood pressure rats [18–24].

Physiological and pharmacological approaches to the study of these models have enhanced our understanding of many systems for blood pressure control. During the 1990s, technological advances allowed the use of quantitative trait locus (QTL) mapping to identify chromosomal regions with possible genetic variants affecting blood pressure. Many candidate genes for a role in human hypertension were identified as a consequence of findings in rodent animal models [25–30].

However, a number of problems surfaced when comparing the genetic rat strains. First, it appears that although there are common features [31], early studies discovered evidence for different pathogenic mechanisms between the genetic hypertensive strains [32]. Second, little is known about the developmental period, the specific organ and the sex influence of any particular alteration in gene expression linked to the development of hypertension. Third, treatment outcomes in human populations and animal models are not always comparable. For example, renin—angiotensin system (RAS) blockade with inhibitors of the angiotensin II-converting enzyme (ACEI) or with angiotensin II receptor blockers (ARB) has a significant but relatively minor influence in the treatment of human essential hypertension [33–35]. Frequently, ACEIs or ARBs are not sufficient to control the disease when used alone. On the other hand, RAS blockade completely normalizes the blood pressure in SHR or Lyon hypertensive rats, animal models of normal or low plasma renin activity (PRA) [36,37]. This paradox may be best explained by the influence of local RAS systems in genetically hypertensive rats, considered far more important than the classical circulating RAS [38–40]. Fourth, gene studies may not reflect protein levels and turnover, or posttranslational protein modifications. Fifth, and most importantly, the consensus has emerged that genetic rat models of hypertension lack adequate controls [19]. This is especially true for SHR, but the problem extends to all available parent genetic rat hypertensive models. In SHR, a phenotypic difference between this strain and their normotensive controls WKY rats may be due to simple strain differences unrelated to increased blood pressure, or even to the secondary effects of blood pressure elevation itself [19].

Nevertheless, rodent models of genetic hypertension still provide some definite advantages. First, the models continue to provide new insights into important mechanisms for blood pressure control in rodents and humans [7]. Second, the models can be well characterized and the influence of specific treatments carefully determined. Third, many candidate genes first identified in animal models have been extensively studied in humans generating testable hypotheses of interest. Reciprocally, candidate genes identified in humans by genome-wide association studies may be tested in rat models [7]. In addition, there is a reasonable significant blood pressure QLT concordance between rodents and humans, as recognized by comparative genomic analysis of syntenic regions from rat, mouse and human [41].

The Lyon genetically hypertensive rat has been the subject of many significant studies in the past 30 years. In a study published in this issue, Gilibert *et al.* [42] followed up on previous studies from the same group based on intercrosses between Lyon hypertensive and Lyon normotensive strains. Their earlier studies revealed linkage areas for blood pressure regulation, body weight and lipid metabolism in chromosomes 1, 2, 3, 5, 7, 10, 13 and 17 [43]. This work is a good complement to the analysis of other rodent models of hypertension, notably the SHR. Lyon hypertensive and SHRs are associated with normal or low PRA [24] and, paradoxically, they are highly sensitive to RAS inhibition [37]. Studies on Lyon hypertensive rats revealed additional influences regulating the blood pressure variability, such as exaggerated brain sympathetic activity [44], increased vascular reactivity to angiotensin II [45], elevated mineralocorticoid [46] and thromboxane production [47], reduced sodium excretion ability and salt sensitivity [48] and association with metabolic abnormalities [49].

Initial genetic studies identified QTLs in the rat genome with possible roles in blood pressure regulation. To confine the chromosomal regions carrying the QTL in question and allow physical mapping, researchers generated congenic strains by mating two inbred strains after selecting a particular phenotype and a defined chromosomal region introgressed from the donor strain onto the recipient strain. Generations of backcrossing ensured that the new strains were essentially isogenic with the original inbred strain except for the selected differential chromosomal segment. Thus, results obtained with the use of congenic strains validate findings obtained by QLT identification. Congenic strains have another important advantage, as they

overcome the lack of appropriate normotensive controls [19]. The possibility of combining consomic rat strains with microarray analysis permits further focus on the study of genes of interest [50].

