Genetics of Human Hypertension

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Background: Hypertension is a multifactorial disease involving interactions among genetic, environmental, demographic, vascular and neuroendocrine factors. Essential hypertension is the most frequent diagnosis in this syndrome, indicating that a monocausal etiology has not been identified. However, a number of risk factors underlying essential hypertension have also been identified including age, sex, genetics, demographic factors, and others. Remarkable progress in molecular biological research has been achieved in clarifying the molecular basis of Mendelian hypertensive disorders. Causative genes and chromosomal fragments harboring disease susceptibility genes have been identified, e.g., for glucocorticoid-remediable aldosteronism, Liddle's syndrome, mineralocorticoid excess.

Molucular Genetic Studies: Molecular genetic studies have now identified mutations in eight genes that cause Mendelian forms of hypertension and nine genes that cause Mendelian forms of hypotension in humans. No single genetic variant has emerged from linkage or association analyses as consistently related to blood pressure level in every sample and in all populations. However, a number of polymorphisms in candidate genes have been associated with differences in blood pressure. Most prominent have been the polymorphisms in the renin-angiotensin-aldosterone system.

Conclusion: Essential hypertension is likely to be a polygenic disorder that results from the inheritance of a number of susceptibility genes and involves multiple environmental determinants. These determinants complicate the study of blood pressure variations in the general population. The complex nature of the hypertension phenotype makes large-scale studies indispensable, when screening of familial and genetic factors is intended.

Key Words: Genetics · Polymorphism · Blood pressure · Hypertension

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Genetik der Hypertonie des Menschen

Hintergrund: Die Prävalenz der Hypertonie in epidemiologischen Untersuchungen liegt zwischen 25% und 35%. Die häufigste Diagnose stellt hierbei die essentielle, ätiologisch nicht geklärte Hypertonie dar. Sie ist eine multifaktorielle Erkrankung, deren Ausprägung von diversen (Risiko-)Faktoren beeinflusst wird. Hierzu gehören auch das Alter, das Geschlecht und der familiäre Hintergrund.

Aus epidemiologischen Studien lässt sich ableiten, dass bei Fällen von familiärer Hypertonie eine Mendel'sche Vererbung in ca. 20% der Familien nachgewiesen werden kann. Fortschritte konnten bisher vor allem in der Klärung der molekularen Basis der monogen vererbten Hypertonie verzeichnet werden, denn deren Gene lassen sich leichter finden als Gene, die an multifaktoriellen Erkrankungen beteiligt sind.

Molekulargenetische Strategien: Zur molekulargenetischen Analyse der Hypertonie werden gegenwärtig vier Strategien angewandt:

1. die Untersuchung der Hypertonieformen, deren Vererbung den Mendel'schen Gesetzmäßigkeiten folgt;
2. die Untersuchung von Kandidatengenen, deren biochemische bzw. physiologische Funktion mit der Erkrankung verbunden ist;
3. die Untersuchung von chromosomalen Regionen oder Kandidatengenen, die sich in hypertensiven Tiermodell verändert zeigen;
4. systematische genomweite Linkage-Analysen.

Ergebnisse: Im letzten Jahrzehnt konnten so Gene identifiziert werden, die für die monogene Hypertonie sowie für die monogene Hypotonie verantwortlich sind. In Tabelle 1 finden sich für die monogene Hypertonie u.a. der durch Glukokortikoidgabe behandelbare Aldosteronismus (Duplikation der Aldosteronsynthase und 11β-Hydroxylase), das Mineralokortikoidexzess-Syndrom (Mutationen in der 11β-Hydroxylase), die durch Schwangerschaft exazerbierte Hypertonie

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(Mutationen an der Liganden bindenden Domäne des Mineralokortikoidrezeptors), der Pseudohypoaldosteronismus Typ 2 (Mutationen in mindestens einem von drei Genen in den Chromosomen 1q31–42, 12p13, 17p11–q21), die Hypertonie mit Brachydaktylie (mit Mutationen in 12p11.2–12.2), die Missense-Mutationen im Peroxisom-Proliferator-aktivierten Rezeptor γ sowie das Liddle-Syndrom mit Mutationen im epithelialen Natriumkanal.

