Monogenic and Polygenic Contributions to Hypertension

6

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Abstract

This chapter provides an overview of the genetics of hypertension, reviewing what is known about rare Mendelian forms of hypertension, which can be explained by mutations in single genes, as well as the genetics of primary hypertension. Different approaches such as candidate gene approaches, linkage studies, and genome-wide association studies are discussed. It is hoped that this chapter will provide a concise primer for reading the literature in the area of genetics and hypertension.

Keywords

Monogenic • Polygenic • Familial hypertension • Mendelian I • Low-renin hypertension

Introduction

More than 12 years have elapsed since the publications in February 2001 that provided the first maps of the human genome [1, 2]. While genes involved in a number of rare, monogenic forms of hypertension have been identified, the genetics of primary hypertension has eluded delineation, likely because it has multiple genetic determinants. However, many recently developed tools are available to reveal the genetic aspects of primary hypertension, and a growing number of studies have identified many genetic associations with the condition, which is widely viewed as a polygenic disorder. This chapter discusses both monogenic and polygenic aspects of hypertension. We also discuss the current clinical implications of genetic studies and information in our approach to hypertension [3].

Monogenic Forms of Human Hypertension

Genes for a number of monogenic forms of human hypertension have been identified via positional cloning [in the past called "reverse genetics"] [4–6]. In this approach, large kindreds with many

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J.T. Flynn et al. (eds.), *Pediatric Hypertension*, Clinical Hypertension and Vascular Diseases,
DOI 10.1007/978-1-62703-490-6_6,

affected family members are phenotyped, and the mode of inheritance determined – that is, is the disease autosomal recessive, autosomal dominant, sex linked, and codominant, in its clinical transmission. Subsequently, linkage analysis is performed using highly polymorphic genetic markers such as microsatellite markers that occur widely throughout the genome, evenly spaced at approximately 10 centimorgan [cM] intervals. Since most people (about 70 %) are heterozygous, the inheritance of alleles can be traced through large pedigrees. In a successful linkage analysis, a specific chromosomal region in the genome linked to the trait is identified. A LOD [logarithm of the odds] score describes the presence of such a region. The generally accepted LOD score indicating linkage is greater than 3.3 [corresponding to a significance level genome wide of 4.5×10^{-5} [4]]. Once linkage is identified, a search for known candidate genes in the area of putative linkage commences. A search using additional highly polymorphic markers may also narrow the area of interest, leading to sequences of possible genes within the area.

A number of monogenic forms of hypertension have been identified to date. A number are due to gain-of-function mutations [7–9], most of which involve the renal handling of salt and/or the overproduction of mineralocorticoids or increased mineralocorticoid activity. Severe hypertension, often from early life – even infancy – is not unusual in such conditions. Clinical hallmarks include apparent volume expansion and suppressed plasma renin activity with variable hypokalemia. An approach to evaluation of those forms of hypertension associated with hypokalemia and suppressed renin activity is shown in Fig. 6.1 [10].

Gain-of-function mutations in transporters in the distal renal tubules result in hypertension via salt and water retention [11]. (While mutations and polymorphisms in the genes of various

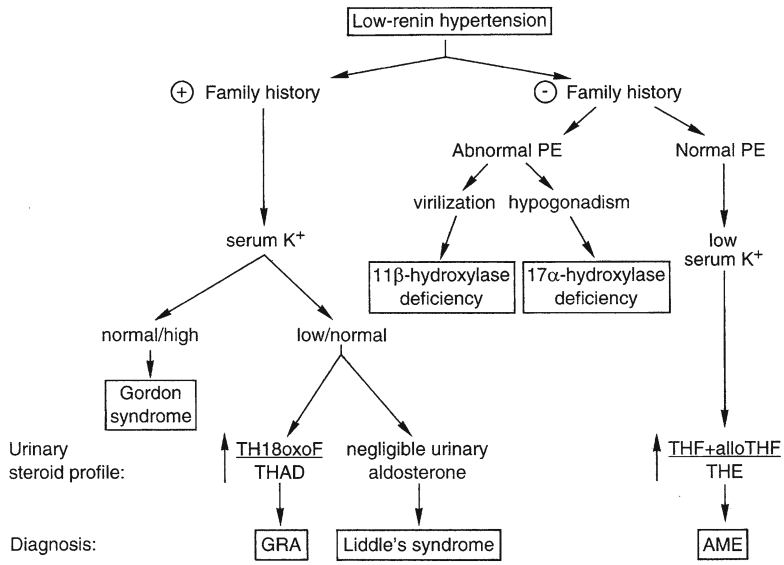

Fig. 6.1 Evaluation of patients with hypertension and low plasma renin. Such disorders are either autosomal dominant, generally with a positive family history, or autosomal recessive, generally with a negative family history. Children with glucocorticoid-responsive aldosteronism (GRA), Liddle syndrome, and apparent mineralocorticoid excess (AME) all have normal physical examinations (PE), low plasma renin activity (PRA) or concentration, and hypokalemia. Characteristic urinary steroid profiles and genetic testing distinguish these syndromes. K+, potassium, TH18oxoF/THAD ratio, ratio of urinary 18-oxotetrahydrocortisol (TH18oxoF) to urinary tetrahydroaldosterone (THAD), which has a normal of 0–0.4, and GRA patients >1. THF plus alloTHF/THE ratio of the combined urinary tetrahydrocortisol (THF) and allotetrahydrocortisol (alloTHF) to urinary tetrahydrocortisone (THE), which has a normal of <1.3, while AME patients are 5–10-fold higher (From Yiu VW, Dluhy RG, Lifton RP, Guay-Woodford LM. Low peripheral plasma renin activity as a critical marker in pediatric hypertension. Pediatr Nephrol. 1997;11: 343–6, with permission)

