Present status of genetic mechanisms in hypertension

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Mendelian hypertension is the bright spot in the area of molecular genetics of human hypertension. The attitude here is that by elucidating rare mendelian diseases, mechanisms of disease applicable to primary hypertension are understood [1]. This promise has been kept largely through the efforts and successes of Lifton et al [2]. Through their work, clinicians have been introduced to numerous disease mechanisms.

Glucocorticoid-remediable aldosteronism

Patients with glucocorticoid-remediable aldosteronism have autosomal-dominant hypertension and are usually suspected of having primary aldosteronism. They have a volume expansion, a salt-sensitive form of hypertension, tend to metabolic alkalosis with hypokalemia, and respond to both thiazide diuretics and spironolactone. Their renin values are low, whereas the aldosterone values are elevated. The patients also have 18-hydroxycortisol and 18-oxocortisol, steroids not normally found in urine. Recognizing these abnormal products (an intermediate phenotype) led to solving the mystery. Replacement amounts of prednisone ameliorate the hypertension, cause the abnormal steroids to disappear, and give the syndrome its name. The abnormal cortisol derivatives and the favorable effects of glucocorticoid treatment suggested that inner cortical zones, which

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express the gene for 17β-hydroxylase (CYP17) and are adrenocorticotropic hormone–responsive, were the source of the excess mineralocorticoids. Two distinct gene products, 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), perform the terminal steps in glucocorticoid and mineralocorticoid biosynthesis, respectively. A linkage analysis in a large pedigree localized the responsible gene to chromosome 8q, the site where the genes for 11β-hydroxylase and aldosterone synthase also reside [3]. In affected individuals, a chimeric gene consisting of the promotor-regulatory region of 11β-hydroxylase and the structural portion of aldosterone synthase is located between CYP11B2 and CYP11B1. The chimeric gene results from a miotic mismatch and unequal crossing over (Fig. 1). The protein product performs all reactions required for aldosterone production; however, the protein is adrenocorticotropic hormone rather than angiotensin (Ang) II–dependent. Ectopic expression of this protein in the inner cortical zones permits the formation of 18-hydroxy cortisol and 18-oxocortisol. Finally, suppressing steroidogenesis in the inner cortical zones with exogenous glucocorticoids alleviates the hypertension.

**Liddle’s syndrome**

Liddle described patients with autosomal-dominant monogenic hypertension who also tended to metabolic alkalosis with hypokalemia. His

![Diagram](image)

**Fig. 1.** A chimeric gene is formed by miotic mismatch and unequal crossing over with the promotor region of the 11β-hydroxylase gene (**dark box**) and the coding region of the aldosterone synthase gene (**white box**). As a result, the aldosterone synthase gene is under control of adrenocorticotropic hormone in the inner cortical zone. Aldo, aldosterone; Ang II, angiotensin II.
patients had low renin and low aldosterone values; however, they did not respond to spironolactone, whereas thiazides and triamterene reduced the blood pressure. This observation convinced Liddle that they probably did not have a form of mineralocorticoid excess. Liddle speculated that they would show a distal tubular defect of enhanced sodium and chloride reabsorption. A renal transplant performed on a patient with Liddle’s syndrome who developed renal failure cured the disease, providing strong evidence that the problem resided within the kidneys rather than in a regulatory system [4]. Shimkets et al [5] subsequently localized the responsible gene of a family with Liddle’s syndrome to chromosome 16p and were able to show that the gene encodes for the β subunit of the epithelial sodium channel (ENaC). The channel is amiloride and triamterene sensitive, explaining the efficacy of these drugs. The channel remains inappropriately permeable even in the face of high salt intake, thereby explaining the salt-sensitive hypertension. Subsequently a mutation in the γ subunit of ENaC was found, which can also result in Liddle’s syndrome [6]. The molecular mechanisms of Liddle’s syndrome involve alteration or deletion in the cytoplasmic tails of the β or γ subunits. As a consequence, the channels are not internalized (clathrin-coated pits pathway) or degraded (Nedd4 pathway), and instead remain activated on the cell surface [7].