Bei der Suche mit Kandidatengenen wurden überwiegend Gene untersucht und in einzelnen, aber nicht in allen Studien identifiziert, die das Renin-Angiotensin-System (Angiotensinogen, Renin, Angiotensinkonversionsenzym [ACE], Angiotensin-[AT-]II-Typ-1- und -2-Rezeptoren), das sympathische Nervensystem (β_1- und β_2-Rezeptor), Ionentransporter (G-Protein-b3-Untereinheit) oder nachgeordnete enzymatische Kaskaden bzw. vasoaktive Peptide (eNOS, ANP, ADM), Lipoproteine und insulinresistenzrelevante Gene betreffen (Tabelle 2). Die Ergebnisse des genomweiten Kandidatengenscreenings weisen auf Veränderungen in Chromosom 3 für den AT-II-Typ-1-Rezeptor, in Chromosom 5 für den β_2-Adrenozeptor, in Chromosom 8 für die Lipoproteinlipase und in Chromosom 17 für das ACE hin (Tabelle 3).

Polymorphismen im Angiotensinogen- und im ACE-Gen wurden besonders in kleineren Studien mehrfach beschrieben, in größeren Studien aber nicht regelhaft bestätigt.

Das Wissen um Gene, die an der Pathogenese der Hypertonie in Tiermodellen beteiligt sind, ist auch deshalb besonders hilfreich in der Ursachenforschung der Hypertonie des Menschen, weil damit verschiedene Probleme umgangen werden können: So ist die genetische Homogenität bei Inzuchttieren hoch, und die Umgebungseinflüsse sind kontrollierbar – beides Faktoren, die bei der humangenetischen Forschung selbstredend erschwert sind.

Schlussfolgerung: Mit der molekularen Genetik konnten so Fortschritte in der Aufklärung der Genetik der Hypertonie gemacht werden. Untersuchungen zur Mendel'schen Vererbung der Hypertonie führten zur Identifikation verschiedener krankheitsverursachender Gene. Ein genomweites Screening konnte eine Anzahl von potentiellen chromosomalen Loci zeigen. Ein einziges (mutiertes) Hypertoniegen selbst gibt es nicht! Vielmehr ist es das Zusammenspiel polygener Veranlagungen mit Umweltfaktoren, die den Phänotyp der essentiellen Hypertonie ausprägen. Um diese Interaktionen weiter zu analysieren, sind weitere Populationsstudien unumgänglich.

Schlüsselwörter Genetik · Polymorphismus · Blutdruck · Hypertonie

Introduction

Cardiovascular diseases are the major cause of death in industrialized societies, and hypertension is the major treatable risk factor of these cardiovascular disorders [2]. Elevated arterial blood pressure, or hypertension, affects about 25–35% of the adult population in industrialized societies [44]. Since the etiology is unknown in most cases, these patients are classified as having "essential hypertension" [3]. Essential hypertension is a multifactorial disease, and a number of risk factors underlying hypertension including age, sex, family history of hypertension, demographic factors, overweight, diabetes mellitus, excess consumption of sodium, physical inactivity, smoking, and excess coffee and alcohol consumption have been identified [7]. These risk factors can be divided into two groups: factors that are not modifiable, such as age, sex, ethnicity, and genetic factors; and factors that can be modified and may decrease or even prevent hypertension. Many clinical trials have shown that reductions in blood pressure reduce the incidence of stroke and myocardial infarction [1].

Population-based studies have demonstrated, that hypertension occurs in families, and Mendelian inheritance can be shown in about 20% of families and varies around 60% in twin studies [44]. Progresses in molecular biologic research led to clearing up of some pathophysiologic pathways. The recently completed sequencing of the human genome has focused attention on the potential for genetic information to benefit the diagnosis, evaluation and treatment of hypertension [48].