components of the renin-angiotensin-aldosterone system [RAAS] may lead to excessive renal sodium retention, no single RAAS polymorphism causes monogenic hypertension.) Phenotypically, most monogenic hypertension can be divided into disorders caused by mutations that lead to overproduction of mineralocorticoids or increased mineralocorticoid activity and those that result in abnormalities of electrolyte transport, focusing attention on the role of the kidney in hypertension (Table 6.1) [7]. Additionally, some mutations in proto-oncogenes and genes that involve response to hypoxia have been linked to chromaffin tumors (Table 6.2) [12]. Information about the most common forms of monogenic hypertension [13] follows.

Glucocorticoid-Remediable Aldosteronism or Familial Hyperaldosteronism Type 1 [OMIM #103900]

Glucocorticoid-remediable aldosteronism (GRA) or familial hyperaldosteronism type 1, an autosomal dominant disorder, is considered the most common type of monogenic hypertension and presents in early infancy in some patients [14–18]. GRA has been recognized since the 1960s, when Sutherland et al. [19] and New et al. [20] reported patients with severe hypertension accompanied by suppressed renin and increased aldosterone secretion that were found to be treatable with dexamethasone. (GRA is listed in the Online Mendelian Inheritance in Man index [OMIM] as #103900 [OMIM can be accessed at http://www.ncbi.nlm.nih.gov/Omim]; note that the OMIM numbers for other Mendelian disorders will also be listed for other disorders when available.) The hypertension in GRA is moderate to severe, owing to increased aldosterone secretion driven by adrenocorticotropic hormone (ACTH).

A chimeric gene containing the 5′ regulatory sequences of 11 beta hydroxylase [which confers ACTH responsiveness] fused with the distal coding sequences of aldosterone synthase causes ACTH rather than angiotensin II or potassium as the main controller of aldosterone secretion [21, 22]. Both serum and urine aldosterone levels tend to be elevated, though not invariably. The chimeric gene product converts cortisol to 18-hydroxy and 18-oxo metabolites [23–25], which can be detected in urine and are pathognomonic. The elevations of urinary cortisol metabolites TH18oxoF and 18-hydroxycortisol and an elevated ratio of TH18oxoF/THAD metabolites may distinguish GRA patients from others with AME or Liddle syndrome [26]. However, specific genetic testing, which is both sensitive and specific, has largely supplanted the urinary testing when the condition is suspected.

Not all affected members of GRA families develop hypertension in childhood [27–29]. Dluhy et al. [27] assessed 20 children in 10 unrelated GRA pedigrees and observed that 16 of the 20 developed hypertension, as early as 1 month of age. However, four children were normotensive. Monotherapy using glucocorticoid suppression or aldosterone receptor and epithelial sodium cotransporter (ENaC) antagonists was sufficient to control BP in half of the hypertensive children, though the others required polypharmacy, and three had uncontrollable hypertension [27].

Cerebral hemorrhage at an early age (mean age, 32 years) is common in GRA pedigrees. And almost half of reported pedigrees [48 %] and 18 % of individual GRA patients have been noted to develop cerebrovascular complications [7, 8, 21].

Familial Hyperaldosteronism Type 2 OMIM #605635

This form of hyperaldosteronism, which appears to be autosomal dominant, is distinct from type 1 and is associated with hyperplasia of the adrenal cortex, an adenoma producing aldosterone or both [30–33]. It has been estimated to be fivefold more common than GRA [33]. Dexamethasone fails to suppress the hypertension. To date, no mutation has been identified, though linkage studies have identified a five megabase locus on chromosome 7p22. The Stowasser group [33] has examined a number of candidate genes within 7p22, many of which involve cell growth, but has still not yet definitively identified the gene responsible.

Table 6.1 Adapted and expanded from [147]

Signs and sx	Hormonal findings	Source	Genetics	Comment
Steroidogenic enzyme defects				
Steroid 11β- hydroxylase deficiency	⇓ PRA and aldo; high serum androgens/ urine 17 ketosteroids; elevated DOC and 11-deoxycortisol	Adrenal: zona fasciculata	CYP11B1 mutation [encodes cytochrome P_{450}11β/18 of ZF]; impairs synthesis of cortisol and ZF 17-deoxysteroids	Hypertensive virilizing CAH; most patients identified by time they are hypertensive. Increased BP may also occur from medication side effects
Steroid 11α-hydroxylase/ 17,20-lyase deficiency	⇓ PRA and aldo; low serum/urinary 17-hydroxysteroids; decreased cortisol	Adrenal: zona fasciculata; Gonadal: interstitial cells [Leydig in testis; theca in ovary]	CYP17 mutation [encodes cytochrome P_{450}C17] impairs cortisol and sex steroid production	CAH with male pseudoher-maphroditism; female external genital phenotype in males; primary amenorrhea in females
	⇑ Corticosterone [B] and DOC in plasma; serum androgens and estrogens very low; serum gonadotropins very high			
Hyperaldosteronism				
Primary aldosteronism	⇓ PRA; plasma aldosterone, 18-OH- and 18 oxoF; normal 18-OH/aldo ratio	Adrenal adenoma: clear cell tumor with suppression of ipsilateral ZG	Unknown; very rare in children; female: male ratio is 2.5–3/1	Conn syndrome with aldo-producing adenoma; muscle weakness and low K+ in sodium-replete state
Adrenocortical hyperplasia	As above, source of hormone established by radiology or scans	Adrenal: focal or diffuse adrenal cortical hyperplasia	Unknown	As above
Idiopathic primary aldosteronism	High plasma aldo; elevated 18-OHF/aldo ratio	Adrenal: hyperactivity of ZG of adrenal cortex	Unknown	As above
Glucocorticoid-remediable aldosteronism [GRA]	Plasma and urinary aldo responsive to ACTH; dexamethasone suppressible within 48 h; ⇑ urine and plasma 18OHS,18-OHF, and 18 oxoF	Adrenal: abnormal presence of enzymatic activity in adrenal ZF, allowing completion of aldo synthesis from 17-deoxy steroids	Chimeric gene that is expressed at high level in ZF [regulated like CYP11B1] and has 18-oxidase activity [CYP11B2 functionality]	Hypokalemia in sodium-replete state
Apparent mineralalocorti-coid excess [AME]	⇑ Plasma ACTH and secretory rates of all corticosteroids; nl serum F [delayed plasma clearance]	⇑ Plasma F bioact. in periphery [F → E] of bi-dir. 11βOHSD or slow clearance by 5 α/β reduction to allo dihydro-F	Type 2 11βOHSD mutations	Cardiac conduction changes; LVH, vessel remodeling; some calcium abnormalities; nephrocalcinosis; rickets