**Apparent mineralocorticoid excess**

Genetic apparent mineralocorticoid excess resembles the syndrome observed in persons ingesting large amounts of licorice. Licorice gluttony and treatment with carbenoxolone both cause a volume expansion, low renin, low aldosterone, salt-sensitive form of hypertension, which may also feature metabolic alkalosis and hypokalemia. Interestingly, the hypertension responds to both thiazide and spironolactone, but no abnormal steroid products are present in the urine. Both licorice and carbenoxolone contain glycyrrhetinic acid, which was found to inhibit the enzyme 11β-hydroxysteroid dehydrogenase. The renal isoform of 11β-hydroxysteroid dehydrogenase is responsible for converting cortisol to cortisone. In the distal renal tubule, this step is crucial for protecting the mineralocorticoid receptor, which has the same affinity for cortisol as it does for aldosterone. This step protects humans from developing apparent mineralocorticoid excess. Inhibition of 11β-hydroxysteroid dehydrogenase results in apparent mineralocorticoid excess. Interestingly, apparent mineralocorticoid excess may also occur as a rare, autosomal-recessive form of hypertension. The 11β-hydroxysteroid dehydrogenase gene became a prime candidate. The clinical clues helpful in resolving this condition were volume-dependent salt-sensitive hypertension, tendency to hypokalemia and metabolic alkalosis, low renin and low aldosterone values, responsiveness to both thiazides and spironolactone despite absence of aldosterone or any
abnormal mineralocorticoid products, and resemblance to licorice gluttony. Mune et al [8] found mutations in the renal-specific isoform gene for 11 $\beta$-hydroxysteroid dehydrogenase that rendered the product incapable of converting cortisol to cortisone (Fig. 2). The mineralocorticoid receptor is unprotected from cortisol in these patients and cortisol functions to occupy the mineralocorticoid receptor. Li et al [9] raised the fascinating possibility that apparent mineralocorticoid excess might be relevant in the heterozygous state. They observed a patient with hypertension at age 38 years, who had a daughter with homozygous apparent mineralocorticoid excess. The patient had low renin and aldosterone concentrations and was found to have a mutation in the gene for 11 $\beta$-hydroxysteroid dehydrogenase.

**Mineralocorticoid receptor**

Geller et al [10] recently presented a new mendelian form of hypertension caused by an activating mutation in the mineralocorticoid receptor. The investigators screened for mutations in the mineralocorticoid receptor in seven unrelated patients referred for possible monogenic hypertension with
the single-strand conformation polymorphism technique. One patient had a heterozygous mutation at codon 810 in the mineralocorticoid receptor gene, resulting in a leucine for serine substitution. This residue lies in the hormone-binding domain. The patient’s relatives were carefully examined. The index case had severe hypertension, as did four relatives. Affected persons all exhibited the leucine for serine substitutions, had low plasma renin activities, and low aldosterone concentrations. Because the phenotype resembles Liddle’s syndrome, the investigators ruled out the presence of ENaC mutations. The authors speculate that the mineralocorticoid receptor gene mutation is an activating mutation in the receptor. Interestingly, affected women exhibit a worsening of hypertension during pregnancy, suggesting that progesterone occupancy of the receptor results in activation rather than inhibition of aldosterone-like effects. Similarly, spironolactone makes the blood pressure elevation worse, rather than better. Geller et al [10] were successful in elucidating the mechanism of the mutation. The MR-S810L mutation allows mineralocorticoid receptor activation by steroids lacking 21-hydroxyl groups. The L810 residue in helix 5 of the ligand-binding domain makes a new van der Waals interaction with A773 in helix 3. This interaction eliminates the requirement for the 21-hydroxyl group of aldosterone to interact with N770 in helix 3. The modification explains why compounds that are normally antagonists now are agonists for the receptor.