Remarkable progress has been achieved in clarifying the molecular basis of Mendelian hypertensive disorders [25]. Causative genes and chromosomal fragments harboring disease susceptibility genes have been identified for glucocorticoid-remediable aldosteronism [26], Liddle's syndrome [15, 40], mineralocorticoid excess [30] among others. Even when the genes themselves have not yet been identified, the genetic loci have been mapped, as in Gordon's syndrome [29], and in a pedigree affected with hypertension and brachydactyly [41].

Considerable efforts have also been made to identify the genes responsible for the development of essential hypertension. The task is extremely difficult for several reasons. The heritability of hypertension is low (only about 30% of blood pressure variance is attributable to genetic factors). On the other hand, although extensive searches have been performed for essential hypertension, most of the results have been inconclusive. Several explanations may be proposed for the difficulties in detecting susceptibility genes for essential hypertension [8]. Nothing is known about the number of genes in-

volved, their mode of transmission, their quantitative effect on blood pressure, their interaction with other genes, or their modulation by environmental factors.

Essential hypertension is likely to be a polygenic disorder that results from the inheritance of a number of susceptibility genes and involves multiple environmental determinants. These determinants complicate the study of blood pressure variations in the general population. The common strategy of linkage mapping in affected families to identify chromosomal loci, from which candidate genes and genotypes can be tested, has not been successful for heritable diseases that involve multiple genes and gene-environment interactions [10]. Although many research efforts have been done, the specific causes of essential hypertension remain incompletely understood. So it may be, that blood pressure is dependent on a mosaic of many loci, each with a small influence or with a contribution differing according to sex [16], race, age [28], or lifestyle [44] (Figure 1).

Strategies to Investigate the Genetic Basis of Hypertension

Two principal strategies – association study and linkage analysis – have been used to investigate the genetic basis of essential hypertension. These two strategies are not mutually exclusive, but can be merged into a single analytical method, such as the transmission/disequilibrium test (TDT) [43]. Each has advantages and disadvantages depending on the situations tested. An association, i.e., case-control study (which tests for different allele or genotype frequencies between case and control populations) allows the use of unrelated individuals, it is easier to collect a large set of samples using this paradigm than using a pedigree-based linkage analysis. In general, a case-control study has greater statistical power than a linkage analysis, but it is also more liable to show false positive results.

Human hypertension loci have been mapped by several linkage analysis studies [22, 24, 33–35, 39]. In these cases, linkage analysis uses collections of related individuals with members who manifest hypertension, to examine the co-inheritance with hypertension of widely distributed markers in order to infer the genomic position of alleles contributing to hypertension. By contrast, the genome-wide association studies which examine populations, not related individuals, compare the genotypes of a large number of polymorphic markers in subjects who manifest hypertension compared with controls.

The usual strategy of linkage mapping in affected families to identify chromosomal loci from which candidate genes and genotypes are selected has not been similarly successful for hypertension, because high blood pressure involves multiple genes and gene-environment interactions.

Development of extensive collections of single nucleotide polymorphisms (SNPs) raises the possibility, that these SNPs can be used as markers in genome-wide association mapping studies, to identify hypertension susceptibility loci. SNPs are stable, they are di-allelic, the two alleles representing the "wild-type" and the variant form [10].

Association studies are adequate for testing candidate genes, or narrowing down to a particular gene once α region of linkage has been detected.