Nonsteroidal defects				
Liddle syndrome	Low plasma renin, low or normal K+; negligible urinary aldosterone	Not a disorder of steroidogenesis, but of transport	Autosomal dominant Abnormality in epithelial sodium transporter, EnaC, in which channel is constitutively active	Responds to triamterene
Pseudohypoaldosteronism II – Gordon syndrome	Low plasma renin, normal or elevated K+	Not a disorder of steroidogenesis, but of transport	Autosomal dominant Abnormality in WNK1 or WNK4	Responds to thiazides
Hypertension exacerbated by pregnancy		Missense mutation of the mineralocorticoid receptor converts antagonists (such as progesterone) to agonists	NR3C2	
Mutations in peroxisome-activated receptor gamma		Loss of function mutation results in insulin resistance and hypertension	PPARG	

Table 6.2 Mutations associated with pheochromocytomas and paragangliomas

Syndrome	Mutated gene in germ line	Clinical phenotype	Risk of pheochromocytoma
MEN-2A	RET proto-oncogene	Medullary carcinoma of the thyroid, hyperparathyroidism	50 %
MEN-2B	RET proto-oncogene	Medullary carcinoma of the thyroid, multiple mucosal neuromas, marfanoid habitus, hyperparathyroidism	50 %
Neurofibromatosis type 1	NF1	Neurofibromas of peripheral nerves, café au lait spots	1 %
von Hippel-Lindau disease (retinal cerebellar hemangioblastosis)	VHL	Retinal angiomata, CNS hemangioblastoma, renal-cell carcinoma, pancreatic and renal cysts	10–20 %
Familial paraganglioma syndrome	SDHD, SDHB, SDHC	Carotid-body tumor (chemodectoma)	20 % (estimated)

With permission from Dluhy RG. Pheochromocytoma: the death of an axiom. N Engl J Med. 2002;346:1486–8
MEN-2A multiple endocrine neoplasia type 2A, *MEN-2B* multiple endocrine neoplasia type 2B, *CNS* central nervous system, *SDHD* the gene for succinate dehydrogenase subunit D, and *SDHB* for subunit B, and *SDHC* for subunit C

Familial Hyperaldosteronism Type 3 [OMIM# 613677]:

FH type 3 is very rare and is also called Geller syndrome; it is now known that a heterozygous mutation in the KCNJ5 gene, which is on chromosome 11q24, leads to familial hyperaldosteronism type III [33–37].

Apparent Mineralocorticoid Excess [AME] [OMIM # 218030]

Low-renin hypertension, often severe and accompanied by hypokalemia and metabolic alkalosis [38], is the hallmark of apparent mineralocorticoid excess [AME], first described in 1977 by New et al. [39, 40]. Spironolactone is often effective initially, but patients often become refractory to this drug. In AME, 11β-hydroxysteroid dehydrogenase (11β-HSD) is absent, resulting in hypertension in which cortisol acts as if it were a potent mineralocorticoid. The microsomal enzyme, 11β-hydroxysteroid dehydrogenase, interconverts active 11-hydroxyglucocorticoids to inactive ketometabolites. Cortisol, as well as aldosterone, has an affinity for the mineralocorticoid receptor. Normally, 11β-HSD is protective, preventing binding of cortisol to the mineralocorticoid receptor, but in AME, the slower-than-normal metabolism of cortisol to cortisone results in cortisol acting as a potent mineralocorticoid [39, 40], while metabolism of cortisone to cortisol is normal.

Persons with classic AME usually develop symptoms in early childhood, often presenting with failure to thrive, severe hypertension, and persistent polydipsia. Affected patients appear volume expanded and respond to dietary sodium restriction. Plasma renin activity is very low. Affected children are at high risk for cardiovascular complications, and some develop nephrocalcinosis and renal failure [41]; early therapy may lead to better outcome. A high cortisol: cortisone ratio in plasma or an abnormal urinary ratio of tetrahydrocortisol/tetrahydrocortisone (THF/THE), in which THF predominates and makes the diagnosis.

