Genetics, Hypertension, and Cardiovascular Disease

by Mark Houston, MD

Editor Note: This article is Chapter 11 in the book *Controlling High Blood Pressure Through Nutrition, Supplements, Lifestyle, and Drugs* by Mark Houston, MD, and Lee Bell (CRC Press, Taylor & Francis, LLC; 2021). Dr. Houston also published a new book, *The Truth About Heart Disease* (CRC Press, Taylor & Francis, LLC), in 2022. Both books are available at Amazon, and bulk orders may be obtained from the publisher.

If one of your parents had high blood pressure, you have a 25% chance of developing high blood pressure yourself. If both parents had high blood pressure, then the risk is about 50% that you will have high blood pressure. If your parents or a sibling developed high blood pressure before the age of 50 years then your risk is even higher to develop high blood pressure, but it will also occur at an earlier age. Numerous genes that cause hypertension can be specific for treatment with a drug, a supplement, an electrolyte, and with a diet or nutrition. There are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes underlying the concept of "family history of hypertension." This genetic testing will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized, and precision treatment program without any of the guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs, less cost, and better cardiovascular outcomes. The Cardia X genetic profile from Vibrant Labs America in San Francisco measures 25 genes related to cardiovascular disease and hypertension. The "family history" is your primary risk factor to develop high blood pressure and now you can find out what the specific genes are in many cases.[1-65]

Genetics and nutrigenomics (the effect of nutrition and supplements on genes) provide us with an expanded perspective on the prevention and treatment of hypertension and cardiovascular disease. In cardiovascular management, nutrigenomics encompasses genetic testing and the identification of single nucleotide polymorphisms (SNPs), nutrient-genetic interactions, and how the genes express themselves. The genes may be "turned on" or "turned off" by nutrition, supplements, drugs, and other environmental factors. This is referred to as gene expression.[1-65]

Most genetic expression is driven by inflammation, and the majority of the genes, once turned on, promote an inflammatory response. Most of the active areas on genes associated with hypertension, heart attack, heart failure, and coronary heart disease are expressed through inflammation, oxidative stress, and immune-vascular dysfunction. A similar dynamic is evident in the vascular system. Regardless of the type of insult, blood vessels respond to insults via these same three mechanisms: inflammation, oxidative stress, and immune-vascular dysfunction.[1-65]

Consequently, the inflammatory pathways have become the primary focus in the management of genetic expression and of genetic risk for hypertension and cardiovascular disease. The prevention and the reduction of cardiovascular disease hypertension are not likely to improve without using genetic testing. Let us look at some of these influences on your genes such as nutrients, diet and nutrition, electrolytes, supplements, and drugs.[1-65]

Nutrients. Nutritional factors provide information that determines whether our genes are turned on or turned off, with a corresponding beneficial or detrimental outcome. One change in a single nutrient such as magnesium may cause 300 different changes in downstream mediators related to cardiovascular function and health. This is just one example of environmental influences and the importance of genetic expression. When there is interference with a metabolic pathway, a single area of abnormality can result in a myriad of defects and a spoke-like effect, resulting in a ripple of downstream changes in many metabolic pathways.

Epigenetics. There are several issues we want to define in patients. One is their genetic profile, the genes they were dealt. There are also epigenetic influences that are not genetic that alter the function of DNA that are termed methylation, histone modification, and non-coded messenger RNA function. These influences are not in the genetic code but can be passed on from mother to fetus and from generation to generation. For example, a mother that is malnourished during pregnancy is more likely to have a child that develops hypertension later in life. This risk for hypertension can then be passed on "epigenetically" to future generations. The final aspect is gene expression, as genes express themselves in response to nourishment or insults from different types of information coming in from the environment. Genetics have become

important in determining not only dietary intake but also medication use in many patients, based on their genetic profile.