Generation of congenic strains has been successfully utilized by several groups by introgressing target chromosomal regions from the hypertension-resistant Brown Norway strain onto the SHR genome [51] or from regions of several genetically hypertensive rat chromosomes onto the Brown Norway background [52]. The Lyon investigators have recently constructed reciprocal consomic strains, a variation of congenic strains in which a whole chromosome rather than a chromosomal region is back-crossed [53]. In a recent study, the authors reciprocally backcrossed chromosome 17 in Lyon hypertensive and Brown Norway rats. Their rationale for choosing the Brown Norway strain, which shares less than 5% genome identity with the Lyon hypertensive strain, was that this approach would greatly enhance the possibility of identifying disease-susceptible alleles. Many such alleles may be undetectable when comparing the Lyon hypertensive and Lyon normotensive strains, sharing over 90% gene identity with each other. In the first of their studies, Gilibert *et al.* [53] used the Brown Norway / Lyon hypertensive reciprocal consomic approach. They found that whereas introgression of chromosome 17 from Brown Norway rats onto Lyon hypertensive rats protected them from hypertension and metabolic abnormalities, introgression of chromosome 17 from Lyon hypertensive rats onto Brown Norway rats was overcome by homeostatic mechanisms in the Brown Norway genome [53].

In their paper published in this issue, Gilibert *et al.* [42] present the results of a novel consomic study, reciprocally introgressing chromosome 13 in Lyon hypertensive and Brown Norway strains [42]. This is a follow-up of earlier work in which they use intercrosses from Lyon hypertensive and Lyon normotensive strains to demonstrate linkage areas for blood pressure control in chromosome 13, possibly involving the renin gene [43]. The authors report that the Brown Norway chromosome 13 reduces blood pressure, cholesterol and triglycerides and raises body weight when introgressed in the Lyon hypertensive background. Conversely, the Lyon hypertensive chromosome 13 does not modify blood pressure, cholesterol and triglycerides when introgressed in the Brown Norway background. In addition, the results clearly show that the influence of chromosome 13 on blood pressure is quite modest overall, although statistically significant. Such relatively minor influence is expected, as it is well known that many genes located in different chromosomes may be linked to blood pressure variability.

The authors report that substitution of chromosome 13, which contains the renin gene, does not affect PRA in spite of the clear reduction in systemic blood pressure. This is of interest because initial linkage analysis studies on this strain indicated the presence of QTLs influencing blood pressure in or near the renin gene [43]. The present findings may be interpreted as absence of a RAS contribution to the blood pressure variability associated with chromosome 13. It is of note that in a previous report, substitution of chromosome 13 from Brown Norway rats into the Dahl salt-sensitive genetic background apparently switched production of vasoconstrictor to vasodilator factors during hypoxia, and the findings were interpreted as a consequence of normalization of the RAS [54]. Unfortunately, the regulation of local RAS systems in the Lyon hypertensive rat has never been studied in detail.

Important conclusions may be drawn from the present study. The research indicates a significant contribution of chromosome 13 in blood pressure and metabolic variability. It is also of note that the genetic background of the Brown Norway rat is very different from that of the Lyon normotensive rats, the control strain used in previous studies. For example, there is no evidence of QTLs for cholesterol or triglycerides between Lyon hypertensive and Lyon normotensive rats. As the Brown Norway rat has not been used for linkage studies, it is not

possible to propose specific genes involved in the resistance of the Brown Norway strain to blood pressure or metabolic alterations. Furthermore, the authors did not study sex differences in the present consomic study. This is unfortunate because a recent publication revealed important sex differences in a consomic study including the introgression of chromosome 13 from the Brown Norway rat onto the Dahl salt-sensitive strain [55]. Gilibert *et al.* [42] acknowledge that their work is the initial step allowing further genetic analysis of these factors. They proposed follow-up studies with overlapping congenic strains derived from the consomics used here. These experiments will permit them to narrow down the introgressed region and to perform physical mapping, which may allow them to identify specific genes. It is also clear that other genes located in chromosomes besides chromosome 13 probably interact epistatically to play important roles, as Gilibert *et al.* [42] demonstrate that introgression of chromosome 13 from the Lyon hypertensive rat in the Brown Norway genome fails to increase blood pressure or affect lipid metabolism.