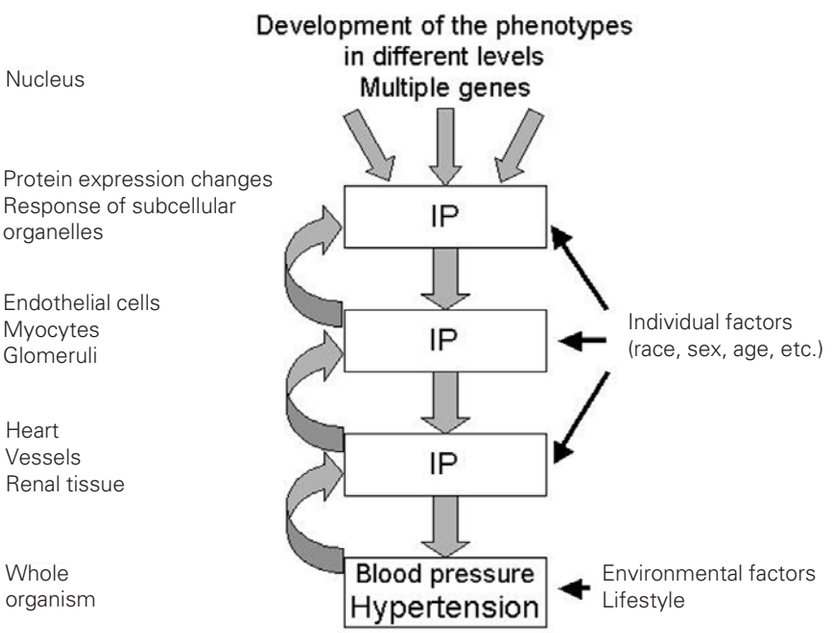

Figure 1. Schematic representation of blood pressure as a complex multigenic disease, affected by host and environmental feedback control (adapted from [44]). IP: intermediate phenotypes. Curved arrows represent feedback loops.

Abbildung 1. Schematische Darstellung des Blutdrucks als eine komplexe multigene Erkrankung, die von persönlichen Faktoren wie Rasse, Geschlecht usw. sowie von Umweltbedingungen und Lebensstil beeinflusst wird (verändert nach [44]). IP: intermediäre Phänotypen; gebogene Pfeile stellen Rückkopplungen dar.

Four main strategies have been used to examine the linkage of genes or chromosome regions to hypertension, depending on the method used to select the loci to be tested, and the type of families to be studied [20]:

1. studies of Mendelian forms of hypertension;
2. testing of candidate genes chosen on the basis of their known biochemical or physiologic function;
3. investigation of chromosome regions homologous to those that segregate with blood pressure in animal models, or regions harboring particular genes that show linkage in animal models;
4. systematic genome-wide searches for linkage (or linkage disequilibrium).

Mendelian Forms of Hypertension

Genes, that are involved in monogenic hypertension, are much easier to map than those in a multifactorial form of the disease. The investigation of heritable susceptibility to disease is an effort to associate the disease phenotype with the underlying genotype. Such genotype:phenotype associations have been demonstrated for a large number of monogenetic disorders. The investigation of rare Mendelian forms of blood pressure variation, in which mutations in single gene mutations have been detected, has been very informative. These mutations, which impair renal salt handling, provide a molecular basis for understanding the pathogenesis of hypertension. Investigation of families with severe hypertension or hypotension has identified mutations in genes that regulate these pathways.

Several rare syndromes are associated with hypertension. They are influenced by one or more mutations, whereby most of the causative genes identified for Mendelian forms of hypertension have turned out to be involved in the renin-angiotensin system or components downstream (Figure 2). These findings support the possible etiologic importance of the renin-angiotensin system in hypertension.

The rare Mendelian forms, where mutations in single genes cause variations in blood pressure, provide a molecular basis for understanding the pathogenesis of hypertension. Now mutations in eight genes that cause Mendelian forms of hypertension and nine genes that cause Mendelian forms of hypotension in humans have been identified [27]. These genes typically impart very large effects on blood pressure (Table 1). Given the diversity of physiologic systems that affect blood pressure, it is surprising that the mutated gene products in all cases act in the same physiologic pathway in the kidney, altering net renal salt reabsorption [27]. Mutations that increase sodium reabsorption and cause hypertension include mutations in the mineralocorticoid receptor (hypertension exacerbated by pregnancy) [13], aldosterone synthase (glucocorticoid-remediable aldosteronism), other enzymes synthesizing steroids that activate the mineralocorticoid receptor (11β-hydroxysteroid dehydrogenase, 17α-hydroxylase and 11β-hydroxylase), the β- and γ-subunits of the renal epithelial sodium channel (Liddle's syndrome) and the serine-threonine kinases (WNK1 and WNK4 in pseudohypoaldosteronism type