Several variants of AME have been reported, including a mild form in a Mennonite kindred in which there is a P227L mutation in the HSD11B2 gene [42, 43], a coactivator defect with resistance to multiple steroids [44], and hypertension without the characteristic findings of AME in a heterozygous father and homozygous daughter who have mutations in 11 β HSD2 [45]. Coeli et al. reported a Brazilian child with a homozygous missense mutation p.R186C in the HSD11B2 gene [46].

The hypertension in AME appears renally mediated, but recent evidence suggests that ultimately, the disorder changes from one with increased sodium resorption to a vascular form of hypertension [47].

Mineralocorticoid Receptor Gain-of-Function Mutation

A novel form of monogenic hypertension due to a gain-of-function mutation in the mineralocorticoid receptor, causing it to remain bound to its steroid ligands, has also been described. The first known case was a teenage boy with hypertension, who had low renin and aldosterone levels, as well as mild hypokalemia [48]. In toto, 11 persons in the patient's family had a point mutation, which influences an important binding region of the receptor – a serine at amino acid 810 in the mineralocorticoid receptor is changed to leucine (S810L)

Affected persons have refractory hypertension, and women with this mutation have severely elevated BP during pregnancy [49, 50]. Early death due to heart failure occurred in the index family [48].

It appears that the S810L mutation leads to a conformational change in the receptor that heightens the stability of steroid-receptor complexes. The mutation thus results in a steric hindrance resulting in a bending of the molecule that makes it difficult for known agonists and antagonists to act normally. Some antagonists that cannot act on the normal ["wild type"] receptor work in this mutation: these include RU 486, 5-pregnane-20-one, and 4,9-androstadiene-3,17-dione [51].

Steroidogenic Enzyme Defects Leading to Hypertension

Rare autosomal recessive defects in steroidogenesis associated with hypertension were recognized well before the genomic era. Cortisol is normally synthesized under the control of ACTH in the zona fasciculata, while aldosterone is synthesized largely under the influence of angiotensin II and potassium in the zona glomerulosa. Aldosterone synthesis is not normally controlled by ACTH, but if any of the several enzymes that are involved in cortisol biosynthesis is abnormal, the usual feedback loop is interrupted. Consequently, plasma ACTH will increase in an attempt to produce cortisol, and aberrant products will accumulate, some of which lead to hypertension. This is discussed in more detail in Chap. 25.

The inherited defects of steroid biosynthesis – all autosomal recessive – are, as a group, termed congenital adrenal hyperplasia (CAH), and each results in a characteristic clinical and biochemical profile [52–54]. Any enzyme in the pathways of steroidogenesis may contain a mutation; the most commonly affected is 21-hydroxylase. Mutations in 21-hydroxylase are not, however, generally associated with hypertension. Enzyme mutations that are associated with hypertension include [in order of frequency] 11β-hydroxylase >3β-hydroxysteroid dehydrogenase>17α-hydroxylase and cholesterol desmolase. Patients with the 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase defects have a tendency to retain salt, becoming hypertensive. It is also important to remember that any person with CAH may develop hypertension owing to overzealous replacement therapy.

Steroid 11β-Hydroxylase Deficiency

The mineralocorticoid excess in 11β-hydroxylase deficiency [52–58], a form of CAH accompanied by virilization, leads to decreased sodium excretion with resultant volume expansion, renin suppression, and hypertension. Elevated BP is not invariant in 11β-hydroxylase deficiency and most often is discovered in later childhood or adolescence, often with an inconsistent correlation to the biochemical profile [52–58]. Hypokalemia is variable, but total body potassium may be markedly depleted in the face of normal serum or plasma potassium. Renin is generally decreased, but aldosterone is increased.

Therapy of 11β-hydroxylase deficiency should focus on normalizing steroids. Administered glucocorticoids should normalize cortisol and reduce ACTH secretion and levels to normal, thus stopping over secretion of deoxycorticosterone (DOC). Hypertension generally resolves

with such therapy [53]. When hypertension is severe, antihypertensive therapy should be used instituted until the BP is controlled; such therapy can be tapered later.

Additional mutations can cause this syndrome. For example, a patient with 11β-hydroxylation inhibition for 17α-hydroxylated steroids but with intact 17-deoxysteroid hydroxylation has been reported [58]. Multiple mutations affecting the CYP11B1 gene have been described; these include frameshifts, point mutations, extra triplet repeats, and stop mutations [38, 59–62].

Steroid 17α-Hydroxylase Deficiency

Abnormalities in 17α-hydroxylase affect both the adrenals and gonads, since a dysfunctional 17α-hydroxylase enzyme results in decreased synthesis of both cortisol and sex steroids [63–66]. Affected persons appear phenotypically female [or occasionally have ambiguous genitalia], irrespective of their genetic sex, and puberty does not occur. Consequently, most cases are discovered after a girl fails to enter puberty [65]. An inguinal hernia is another mode of presentation. Hypertension and hypokalemia are characteristic, owing to impressive overproduction of corticosterone [compound B].

Glucocorticoid replacement is an effective therapy. However, should replacement therapy fail to control the hypertension, appropriate therapy with antihypertensive medication(s) should be instituted to achieve BP control.

Mutations in Renal Transporters Causing Low-Renin Hypertension

Pseudohypoaldosteronism Type II: Gordon Syndrome [OMIM#145260]

Pseudohypoaldosteronism type II, Gordon syndrome, or familial hyperkalemia (OMIM #145260), an autosomal dominant form of hypertension associated with hyperkalemia, acidemia, and increased salt reabsorption by the kidney, is caused by mutations in the WNK1 and WNK 4 kinase family [67–71]. Though the physiology and response to diuretics suggested a defect in renal ion transport in the presence of normal glomerular filtration rate, the genetics have only recently been delineated.