Pseudohypoaldosteronism type II

Pseudohypoaldosteronism type II features familial hypertension with hyperkalemia, slight hyperchloremic metabolic acidosis, and otherwise normal kidney function. Thiazide diuretics are highly effective in this syndrome, commensurate with salt sensitivity. A multilocus linkage analysis demonstrated linkage to chromosomes 1q and 17p [11]. Interestingly, the chromosome 17p locus overlaps a syntenic interval in the rat that contains a blood pressure quantitative trait locus. Recently, Disse-Nicodeme et al [12] described a new locus on chromosome 12p13. They analyzed a large French kindred in which 12 affected members over three generations confirmed the autosomal-dominant inheritance. Affected subjects had hypertension together with long-term hyperkalemia, hyperchloremia, normal plasma creatinine, and low renin levels. The aldosterone values are elevated, probably because of the hyperkalemia.

Wilson et al [13] unraveled the puzzle. They identified two genes causing pseudohypoaldosteronism type II. Both genes encode members of the WNK (with no lysine) family of serine-threonine kinases. Disease-causing mutations in WNK1 are large intronic deletions that increase WNK1 expression. The mutations in WNK4 are missense. They cluster in a short, highly conserved segment of the encoded protein. Both proteins are expressed in the distal nephron. WNK1 is cytoplasmic, whereas WNK4 localizes to tight junctions. These two gene products may represent new
drug targets for future therapies. Recent work by Yang et al [14] used the *Xenopus* oocyte system to show that WNK4 suppresses the thiazide-sensitive sodium chloride cotransporter. Wilson et al [15] have presented similar findings. WNK1 expression prevents the WNK4 suppression of the cotransporter. The WNK kinases serve as a sodium regulatory pathway in the distal nephron (Fig. 3).

**Autosomal-dominant hypertension with brachydactyly**

Bilginturan et al [16] first described this form of monogenic hypertension in 1974. Affected family members, who feature brachydactyly type E, have a dramatic increase in blood pressure with age and die before the age of 50 years by multiple strokes. The Turkish family was re-examined in 1994 [17]. The hypertension easily can be distinguished from other mendelian hypertensive syndromes described thus far. The patients are not salt-sensitive and have normal renin, angiotensin, aldosterone, and catecholamine responses. By measuring plasma renin activity and plasma aldosterone supine and upright, other conditions can be conveniently excluded [18]. The phenotyping efforts showed that the patients do not respond to any particular form of medication [19]. β-Blocker, calcium antagonists, α-blocker, and angiotensin converting enzyme inhibitor all improve blood pressure without significant difference. A multidrug therapy is required for the treatment of patients. The mechanism of the hypertension is unknown. An additional phenotype was

![Urine side](image-url) ![Blood side](image-url)

Fig. 3. The distal nephron. The thiazide-sensitive Na, Cl cotransporter is overactive in pseudohypoaldosteronism type 2. As a result, less Na is available for the ENaC and less K and H ions are excreted in the cortical collecting duct. The syndrome features volume expansion, hypertension, hyperkalemia, and mild hyperchloremic metabolic acidosis. “With-no-lysine” kinase 4 down-regulates the cotransporter. When the kinase is mutated, the cotransporter is hyperactive. WNK1 regulates WNK4 downward. Gain-of-function mutations in WNK1 down-regulate WNK4 causing cotransporter hyperactivity. WNK, with-no-lysine.
discovered, however, which may provide a clue, namely anomalous vessels in the posterior fossa that may impinge on the brainstem [20]. Based on these results detailed autonomic testing was performed [21]. The author and his group found that the ability of the baroreflex to buffer changes in vascular tone was severely impaired. The hypertension could be related to abnormal baroreceptor reflex function in these subjects. Efforts are under way to clone the genes responsible, as reviewed in detail elsewhere [22].

**Essential hypertension**

Hamilton, Roberts, Sowry, and Pickering first addressed hypertension as a complex genetic trait. They conducted studies in three groups of subjects: (1) a sample of the population at large, (2) first-degree relatives of patients with essential hypertension, and (3) first-degree relatives of persons without essential hypertension. Careful matching for age and gender was performed. The investigators found that the frequency distribution curves of arterial pressure gradually moved upward and spread out as age advances. At no age was there a clear division into normal or high blood pressure. These results were similar to those found by Francis Galton for height. Galton showed that height is inherited as a graded characteristic over the whole range of heights encountered. The results also introduced the notion that elevated blood pressure is not a function of one gene, but rather a host of genes, each contributing a small effect [23].