Diet

Mediterranean diet. We know the Mediterranean diet (MedDiet) turns on numerous beneficial genetic pathways that can reduce the risk for hypertension, cardiovascular disease, as well as the risk for type II diabetes. If you consume a Western diet, it will result in totally different outcomes in terms of gene expression, since most of the foods included in a Western dietary pattern have been shown to express 30–40 different inflammatory and immune pathways.

The MedDiet has an advantageous effect on many genes. In a clinical trial of this diet, other prevalent beneficial effects were related to atherosclerosis and hypertension. The MedDiet, in combination with CoEnyme Q 10 (CoQ10), has been shown to be the most beneficial intervention for healthy aging, preventing processes and diseases related to chronic oxidative stress, hypertension, and coronary heart disease. Changes in genetic expression toward a protective mode were often associated with improvement in systemic markers for inflammation, immune function, oxidative stress, hypertension, and coronary heart disease.

Pritikin and DASH diets. The Pritikin diet is one of the most effective ways to turn off the gene expression that increases the risk for hypertension and cardiovascular disease. The Pritikin diet can reduce risk of cardiovascular disease by as much as 30–35%. That benefit is directly correlated with the diet itself but is also enhanced when supplementing with nutrients such as CoQ10. The DASH-1 and DASH-2 diets have also been found beneficial in relation to changes in inflammatory genes, reducing the blood pressure, and improving the response to the types of medications prescribed for hypertension.

Specific Nutrients

Electrolytes. The electrolytes, particularly sodium, potassium, and magnesium, can change genetic expression, salt sensitivity, intravascular volume, blood pressure, risk for coronary heart disease, heart attack, cardiac arrhythmias, and congestive heart failure. In terms of salt sensitivity, one of the most important is cytochrome P4A11 (expressed as CYP4A11), which relates to sodium and water diuresis and the role of the epithelial sodium channel (ENaC) function in the kidney tubules. Patients who have resistant hypertension due to CYP4A11 and are treated with the drug amiloride have dramatic reductions in blood pressure and often can discontinue or reduce the dose of other antihypertensive drugs.

Omega 3 fatty acids. Omega 3 fatty acids affect a large number of genes that reverse changes in our metabolic profile and in our genes that can improve mitochondrial health. As a result, adenosine tri-phosphate (ATP) production goes up, cells are healthier, and patients live longer. ATP is the energy produced by the mitochondria in our cells from metabolism of our food. The mitochondria are like small "nuclear power plants". We know that omega 3 fatty acids by themselves have dramatic effects on many receptors that can have enormous influences, reversing inflammation, oxidative stress, blood pressure, and risk for heart disease. In specific studies, omega 3 fats changed expression of 610 genes in men and 250 genes in women.

Monounsaturated fats. Olive oil and nuts contain monounsaturated fat that will have a positive impact on different SNPs and receptors, improving hypertension, coronary heart disease, and diabetes mellitus. Even without the MedDiet, olive oil and nuts given as a supplement can have dramatic and highly beneficial influences on genetic expression related to the three finite vascular responses for reducing blood pressure and cardiovascular disease.

Genes Relevant to Cardiovascular Risk

Every patient should have their cardiovascular genetics tested by their physician (Tables 11.1 and 11.2). The recommended lab is Vibrant America Labs. The genes are as follows:

Gene 9p21. One of the primary genes we are now measuring is the 9p21 gene that increases the risk of atherosclerosis, coronary heart disease, and heart attack. Patients who have a heterozygote SNP (1/2 of the gene) for 9p21 have a risk for heart attack that is increased by 50%. When a patient has a homozygote SNP (both halves of the gene), the risk goes up to approximately 100%. However, there are many other genes that should also be evaluated, not just for coronary heart disease but also for hypertension and dyslipidemia (abnormal cholesterol).

Genes may be "turned on" or "turned off" by nutrition, supplements, drugs, and other environmental factors.

GLU 1q25 increases the risk of heart disease and heart attack in diabetes mellitus.