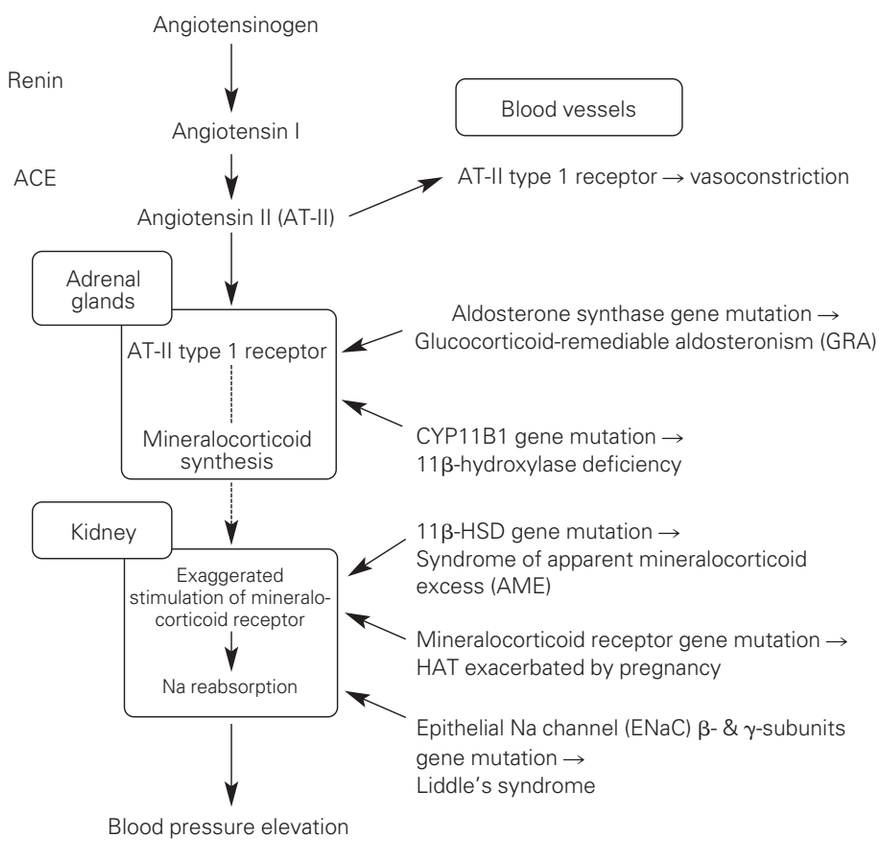

Figure 2. Schematic representation of genes identified for monogenic hypertension (from [20]).

Abbildung 2. Schematische Darstellung bereits identifizierter Gene, die mit der monogenen Hypertonie in Verbindung gebracht werden (aus [20]).

2). Loss-of-function mutations were found to impair renal sodium reabsorption thus causing hypotension. They include genes encoding the mineralocorticoid receptor (autosomal dominant pseudohypoaldosteronism type 1), aldosterone synthase, 21-hydroxylase, the β- and γ-subunits of the epithelial sodium channel (EnaC; recessive pseudohypoaldosteronism type 1), the ATP-sensitive potassium channel ROMK (Bartter's syndrome type 2), and chloride channel CLC-NKB (Bartter's syndrome type 3). Different mutations, often in the same gene, may cause hyper- or hypotension [48]. However, monogenic disorders of blood pressure regulation are rare and do not explain blood pressure variability in the population at large [23]. Nevertheless, these rare single gene mutations are still of importance because they provide insight into biochemical, physiologic and anatomic pathways through which common genetic variations may influence blood pressure.

However, no single genetic variant has emerged from linkage or association analyses as consistently related to an elevated blood pressure level in every sample and in all populations.

Candidate Genes Chosen on the Basis of their Known Biochemical or Physiologic Function

Polymorphisms in candidate genes encoding proteins with known biochemical or physiologic function for blood pressure regulation have been identified in the renin-angiotensin-aldosterone system for angiotensinogen (AGT) [17], angiotensin-converting enzyme (ACE) [32], angiotensin (AT) II receptor (type 1) [6], and aldosterone synthase [37]. The end product of this cascade, AT II, may enhance renal tubular sodium reabsorption by stimulating the aldosterone synthesis and release.