**Association studies**

Most studies into the molecular genetics of hypertension have relied on association (Fig. 4). Hundreds of association studies on some aspect of hypertension or blood pressure have been reported. Unfortunately, the contribution of most association studies to the understanding of hypertension and its genetic determinants has been modest. Recently, criteria have been suggested for high-quality association studies. Reviewing these criteria is worthwhile because one can rest assured the reviewers judging subsequent association studies will review them carefully [24]. These criteria are large sample size, small P values, biologic plausibility, functional significance, independent replication in several populations, confirmation in family-based studies, and high odds ratios or high attributable risk.

**Renin-angiotensin-aldosterone system genes**

The angiotensin converting enzyme insertion-deletion polymorphism has perhaps been the most consistent mutation associated with cardiovascular disease in the general population. The demonstration of associations to blood pressure has been difficult. The insertion-deletion polymorphism is an
Alu repeat in intron 16. Rieder et al [25] recently showed that 78 varying sites were present in the angiotensin converting enzyme gene, which resolved into 13 distinct haplotypes. Of the variant sites, 17 were in linkage disequilibrium with the Alu repeat in intron 16. The D allele is associated with higher angiotensin converting enzyme levels and not surprisingly with heart disease, hypertension, response to angiotensin converting enzyme inhibitors, and so forth [26]. Interestingly, the D allele has also been associated with longevity. An interaction between the angiotensin converting enzyme polymorphisms and variants in the adducin (below) gene show how variants in several genes can be examined in terms of phenotypes in the same study [27].

The angiotensinogen gene has been an attractive candidate gene for hypertension. The M235T polymorphism has been the most widely studied. This polymorphism is in linkage disequilibrium with a promoter variant (A-6G) that may be of functional significance and is associated with angiotensinogen levels. The impact on blood pressure may be as high as 1 to 2 mm Hg. A meta-analysis of numerous association studies has been published [28]. CYP11B2 has been implicated in essential hypertension [29]. A −344T polymorphism was identified, in which hypertensive persons had a higher proportion of the T allele. A similar association was found in sibpairs; however, in that study, linkage could not be verified [30]. Multiple gene analysis in a large epidemiologic cohort has recently been reported [31]. This study concluded that angiotensin converting enzyme polymorphisms are associated with obesity.

Epithelial sodium channel-related genes, adducin, and 11 β-hydroxysteroid dehydrogenase

Ambrosius et al [32] investigated genetic variants in ENaC in relation to aldosterone and potassium excretion and risk for hypertension on 249 white
and 181 black young people. They studied five variants; all but one was more common in blacks than whites. G442V in the β-subunit was present in 16% of blacks and only one white. This variant was associated with greater sodium retention and lower aldosterone values. The variant could not be associated with hypertension, however, in an older cohort. Expression of variants in *Xenopus* oocytes did not result in changes in basal Na$^+$ current. Persu et al [33] used single-strand conformation polymorphism to screen samples from 245 normal and 453 hypertensive subjects. The search was expanded to a subset of 65 patients with low renin hypertension. Four neutral polymorphisms were detected. The variants, however, were found in equal numbers in normotensive and hypertensive subjects. Regulators of ENaC have also received attention. The ENaC subunits contain PY motifs that are deleted in Liddle’s syndrome. Recent studies demonstrate that Nedd4 is a negative regulator of ENaC [34]. Any role for Nedd4 in hypertension, however, remains to be defined.