Affected persons have low-renin hypertension and improve with thiazide diuretics or with triamterene [71]. Aldosterone receptor antagonists do not correct the observed abnormalities.

PHAII genes have been mapped to chromosomes 17, 1, and 12 [67, 68]. One kindred was found to have mutations in WNK1 – large intronic deletions that increase WNK1 expression. Another kindred with missense mutations in WNK4, which is on chromosome 17, has been described. While WNK 1 is widely expressed, WNK4 is expressed primarily in the kidney, localized to tight junctions. WNKs alter the handling of potassium and hydrogen in the collecting duct, leading to increased salt resorption and increased intravascular volume by as yet unknown means.

Liddle Syndrome [OMIM # 177200]

In 1963, Liddle [72] described the early onset of autosomal dominant hypertension in a family in whom hypokalemia, low renin, and aldosterone concentrations were noted in affected members. Inhibitors of renal epithelial sodium transport such as triamterene worked well in controlling the hypertension, but inhibitors of the mineralocorticoid receptor did not. A general abnormality in sodium transport seemed apparent, as the red blood cell transport systems were not normal [73]. A major abnormality in renal salt handling seemed likely when a patient with Liddle syndrome underwent a renal transplant and hypertension and hypokalemia resolved posttransplant [74].

While the clinical picture of Liddle syndrome is one of aldosterone excess, aldosterone levels as well as renin levels are very low [10]. Hypokalemia is not invariably present. A defect in renal sodium transport is now known to cause Liddle syndrome. The mineralocorticoid-dependent sodium transport within the renal epithelia requires activation of the epithelial sodium channel [ENaC], which is composed of at least three subunits normally regulated by aldosterone. Mutations in the beta and gamma subunits of the ENaC have been identified [both lie on chromosome 16] [75, 76]. Thus, the defect in Liddle syndrome leads to constitutive activation of amiloride-sensitive epithelial sodium

channels (ENaC) in distal renal tubules, causing excess sodium reabsorption. Additionally, these gain-in-function mutations prolong the half-life of ENaCs at the renal distal tubule apical cell surface, resulting in increased channel number [77].

Pheochromocytoma-Predisposing Syndromes

A variety of RET proto-oncogene mutations and abnormalities in tumor-suppressor genes are associated with autosomal dominant inheritance of pheochromocytomas, as summarized in Table 6.2 [12, 78–83]. A number of paraganglioma and pheochromocytoma susceptibility genes inherited in an autosomal dominant pattern appear to convey a propensity toward developing such tumors [12]. Both glomus tumors and pheochromocytomas derive from neural crest tissues, and the genes identified in one type of tumor may appear in the other [84]. For instance, germ-line mutations have been reported both in families with autosomal dominant glomus tumors [as well as in registries with sporadic cases of pheochromocytoma] [85]. In addition, other pheochromocytoma susceptibility genes include the proto-oncogene *RET* (multiple endocrine neoplasia syndrome type 2 [MEN-2]), the tumor-suppressor gene *VHL* seen in families with von Hippel-Lindau disease, and the gene that encodes succinate dehydrogenase subunit B (*SDHB*).

The genes involved in some of these tumors appear to encode proteins with a common link involving tissue oxygen metabolism [86–88]. In von Hippel-Lindau disease, there are inactivating [loss-of-function] mutations in the VHL suppressor gene, which encodes a protein integral to the degradation of other proteins – some of which, such as hypoxia-inducible factor, are involved in responding to low oxygen tension. Interestingly, the mitochondrial complex II, important in O_2 sensing and signaling, contains both SDHB [succinate dehydrogenase subunit B] and SDHD [succinate dehydrogenase subunit D]. Thus, mutations in the VHL gene and SDHB and SDHD might lead to increased activation of hypoxic signaling pathways leading to abnormal proliferation.

In multiple endocrinopathy-2 (MEN-2) syndromes, mutations in the *RET* proto-oncogene lead to constitutive activation [activating mutations] of the receptor tyrosine kinase. The end result is hyperplasia of adrenomedullary chromaffin cells [and in the parathyroid, calcitonin-producing parafollicular cells]. In time, these cells undergo a high rate of neoplastic transformation. It now also appears that apparently sporadic chromaffin tumors may contain mutations in these genes as well.

Hypertension with Brachydactyly [OMIM #112410]

Hypertension with brachydactyly, also called brachydactyly, type E, with short stature and hypertension (Bilginturan syndrome), was first described in 1973in a Turkish kindred [89]. Affected persons have shortened phalanges and metacarpals, as well as hypertension. Linkage studies performed in the 1990s mapped this form of hypertension to a region on chromosome 12p, in the region 12p12.2 to p11.2 [90, 91].

Patients with this form of hypertension have normal sympathetic nervous system and renin-angiotensin system responses. In 1996, some abnormal arterial loops were noted on MRI examinations of the cerebellar region. There was speculation that this abnormality could lead to compression of neurovascular bundles that would lead to hypertension [92]. Another family, in Japan, also had similar findings, and a deletion in 12p was reported in that family [93].

There are several candidate genes in the region – a cyclic nucleotide phosphodiesterase (PDE3A) and a sulfonylurea receptor, SUR2, which is a subunit of an ATP-sensitive potassium channel. It was hypothesized that there could be "a chromosomal rearrangement between the candidate genes PDE3A/SUR2/KCNJ8 for hypertension and SOX5 for the skeletal phenotypes, separated by several megabases" (summarized in reference [94]). It then appeared, in studies using bacterial artificial chromosomes, that there was an inversion, deletion, and reinsertion in this region. It appears currently that rather

than a mutation in a single gene, this form of hypertension is caused by the chromosomal rearrangement.