The AGT Gene

The AGT gene has been an attractive candidate gene for hypertension [11]. A linkage of the AGT gene to hypertension was reported quite early by Jeunemaitre et al. in 1992 [18]. In addition to the known physiologic importance of AGT, it seemed reasonable that polymorphisms in this gene might not only be associated with plasma concentrations of AGT, but also increase the risk of developing hypertension. While a number of investigators attempted to reproduce the original findings of linkage and association at the AGT locus, the results have not been always concordant among the studies and have therefore provoked heated arguments [20].

The ACE Gene

The ACE gene has been sequenced in eleven individuals, so that its variants are known. The insertion/deletion polymorphism is an Alu repeat in intron 16. Rieder et

Table 1. Monogenetic diseases that result in hyper- or hypotension (from [31, 44]). ENaC: epithelial sodium channel.
Tabelle 1. Monogenetische Erkrankungen, die zu Hyper- oder Hypotonie führen (aus [31, 44]). ENaC: epithelialer Natriumkanal.

Disease	Mutation	Effect on blood pressure
Glucocorticoid-remediable aldosteronism	Duplication of genes encoding aldosterone synthase and 11β-hydroxylase	Increased
Aldosterone synthase deficiency	Mutations in the gene encoding aldosterone synthase	Decreased
21-Hydrolase deficiency	Mutations in the gene encoding 21-hydroxylase	Decreased
Apparent mineralocorticoid excess	Mutations in the gene encoding 11β-hydroxylase	Increased
Hypertension exacerbated by pregnancy	Mutations in the ligand-binding domain of the mineralocorticoid receptor	Increased
Pseudohypoaldosteronism type 1 (autosomal dominant)	Loss-of-function mutations in mineralocorticoid receptor	Decreased
Pseudohypoaldosteronism type 2	Mutations in at least one of three genes mapped to 1q31–42, 12p13 and 17p11–q21	Increased
Hypertension with brachydactyly	Mutations mapped to 12p11.2–12.2	Increased
Peroxisome proliferator-activated receptor γ	Missense mutation	Increased
Liddle's syndrome	Mutations in the ENaC*β- or γ-subunit	Increased
Pseudohypoaldosteronism type 1 (autosomal recessive)	Loss-of-function mutations in ENaC subunits	Decreased
Gitelman's syndrome	Loss-of-function mutations in the NaCl cotransporter of the distal convoluted tubule	Normal or decreased
Bartter's syndrome	Loss-of-function mutations in genes required for salt reabsorption in the thick ascending loop of Henle	Normal or decreased

al. [36] showed, that 78 varying sites were present in the ACE gene, that resolved into 13 distinct haplotypes.

The ACE locus has been shown to cosegregate with blood pressure in several rat crosses [14], but it remains unclear whether ACE itself or a nearby locus (or loci) actually confers susceptibility to rat hypertension. In humans, convincing evidence of linkage and association of the ACE locus with serum ACE levels have been demonstrated [47], whereas conflicting results have been published regarding the association of ACE variants and hypertension [45].

Studies in whites [12, 32] and in the Japanese [16] independently reported some evidence of linkage between the ACE locus and hypertension in men but not in women. However, it was also shown that the relation between the ACE locus and hypertension was not consistently seen in men but changeable dependent on the participants' age and body weight.

G-Proteins

G-proteins mediate the intracellular effects of many vasoactive and proliferative stimuli. Recently, G-protein signaling was found to be enhanced in cultured cells of various hypertensive subjects. A polymorphism at position 825 (C3T) of the G-protein b3 subunit gene (GNB3) was strictly related to this phenotype [38, 42]. Furthermore, the 825T allele was also significantly associated with lower renin and prorenin levels, whereas the aldosterone-to-renin ratio was elevated in these subjects. This polymorphism does not result in an amino acid substitution, but the disease-type (825T) allele is associated with the occurrence of alternative splicing, which cause the loss of 41 amino acids within highly conserved repeating units of the gene. Significant associations between the 825T allele and diastolic blood pressure, plasma renin, and prorenin levels (inverse), and the aldosterone-to-renin ratio persisted after adjustment for age, sex, body mass index, and systolic blood pressure.