Considerable work has been done on the cytoskeletal protein adducin. Ferrandi et al [35] recently carried knowledge in this area further. They found that both rat and human adducins stimulate Na$^+$-K$^+$-ATPase activity. In rats, adducins increase the ATP affinity for Na$^+$-K$^+$-ATPase. The mechanism of action involves a selective acceleration of conformational change in various pump proteins. Mutant human and rat adducins have higher affinities than wild-type adducins. The observations may be relevant to salt sensitivity. Nevertheless, the results of association studies involving adducin have been conflicting. Glorioso et al [36] recently tried to explain the discrepancies. They studied 490 hypertensives and 176 normotensives in Sassari, Italy, and 468 hypertensives and 181 normotensives from Milan, Italy. The subjects were genotyped for the Gly460Trp polymorphism. A positive association was found in the Milan cohort, but not in the Sassari cohort. Plasma renin activity was lower and the blood pressure response to diuretics greater, however, in persons carrying at least one 460Trp allele, compared with those not having this allele at both sites. The adducin gene hypothesis has been greatly strengthened by the demonstration that β-adducin gene deletion in the mouse results in hypertension [37].

Lovati et al [38] provided very interesting information implicating 11 β-hydroxysteroid dehydrogenase in salt sensitivity of blood pressure. They studied 37 salt-sensitive and 112 salt-resistant normotensive persons. They showed that salt-sensitive persons excreted a ratio of cortisol to cortisone in their urine consistent with a reduced 11 β-hydroxysteroid dehydrogenase activity. They then used a polymorphic microsatellite marker in the gene and showed association between a marker variant and salt sensitivity of blood pressure. This study is the first to show convincing mechanistic genetic evidence concerning salt sensitivity and suggests that 11 β-hydroxysteroid dehydrogenase variants could serve as a genetic marker for the condition. Claims for the glucocorticoid receptor gene and hypertension could not be confirmed. Lin et al [39] examined DNA from
the so-called “4-corners” study. They studied a polymorphism in the gene to show association to high blood pressure and microsatellites to establish linkage of the gene locus to blood pressure. For the groups as a whole, no evidence for association or linkage was found. In gender subgroups, however, weak evidence for association to blood pressure was identified.

G proteins and channels

The putative role of G protein β3 subunit 8235T allele and hypertension has recently been reviewed elsewhere [40]. Baumgart et al [41] reported that carriers of 825T alleles more commonly exhibited ischemic events in response to a α2-adrenergic receptor agonist treatment during coronary angiography than those who did not carry this allele. Siffert et al [42] also identified an association between the 825T allele and obesity in a large, worldwide study. Jacobi et al [43] studied a small number of subjects in considerable detail and found that the 825T allele was associated with impaired left ventricular filling in hypertensive subjects. Dong et al [44] studied 428 men and women of African origin, 40% of who was hypertensive. They found a threefold higher risk of hypertension among the carriers of the T variant both as heterozygotes and homozygotes. The estimate of effect and the blood pressure values in the groups carrying the T variant suggested a dominant model for the T allele. Their study showed a high frequency of the 825T allele in black people, and provides evidence that the T allele may be a susceptibility factor for the development of hypertension in blacks. Given the high frequency of the T allele, even a twofold increased risk of hypertension among the carriers of the T allele might account for 44% of the cases of hypertension in blacks.

Jia et al [45] examined whether or not the GNAS1 locus encoding the Gsa subunit is implicated in hypertension. They found a silent polymorphism (ATT→ATC, Ile131) in exon 5 of the Gsa gene. They then studied this polymorphism in 231 control subjects and 268 hypertensive persons. In untreated hypertensive persons, the polymorphism was related to systolic blood pressure, but not in normotensive individuals. In a multiple regression analysis performed in a β-blocker–treated subgroup, the Gs-α genotype was the sole independent predictor of blood pressure response to beta-blockade. The finding that calcium-regulated potassium channel subunit gene deletion causes hypertension in mice has focused attention on the human genes. Gollasch et al [46] recently found that the BK channel β1 subunit gene is associated with baroreflex regulation of blood pressure.