Apo E4 genotype. The Apo E4 genotype increases risk for coronary heart disease and heart attack. Management of risk factors for patients with the APO E4 allele, especially with the homozygote E4/E4 type, addresses issues such as:

- Increased cholesterol absorption and delayed clearance, resulting in higher serum LDL cholesterol (the bad form of cholesterol).
- Increased coronary heart disease risk with smoking and alcohol intake and overall increased incidence of heart attack, Alzheimer's disease, and dementia.
- Inability to repair the vascular endothelium to produce nitric oxide, which may increase blood pressure.
- Less response to statins to lower cholesterol.
- Best reduction of LDL occurs through dietary restriction of carbohydrates, with low fat diets, and omega 3 fatty acids.

COMT polymorphisms. One of the newest genes that we're looking at is COMT (catechol-*O*-methyltransferase), which provides instructions for the breakdown of norepinephrine and epinephrine (adrenalin from the adrenal glands). If this genetic SNP is present, the patient will have higher levels of norepinephrine and epinephrine in the blood and urine and an increased risk

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of hypertension, coronary heart disease, and heart attack. There is a variation in response depending on which of the specific COMT SNPs the patient carries; for example, aspirin or vitamin E may be beneficial for patients with one type of COMT SNP but detrimental if one of the other SNPs is present.

Glutathione-related SNPs. The risk of myocardial infarction can be increased by 71% if a SNP affecting glutathione metabolism (GSH-Px, glutathione peroxidase) is present. This selenium-dependent enzyme expresses different capacities to neutralize oxidative molecules related to increases in oxidative stress and cardiovascular disease. For these patients, glutathione peroxidase and selenium levels would be key measurements to track for the risk of heart attack:

- Low GSH-Px is a major coronary heart disease risk factor.
- Higher levels of glutathione peroxidase support more rapid recycling of glutathione, resulting in higher availability of glutathione that is one of the most important antioxidants inside the cell.
- Increased glutathione peroxidase (GSH-Px) decreases blood pressure and heart attack.

Genes Relevant to Hypertension

There is a whole host of genetic influences on blood pressure, probably over 30 different genes that we have recognized to date, all of which are helpful in determining both risk for hypertension and risk for cardiovascular target organ damage (Tables 11.1 and 11.2)

These genes are also helpful to determine the response to diet and nutrition, various nutrients, supplements, electrolytes, caffeine, and medications.

P-450-1A2. We know, for example, that someone who consumes caffeine in the form of caffeinated coffee and tea, and has the SNP, cytochrome P-450-1A2 and is a slow metabolizer of caffeine, will increase their risk of tachycardia, hypertension, aortic stiffness, and myocardial infarction. Of course, one could have the right type of SNP for caffeine detoxification and that will reduce their risk. The risk of having this gene is about 50% of the population. The 50% of the population with this gene are slow metabolizers of caffeine, and their risk for hypertension and heart attack actually go up directly based on the amount of caffeine consumption and their age. Before you drink caffeine (coffee, tea), you need to check the gene for cytochrome P-450 function.

TABLE 11.1 Recommended Genetic Testing (Vibrant America Labs)