Other Forms of Mendelian Hypertension

In addition, there have been reports of severe insulin resistance, diabetes mellitus, and elevated BP caused by dominant-negative mutations in human peroxisome proliferator-activated receptor gamma (PPARγ), a transcription factor [95].

PPARγ is important in the differentiation of adipocytes (reviewed in Meirhaeghe and Amouyel [95]). Mutations in PPARγ have been linked to a group of symptoms, including hypertension. Only eight persons have been described to date and have point mutations that are heterozygous (V290M, R425C, P467L, and F388L) [95–99]. The affected patients have had marked insulin resistance, then develop type 2 diabetes, and have dyslipidemia, as well as hypertension. The finding of these patients has been taken widely as a demonstration of the importance of PPARG in metabolic syndrome and in blood pressure control.

There has also been a description of hypertension, hypomagnesemia and hypercholesterolemia due to an abnormality in mitochondrial tRNA. In this case, there is impaired ribosomal binding due to a missense mutation in the mitochondrial tRNA [100].

When to Suspect Monogenic Hypertension

Table 6.3 lists those situations in which the astute clinician should consider monogenic hypertension [8]. These include both clinical and laboratory findings that should point toward further evaluation. Significant among these are a strong family history of hypertension and early onset of hypertension, particularly when the BP is difficult to control within the family. Low plasma renin activity, along with hypokalemia, should also point toward the possibility that a defined form of hypertension may be present.

Table 6.3 When to suspect a hypertensive genetic disorder

Patient is an at risk member of a kindred with a known monogenic hypertensive disorder (e.g., multiple endocrine neoplasia, syndromes)
Patient is a hypertensive child with hypokalemia whose first-degree relatives have hypokalemia and/or hypertension
Patient with juvenile onset of hypertension, particularly if plasma renin is suppressed
Patient has physical findings suggestive of syndromes or hypertensive disorders (e.g., retinal angiomas, neck mass, or hyperparathyroidism in patient with a pheochromocytoma)

Adapted from [8]

Non-Mendelian, Polygenic Hypertension

The genetic contribution to a prevalent condition such as essential [primary] hypertension is widely considered to involve multiple genes and is thus termed polygenic. The possibility for determining the genes that are involved seems far more feasible in the current genomic era, yet clear identification has proved elusive, in part because BP is a continuous variable, and the contribution of any one gene appears to be small. Relevant background for considering the genetic factors predisposing toward hypertension follows:

Experimental Hypertension as a Tool to Investigate Polygenic Hypertension

Many studies in inbred experimental animals, mainly rats and mice, have aimed to identify genes controlling BP (see Chap. 8). In the 1980s, it was estimated that 5–10 genes control BP [101]. In 2000, Rapp summarized available research and estimated that 24 chromosomal regions in 19 chromosomes were associated with hypertension in various rat strains [102]. A recent review by Delles et al. [103] notes that candidate QTLs (quantitative trait loci) have been identified on nearly every chromosome. Studies using inbred rat strains, however, did not identify polygenes and their associated alleles [104].

A large number of chromosomal regions and some candidate genes have also been suggested from experimental studies in mice. For example, targeted gene deletion studies have shown an effect on BP in more than a dozen genes, among which are endothelial nitric oxide synthase, insulin receptor substrate, the dopamine receptor, apolipoprotein E, adducin-alpha, the bradykinin receptor, and the angiotensin type 2 receptor, as well as other members of the RAAS [105].

Genetic manipulation in mice has been successful in exploring contributions of various candidate genes (reviewed in [106]), most notably those of the RAAS through two approaches, overexpression of a given gene [with "transgenic" animals [102]] and deleting gene function [with "knockouts"]. An additional approach is to use gene targeting in embryonic stem [ES] cell cultures [107–109].

Inbred strains rather than transgenic or knockouts have led to important findings [109–112]. A number of studies, notably those of Jacob et al. [109] and Hilbert et al. [110], found linkage in a rat model of hypertension that pointed to the angiotensin-converting enzyme (ACE) gene as important in determining hypertension. Since those reports of more nearly 20 years ago, a large number of clinical studies have suggested a link between ACE polymorphisms in humans and hypertension. See a recent commentary on the value of studies in the rat model [103, 111].

Human Hypertension

A variety of studies have pointed to a link between human hypertension and genes of the RAAS (summarized in references [112, 113]). However, in common diseases such as hypertension, it may be more productive to consider susceptibility alleles rather than disease alleles per se. Furthermore, some people carrying a particular susceptibility allele may not have the disease, either because they do not have the environmental exposure that causes the condition to develop or because they lack another allele [or alleles] that are needed to cause a given clinical problem. Because there are multiple potential interactions, and susceptibility alleles are generally common, following a given allele through pedigrees is difficult. In such a circumstance, segregation analysis is difficult, particularly if a given susceptibility allele has a small effect. Indeed, to date, linkage has been reported on most chromosomes in humans [114–129].