Endothelium-related factors

Kato et al [47] studied 1165 persons and examined the relevance of the 298Glu variant in the endothelial nitric oxide synthase gene. They found no
support for any associations between the variant, hypertension, or blood pressure. Glenn et al [48] studied inducible nitric oxide synthase. They tested NOS2A markers for association and linkage with hypertension in affected Australian Anglo whites. No evidence supporting a relationship with blood pressure was found. Nevertheless, Herlitz et al [49] found that urine flow in response to L-arginine infusions in normal subjects was significantly less pronounced in persons with a positive family history of hypertension, compared with those with a negative family history. The Lys198ASN polymorphism in the endothelin-1 gene has been studied in an association study. Tiret et al [50] found that the polymorphism was associated with blood pressure levels in overweight people. Prostacyclin is a strong, endothelium-derived vasodilator. Iwai et al [51] detected a repeat polymorphism in the human prostacyclin synthase gene. This variant was tested for functional significance in human endothelial cells and was found to influence promoter activity. The authors then performed a very convincing association study in 4971 Japanese participants. Systolic blood pressure, pulse pressure, and the odds ratio of hypertension were all associated with the SS genotype of this polymorphism. The function of the glucagon receptor could conceivably influence vascular behavior on the basis of cAMP responses. A missense mutation (Gly40Ser) in exon 2 of the gene has been shown to exhibit reduced cAMP responses. Brand et al [52] performed an association study of 741 French hypertensive persons and compared them with 412 normotensive controls. The polymorphism may represent a risk for hypertension in men, but apparently not in women.

Sympathetic tone, α-, and β-adrenergic receptors

Leptin has been implicated in sympathetic tone. Paolisso et al [53] recently demonstrated that plasma leptin levels are associated with myocardial wall thickness in hypertensive insulin-resistant men. Ozata et al [54] observed that human leptin deficiency caused by a missense mutation features decreased sympathetic tone. Human α1B-adrenergic receptor polymorphisms have received attention. Büscher et al [55] studied variability in phenylephrine response and essential hypertension. They searched for an effect of α1B-adrenergic receptor polymorphisms, but were not able to find polymorphisms in the coding region of the gene that accounted for variability in phenylephrine responses. Experimental evidence suggests that salt loading induces hypertension by a neurogenic mechanism mediated by the α2-adrenergic receptors. Makaritsis et al [56] studied genetically engineered mice and found that a full complement of α2B-adrenergic receptor genes was necessary to raise blood pressure in response to dietary salt loading, whereas complete absence of the α2C-adrenergic receptor subtype did not preclude salt-induced blood pressure elevations. The β2-adrenergic receptor and its variants have received considerable attention. Earlier studies have shown that the Arg16→Gly variant is
associated with hypertension. Gratze et al [57] showed that a β2-adrenergic receptor variant affects resting blood pressure and agonist-induced vasodilation in young whites. They found that the Gly variant was associated with higher blood pressures. Furthermore, homozygous Gly16 subjects showed a significantly decreased vasodilation during a salbutamol infusion compared with Arg16-Arg subjects. These results are consistent with data from an association study of African-Caribbeans reported earlier, but at variance with an association study from the Bergen Blood Pressure Study [58].

**Human atrial natriuretic peptide and dopamine**

hANP is an attractive candidate gene for hypertension. Mice with a disrupted gene are relatively hypertensive. The role of atrial natriuretic peptide in salt excretion is well appreciated. Nannipieri et al [59] investigated polymorphisms in hANP and studied albuminuria and hypertension. Two hANP polymorphisms were studied, termed ScaI and BstXI. A clinical cohort of 1033 subjects including type 1 and type 2 diabetics participated. The prevalence of hypertension was 30% to 60% depending on the severity or proteinuria. The ScaI polymorphism was inversely associated with nephropathy. The mutated BstXI polymorphism was directly associated with microalbuminuria. The authors reasoned that certain hANP variants might confer a protective effect.