These observations suggest a molecular mechanism that unifies a higher diastolic blood pressure, a lower renin level, and an elevated aldosterone-to-renin ratio, i.e., a combination of features frequently found in patients with arterial hypertension. Although a number of studies have attempted to replicate this association in a variety of populations, conflicting results have been reported [4, 21].

Further candidate genes chosen on the basis of known biochemical or physiologic function are listed in Table 2.

Table 2. Candidate genes chosen on the basis of known biochemical or physiologic function (adapted from [20]).

Tabelle 2. Kandidatengene, ausgewählt aufgrund bekannter biochemischer oder physiologischer Funktion (nach [20]).

Function	Gene
Renin-angiotensin system	Angiotensinogen (AGT) Renin (Ren) Angiotensin converting enzyme (ACE) Angiotensin II type 1 receptor Angiotensin II type 2 receptor
Sympathetic nervous system	β_1-adrenergic receptors β_2-adrenergic receptors
Ion transport	G-protein b3 subunit (GNB3)
Others	
• Vasoactive peptides	(e.g., eNOS, ANP, ADM)
• Components involved in insulin resistance or metabolic function	(e.g., lipoproteins)

Homologous Chromosome Regions, or Regions Harboring Particular Genes that Show Hypertension Linkage in Animal Models

Genes predisposing to hypertension in animal models may also be involved in the etiology of human hypertension. Genes implicated in animal models can be considered candidate regions or genes to be also explored in the human disease [20]. Studies of animal models of hypertension, especially inbred hypertensive rats, circumvent many of the problems encountered in human studies. In animals the blood pressure measurement can be done repeatedly under more controlled conditions and may be more reproducible than in humans. Because of the inbred conditions in animal models, the genetic homogeneity is high, and these animals can be raised in the same environmental conditions.

α-Adducin

An example for this strategy is the finding of the candidate gene α-adducin. Amino acid variations of α-adducin have been shown in the Milan hypertensive strain of inbred rats compared to the Milan normotensive strain [5]. In humans a segregation of microsatellite markers near the α-adducin gene with the association to hypertension and salt sensitivity has been detected by Cusi et al. [9].

Apart from this gene, causative genes remain to be identified for blood pressure in rats. Stoll et al. [46] proposed a "comparative genomics strategy" and predicted 26 chromosomal regions of the human genome that should be prioritized in searches for SNPs and linkage disequilibrium testing.

Table 3. Candidate genes in chromosome regions implied by genome-wide screens.

Tabelle 3. Kandidatengene in Chromosomregionen, die in genomweiten Untersuchungen gefunden wurden.

Chromosome	Gene
Chromosome 3	Angiotensin II type 1 receptor
Chromosome 5	β_2-adrenergic receptor
Chromosome 8	Lipoprotein lipase
Chromosome 17	Angiotensin-converting enzyme (ACE)

Systematic Genome-Wide Searches for Linkage

More than ten chromosomal regions, that are linked with hypertension, have been detected in several genome screens. In these regions, several candidate genes are located (Table 3), e.g., the genes coding for AT II type 1 receptor on chromosome 3 [34], β_2-adrenergic receptor on chromosome 5 [22], and lipoprotein lipase on chromosome 8 [49]. Julier et al. [19] investigated the homologous region on human chromosome 17 in familial essential hypertension using a total of 518 sibling pairs. The region of significant linkage included the ACE locus, but the maximum evidence of linkage was observed at markers located approximately 18 cM proximal to this locus.

Polymorphisms in a determined gene could be associated with the phenotype of hypertension in one ethnic population but not necessarily in another. Therefore, different genes may predispose to the phenotype of hypertension in different populations [20].

Conclusion

The progress in molecular genetics has been of considerable help in understanding the genetics of hypertension. Studies of Mendelian forms of hypertension have led to the identification, or mapping, of several genes. The complex nature of the hypertension phenotype still requires large-scale studies to definitively establish the role of the specific chromosomal regions or genes discussed here, as well as to explore the effect of confounding variables, whether they are individual (sex, ethnic origin, etc.) or environmental.

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