While linkage analysis may constitute an initial step (3–6), it is not as powerful a tool in polygenetic conditions as it is in Mendelian diseases, because many people without the disease may carry the susceptibility allele. Using affected siblings [sib pairs] may be helpful to gain more understanding of the possible genetics (see Fig. 6.2). Siblings who are both affected with a given problem such as hypertension would be anticipated to share more than half their alleles near or at the susceptibility locus, and the chance of this occurrence is then calculated (3–6). A LOD score of greater than 3.6 is taken as evidence of a linked locus, which is often very large (in the range of 20–40 cM). Once a putative linkage is confirmed in a replicate study, finer mapping can be performed to hone in on the genetic region that contains the putative gene. This is done via linkage disequilibrium or association testing between disease and genetic markers, often with single-nucleotide polymorphisms (SNPs). SNPs occur roughly every 1,000 base pairs and lend themselves to automated testing. Using SNPs, a broad region (10–40 cM) can be narrowed to a far smaller region of roughly 1×10^6 base pairs [121, 122].

Genome-wide screens of the human genome aiming to discover hypertension genes have suggested many loci of interest [123, 124]. These genome-wide screens have included subjects with diverse phenotypes and ethnicity; furthermore, selection criteria have varied. The numbers and composition of families have ranged from single, large pedigrees to more than 2,000 sib pairs from 1,500 or so families [123]. Using genomic scan data from four partner networks the US Family Blood Pressure Program (FBPP) [124] sought to use phenotypic strategies that reflect the ethnic demography of the USA. A 140–170 cM region of chromosome 2 was linked to hypertension in several populations – Chinese sibling pairs [120] and Finnish twins [115], as well as a discordant

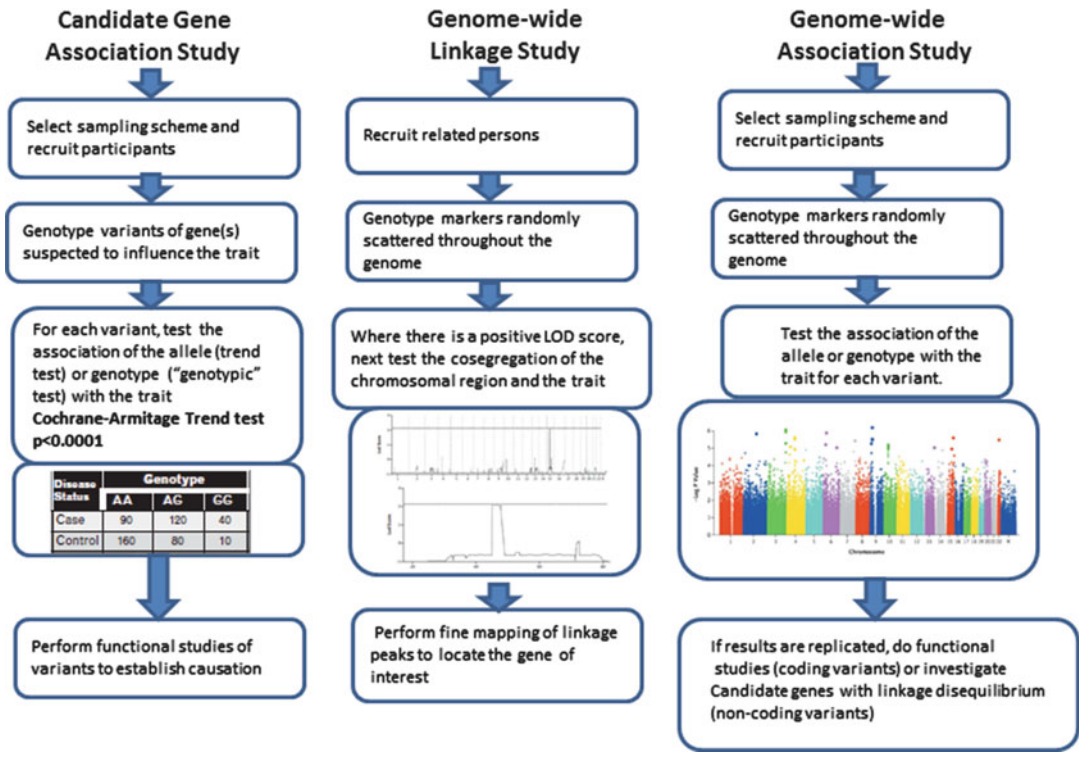

Fig. 6.2 Study designs used to dissect the genetic architecture of common complex traits. This figure shows the flow of studies that utilize candidate gene approaches, genome-wide linkage studies and genome-wide association studies (After Simino J, Rao DC, Freedman BI. Novel findings and future directions on the genetics of hypertension. Curr Opin Nephrol Hypertens. 2012;21(5):500–7, with permission. Insets for genome-wide linkage and genome-wide association studies are from Graphic Arts, the New England Journal of Medicine, with permission)

sibling-pair screen. Recently Caulfield et al. phenotyped 2,010 sib pairs drawn from 1,599 families with severe hypertension as part of the BRIGHT study [Medical Research Council **BRI**tish **G**enetics of **H**yper**T**ension] and performed a 10 cM genome-wide scan [125]. Their linkage analysis identified a locus on chromosome 6q with a LOD score of 3.21 and genome-wide significance of 0.042. However, this locus is at the end of chromosome 6, and the end of a chromosome may generate errors; thus, caution is required in drawing conclusions from these findings. The Caulfield group also found three other loci with LOD scores above 1.57 [125]. One of these loci was the same as that found in the Chinese and Finnish studies [125].

Within the last few years, there have been further genome-wide association studies (GWAS) concerning hypertension reported [130, 131]. In 2007 Levy et al. used an Affymetrix 100 k chip platform and performed a GWAS with the Framingham cohort, yet the initial analysis did not find significance for any single gene [132]. Using the Wellcome Trust Case Control Consortium [WTCCC] and an Affymetrix 500 k chip, another GWAS was reported in 2007, and it, too, did not reach genome-wide significance for any gene [133]. However, a study in which the subjects were from the Korean general population most recently reported genome-wide significance, though a very small effect for the ATPase, Ca++-transporting, plasma membrane 1 (*ATP2B*) gene [134]. These rather disappointing results from GWAS studies on hypertension are discussed to indicate the complexity of primary hypertension.