The study by Gilibert *et al.* [42] reminds us of the need to emphasize the role of the genetic background in the phenotype determination. To this effect, studies of reciprocal consomic or congenic strains are of paramount importance. In the present report, Gilibert *et al.* [42] clearly show that the Brown Norway genetic background confers resistance to increases in blood pressure, cholesterol and triglyceride levels and increases body weight, supporting previous observations [54] and their own findings resulting from the reciprocal introgression of chromosome 17 [53]. They correctly point out the importance of using the Brown Norway rat strain, as its genome has been sequenced and characterized [56–57]. Gilibert *et al.* [42] also recognize that the present and a previous study both demonstrate the presence of powerful homeostatic mechanisms preventing the development of hypertension in the Brown Norway strain [52]. The presence of protective loci in chromosome 13 of the Brown Norway rat against the development of hypertension has been known for several years [7,58,59]. In this chromosome, four distinct regions have been identified and proposed to interact epistatically favoring blood pressure homeostasis [59].

In addition to considering which genes may be directly linked to increases in blood pressure, we may wish to focus on genes that favor resistance to the disease indirectly affecting blood pressure by balancing the expression or activity of prohypertension factors. This concept is not new and has been clearly proposed and studied earlier in rats [7,27,58,59] and mice [60,61]. Moreover, it has been known for some time that normotensive alleles introgressed onto the genome of genetically hypertensive rats have greater effects on blood pressure than similarly introgressed hypertensive alleles [27]. This is particularly important because disease-causing alleles may be the result of alterations in the function of powerful blood pressure homeostatic genes. Similar conclusions may be drawn with respect to triglyceride and cholesterol metabolism because of the obvious strong homeostatic pressure of the Brown Norway genomic background demonstrated in this study. Consomic strain studies revealed that several chromosomes, including chromosome 13 introgressed onto the hypertensive Dahl salt-sensitive strain decreased blood pressure, revealing the presence of genes with powerful homeostatic effects and supporting the present report [55].

A specific example of possible regulatory mechanisms for prohypertensive factors may well illustrate our proposal. Increased local expression of angiotensin II AT₁ receptors is linked to hypertension in experimental rodent models [38,39], explaining the paradoxical effect of RAS blockade in SHR, a model of low PRA. The cross-talk hypothesis postulates a balancing interaction between the two angiotensin II types, the AT₁ and AT₂ receptors [62]. Gene disruption of AT₂ receptors increases blood pressure in mice, increasing the response to angiotensin II [63–65], with a parallel enhanced AT₁ receptor expression and function in several organs [65–68]. Thus, it is logical to propose a regulatory role for AT₂ receptors, not directly as a blood pressure-lowering factor, but indirectly by controlling the activity of a

known prohypertensive factor, the vasoconstrictive, sodium-retentive AT₁ receptor overstimulation.

Further comparative genomics, linkage of cardiovascular phenotypes to the genome sequence, and access to continuously expanded and improved public databases as proposed [50,55,56, 69] may lead to significant advances of major clinical impact. For example, the Institute for Genomic Research (TIGR) rodent expression resource (TRES) and the PhysGen resource have been successfully used for hypothesis generation in cardiovascular research [70]. These remarkable advances have the promise of accelerating our knowledge of this complex and multifactorial disease. One hopes that this will soon lead to breakthroughs in our understanding and treatment of hypertension.

Acknowledgement

The preparation of this article was supported by the Division of Intramural Research Programs, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, United States.

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