Dopamine receptor coupling defects have been described in hypertension [60]. A defective coupling between the D(1) dopamine receptor and the G protein–effector enzyme complex in the proximal tubule of the kidney is associated with impaired renal dopaminergic action in genetic rodent and human essential hypertension. Felder et al [61] reported recently that, in human essential hypertension, single nucleotide polymorphisms of a G protein–coupled receptor kinase, GRK4gamma, increase G protein–coupled receptor kinase (GRK) activity and cause the serine phosphorylation and uncoupling of the D(1) receptor from its G protein-effector enzyme complex in the renal proximal tubule. They transfected Chinese hamster ovary cells and confirmed their suspicions in this cell system. Moreover, expressing GRK4gammaA142V but not the wild-type gene in transgenic mice produced hypertension and impaired the diuretic and natriuretic but not the hypotensive effects of D(1)-like agonist stimulation. Their findings provide a mechanism for the D(1) receptor coupling defect in the kidney and may explain the inability of the kidney properly to excrete sodium in genetic hypertension.

**Human linkage studies for new blood pressure loci and hypertension**

To find new genes responsible for blood pressure regulation and hypertension, their location must first be determined. Here, linkage studies
are necessary. Linkage is quantitated by the logarithm of the odds ratio, or LOD score. A LOD score of greater than or equal to 3 is regarded as significant. Analyses of large families, affected sibpair studies, identical by state or identical by descent are commonly used to link loci on the genome to blood pressure as a continuous trait or to hypertension. Microsatellite markers that feature variable numbers of repeats are used in these studies. The microsatellites are amplified with the polymerase chain reaction and sequenced. The goal is to find microsatellite variants that are always inherited with the trait. These variants are then linked to the trait and provide information regarding its location. The author has used dizygotic twin subjects (sibpairs) and their parents for this purpose (Fig. 5) to find so-called “quantitative trait loci” [62]. A large family-based total genome scan in Chinese hypertensive families recently showed linkage to chromosome 12p (LOD > 3), where the autosomal-dominant hypertension with brachydactyly locus resides [63]. Rankinen et al [64] recently reported on a genome scan for gene loci related to exercise-induced blood pressure elevations from the health risk factors, exercise training and genetics (HERITAGE) Family Study illustrating this approach. Levy et al [65] studied families from the Framingham cohort. They had the advantage of being able to study longitudinal blood pressure values and found a locus on chromosome 17 that yielded a multipoint LOD score of 4.7. For diastolic blood pressure the LOD value was 2. This locus is of interest because of earlier rat studies showing linkage at a site syntenic to this locus [66].

How are the cloning strategies for complex genetic diseases to be performed and how is the track record? Boerwinkel et al [67] recently

![Identity-by-descent linkage analysis](image)

**Fig. 5.** Identity-by-descent linkage analysis, the gene mapping approach. Polymorphic markers (arrow) are selected. DNA is obtained from parents and offspring. If the parents have alleles a-b and b-c, it is expected that 25% of the offspring share no alleles in common, 50% share one allele in common, and 25% share both alleles in common. Statistical deviation from these expectations, either concordancy or discordancy, suggests linkage of the phenotypes are concordant or discordant, respectively. If parents are not available, an identity-by-state analysis must be done and many more pairs are necessary.
presented a brief review on the basic strategy. The method relies on single nucleotide (bi-allelic) polymorphisms (SNPs) mutations that are distributed approximately every 1000 base pairs across the genome. The SNPs represent interindividual variability that distinguishes one person from another. Probably more than 3,000,000 SNPs reside within the genome. With the results of the human genome project soon to be available, investigators will be able to analyze all the SNPs that are likely to be informative. SNPs in coding, noncoding, and regulatory regions are all valuable. The SNPs can be used in haplotype analyses to determine if specific haplotypes are associated with the phenotype. Once SNP mapping is completed, the gene or genes must be sequenced for mutations. Eventually, experimental animal or cellular studies on the gene in question will be necessary to prove how the mutation works.

Recent advances in molecular biology and technology have made it possible to monitor the expression levels of virtually all genes simultaneously [68]. As the tools for gene expression profiling have become more widely available, the number of investigators applying this technology in hypertension research, as in other fields of biomedical research, has grown rapidly. This approach obviously requires functioning cells or tissues for analysis. A direct application to the genetics of human hypertension requires biopsies of small vessels. Such approaches are technically feasible and will undoubtedly soon be applied.

References