1. 9p21 (GG/CC) (inflammation, plaque rupture, thrombosis, aortic aneurysms atherosclerosis, coronary heart disease, heart attack, and diabetes mellitus)
2. 6p24.1 (coronary heart disease)
3. 4q25 (atrial fibrillation)
4. ACE I/D (DD allele) (hypertension, left ventricular hypertrophy, renal failure, coronary heart disease, heart attack, carotid disease, kidney failure, and microalbuminuria)
5. COMT: Val/Val or Met/Met allele (coronary heart disease, heart attack hypertension)
6. 1q25 (GLUL) (coronary heart disease in diabetes)
7. APO E (E4/E4) (coronary heart disease, lipids, dietary response to fats)
8. MTHFR (A1298C and C677T) for methylation (endothelial dysfunction, hypertension, thrombosis, coronary heart disease, heart attack, stroke, and hyper-homocysteinemia).
9. CYP 1A2 (IF/IF) and caffeine (hypertension, heart attack)
10. Corin (hypertension, volume and sodium, heart failure, and preeclampsia and eclampsia)
11. CYP 11 B2 (TT allele) (hypertension and aldosterone)
12. GSH-Px (glutathione peroxidase) (ALA-6 alleles, selenium) (CHD and MI)
13. NOS 3 (nitric oxide, HBP, and CHD)
14. ADR B2 (AA allele vs GG allele) (HBP and DASH diet and drugs)
15. APO A1 and A2 (lipids)
16. CYP4AII and CYP4F2 (HBP, sodium and volume overload, and ENac) (amiloride)
17. MMP-2, MMP-9, and TIMP-1 (cardiovascular remodeling, DD, LVH, CHF, and hypertension)
18. AGTR1, NR3C2, HSD11B1, and B2 (HBP, potassium) and AGTR1 (AA/AC) and ARB response
19. AT1R-AA (AT1R autoantibodies); hypertension (ARB vs ACEI)
20. Blood group type A, B, and AB (vWF and thrombosis)

CYP 11 B2. The CYP 11 B2 is related to resistant hypertension, salt and water retention, increased blood volume, high aldosterone levels, and low blood potassium that can be treated with the drugs spironolactone or eplerenone. These patients may be on four or more drugs for hypertension, and it is still not controlled. This may be a cause of hypertension in 20% of the population that is resistant to other drugs. Once the correct blood pressure medication (spironolactone or eplerenone) and dose is started, in about 6–8 weeks, the blood pressure will decrease often to normal and the previous medications can be stopped. We will review these blood pressure-lowering drugs later in this book.

CYP4A11. Also, in terms of salt sensitivity and resistant hypertension, one of the most important is cytochrome P4A11 (expressed as CYP4A11), which relates to sodium and water diuresis and the role of the ENaC function in the kidney. These patients have an avid reabsorption of sodium in the kidney tubules from the ENaC, which increases the blood volume and blood pressure. Most of these patients have resistant hypertension and are taking three or four drugs, and their blood pressure remains elevated. Patients who have resistant hypertension due to CYP4A11 and treated with the drug amiloride have dramatic reductions in blood pressure and often can discontinue or reduce the dose of other antihypertensive drugs within 2 months. We will review these blood pressure-lowering drugs later in this book.

ACE I/D. The ACE I/D (DD allele) is associated with hypertension, left ventricular hypertrophy (enlargement of the heart), coronary heart disease, heart attack, carotid disease, kidney failure, and microalbuminuria (loss of the protein, albumin, in the urine due to damage of the kidney) These patients respond well to the blood pressure-lowering class called ACEI, or angiotensin-converting enzyme inhibitors. We will review these blood pressure-lowering drugs later in this book.

COMT (Val/Val or Met/Met allele) is causative of hypertension due to high levels of norepinephrine and epinephrine (adrenalin). These hormones cause the

arteries to constrict, become inflamed with an increase in blood pressure.

MTHFR gene is related to methylation and folic acid and other B vitamins and if defective will cause hypertension

GSH-Px (glutathione peroxidase), if abnormal, increases oxidative stress in the artery and causes hypertension.

NOS 3 is an important enzyme in the production of nitric oxide that improves vascular health and lowers blood pressure. If the NOS 3 is defective, then blood pressure increases as does cardiovascular disease. Treatment with high a nitrate/nitrite diet with dark green leafy vegetables, like kale and spinach and with beets or some beet root extracts like NEO 40 will improve nitric oxide levels. We will discuss these treatments in the nutrition section of this book later.

ADR B2 gene is related to how effective the DASH diet will be in lowering blood pressure. If you have a defect in this gene then the DASH 2 diet results in a reflex increase in the enzyme, renin, with increases the formation of the potent vasoconstrictor angiotensin II that increases blood pressure. If this happens, giving an ACEI or ARB (angiotensin receptor blocker) will lower the blood pressure effectively with the DASH diet. We will review these blood pressure-lowering drugs later in this book.