Two consortiums have reported some more encouraging results. The Global BPgen group examined 2.5 million genotyped or imputed SNPs

in 34,433 persons of European background and found eight regions that reached genome-wide significance. These regions were associated with hypertension and lie in close proximity to genes for CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, ZNF652, and PLCD3 and to the chromosome 10 open reading frame 107 (c10orf107) [135]. Further, the so-called CHARGE consortium [136] looked at 29,136 participants and studied 2.5 million genotyped or imputed SNPs; they reported significant associations with hypertension for 10 SNPs and with systolic BP for 13 SNPs and for diastolic BP with 20 SNPs. Their findings plus those of Global BPgen were then subjected to a meta-analysis, and this led to findings of genome-wide significance for a number of genes associated with elevated BP or with systolic or diastolic BP [135]. These included the *ATP2B* gene, as well as *CYP17A1* (steroid 17-alphamonooxygenase), *CSK-ULK3* (adjacent to c-src tyrosine kinase and unc-51- like kinase 3 loci), *TBX3-TBX5* (adjacent to T-box transcription factor TBX3 and T-box transcription factor TBX5 loci), *ULK4* (unc-51-like kinase 4), *PLEKHA7* (pleckstrin homology domain containing family A member 7), *SH2B3* (SH2B adaptor protein 3), and *CACNB2* (calcium channel, voltage-dependent, beta 2 subunit) [135].

Candidate Genes

Another approach in assessing polygenic hypertension is to use candidate genes – genes that already have a known or suspected role in hypertension – that are present near the peak of observed genetic linkage. If the full sequence of the candidate gene is known, then it is relatively easier to go forward.

In the Caulfield study [125], for example, there are a number of candidate genes that are within the linkage analysis-identified areas on chromosomes 2 and 9. Genes that encode serine-threonine kinases, STK39, STK17B are on chromosome 2q; PKNBETA, a protein kinase, is on chromosome 9q; G protein-coupled receptors on chromosome 9 – GPR107 9q and GPR21 on 9q33; and on 2q24.1 there is a potassium channel, KCNJ3.

Use of microarrays to identify differential expression of expressed sequences in tissues from affected and unaffected persons has become common. These arrays are available either as full-length cDNAs or as expressed sequence tags (ESTs)

Candidate Susceptibility Genes

A number of genes have become candidates as susceptibility genes, particularly those of the RAAS. A number of such genes were associated with hypertension and cardiovascular regulation in the pre-genomic era. Many associations have been described or imputed, including not only members of the RAAS but many other genes**.** For example, Izawa et al. [128] chose 27 candidate genes based on reviews of physiology and genetic data that looked at vascular biology, leukocyte and platelet biology, and glucose and lipid metabolism. They then also selected 33 SNPs of these genes, largely related in promoter regions, exons, or spliced donor or acceptor sites in introns and looked at their relationship to hypertension in a cohort of 1,940 persons. They found that polymorphisms in the CC chemokine receptor 2 gene were associated with hypertension in men and the TNF-alpha gene was associated with it in women [117]. In a GWAS in African Americans, Adeyemo et al. [137] suggested that pathway and network approaches might be helpful in identifying or prioritizing various loci.

Variants or Subphenotypes

If a particular variant of a complex disease is clinically distinct, then analysis of so-called subphenotypes via positional cloning may be potentially illuminating [3–5, 118, 120]. In such an instance, there may be fewer susceptibility genes involved. However, subphenotypes may be difficult to study, as the physiology involved may be intricate. An example would be salt-sensitive hypertension [118]. In order to study subjects, it is necessary to perform careful metabolic studies that confirm the subphenotype [hypertension with salt sensitivity] and also is standard during testing.

Present Implications for Pediatric Hypertension

A search for monogenic forms of hypertension is clearly indicated in an infant, child, or teenager with elevated BP and history or signs compatible with one of these diagnoses. If a child is found to have one of the rare forms of monogenic hypertension, there will be specific therapy. Few data, however, exist to guide the clinician in terms of the roles polygenic hypertension in children at the present time. Current approaches, summarized in Fig. 6.2 and in recent reviews [138–144], would still indicate that the concept of a complex set of interactions leads to most cases of hypertension.

Another approach worth mentioning is that of genome-wide admixture mapping – mapping by admixture linkage disequilibrium (MALD), which is used to detect genes in populations that are mixed, for example, where one group's ancestors have more of a given disease than another group [139]. Using a moderate number single-nucleotide polymorphisms (SNPs), this method determines regions in the genome that contain more SNPs from one ancestral group as compared to the others. Then honing down on the area, genes of interest may be found. This approach is very appealing as a means by which to study hypertension in African Americans [145, 146]. For example, MALD was used to find a linkage peak in persons with African ancestry, which has turned up two apolipoprotein L1 (APOL1) variants in the coding region, as well as an adjacent area in the myosin heavy chain 9 gene (MYH9), which are associated with focal segmental glomerulosclerosis and hypertension.

There is no doubt that varied genetic mechanisms that lead to primary hypertension remain to be delineated. In the future gene-environment interactions, pathways that involve multiple gene products, as well as epigenetic phenomena, will be explored. Ultimately, there may be pharmacogenetic approaches by which therapy for hypertension may be individualized.

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