AGTR1 (AT1R-AA) is related to autoantibodies and hypertension. An autoantibody is an abnormal antibody (part of your immune system that attacks your own organs, i.e., attacks "the self"). This autoantibody attaches to and stimulates a receptor called AT1R (angiotensin receptor I) that causes hypertension. ARBs are the most effective treatment to lower blood pressure in patients with this defective gene. We will review these blood pressure-lowering drugs later in this book.

TABLE 11.2
Additional Hypertension Genes

ADD 1,2,3: Adducin
ADM: Adrenomedullin
ADORA2A: Adenosine
NEDD4L
PPARG
STK39
CALCA
GNA 12 and S1: G protein
GNB3: G Protein
GRK 4: G protein coupled receptor kinase type 4
M235T: Angiotensinogen gene

As you can see, there are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes with the idea of "family history of hypertension." This will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized, and precision treatment program without the guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs, less cost, and better cardiovascular outcomes.

Cardiovascular SNPs. Obviously, there are large numbers of cardiovascular SNPs that we could check. At this point, I recommend testing for those that have the best validation, the highest correlation with risk prediction, and those that are easily attainable and have implications for a specific treatment. The genetic tests listed in Table 11.1 define risk for coronary heart disease, arrhythmias, heart failure, and hypertension; these are the genetic factors I recommend that you evaluate. From these tests, you will be able to determine the nutritional programs, medications, and other interventions that are the best.

Response to Specific Blood Pressure-Lowering Drug Classes

- Beta Blockers: rs1801253, GNA S1, ADR B1 GRK4
- Diuretics: ADD 1, GNB3, NOS 3, ACE, ADRBK1, CYP4A11 (amiloride) CYP11B2 (spironolactone and eplerenone), or GRK2
- ACEI: ACE I/D, ADR B1, and M235T
- ARB: ACE I/D, ADR B, AGTR1, and M235T
- Clonidine: GNB3
- CCB (calcium channel blockers) : ACE I/D
- Salt sensitivity: GRK4, M235T

Summary and Key Takeaway Points

1. If one of your parents had high blood pressure, you have a 25% chance of developing high blood pressure yourself. If both parents had high blood pressure, then the risk is 50% that you will have high blood pressure. If your parents or a sibling developed high blood pressure before the age of 50 years then your risk is even higher to develop high blood pressure, but also at an earlier age.
2. Numerous genes that cause hypertension are specific for treatment with a drug, a supplement, an electrolyte, or with a diet and nutrition. There are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes underlying the concept of "family history of hypertension." This will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized and precision treatment program without any guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs and less cost.
3. Evaluate specific genetic SNP's, for cardiovascular disease and hypertension, The Cardia X genetic profile from Vibrant Labs in San Francisco measures 25 genes related to cardiovascular disease and hypertension.
4. Traditional MedDiet with five tablespoons EVOO/day (50 g) and nuts and CoQ10 lowers blood pressure, cardiovascular disease, and diabetes mellitus.
5. Modified low-glycemic DASH 2 for hypertension is recommended. These patients especially respond related to the B2-AR AA/GG alleles.
6. Omega 3 fatty acids should be given to all patients, dose dependent (1–5 g/day to lower blood pressure and reduce cardiovascular disease.
7. Recommended intake of electrolytes is 2 g sodium, 5–10 g of potassium, and 1000 mg of magnesium per day.
8. Avoid caffeine in CYP 1A2 SNP (IF/IF and IF/IA alleles).
9. Selective use of ASA, vitamin E depending on COMT phenotype.
10. 20.5 methylfolate and B vitamins depending on MTHFR genotype for methylation.
11. Selenium should be given with GSH-Px gene if defective
12. Specific antihypertensive drug selection based on genotypes such as ACE I/D, CYPII B2, CYP 4A11, ADRB2, AGTR1, and AGTAA. ◆

References are available online at www.townsendletter.com.