FACULTAD DE MEDICINA
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TRABAJO FIN DE GRADO

Bases genéticas de la hipertensión arterial.

Genetic basis of arterial hypertension.

Autor: D. Xabier Oroz Redondo

Director: D. Gabriel Moncalian Montes

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TFG-Anexo I

Index

1. Abstract

When facing such a common condition as hypertension, it is common to take the environmental and lifestyle factors into account as an etiology, paying less attention to partially or fully genetic forms of hypertension. This review aims to summarize and describe each of the rare but already known monogenic syndromes and to inform of the current state of the undergoing research regarding polygenic forms of hypertension, in which great progress is being made thanks to genome wide association studies. In monogenic hypertension most of the pathophysiology is already known, with direct consequences of improvement in the areas of diagnose and treatment; on polygenic hypertension however, there is still a road ahead before reaching clinical applicability on a large scale.

2. Methods

Systematic review of scientific papers searching in PubMed, UpToDate and The Cochrane Library Plus, without date limit, taking into account papers written in English and Spanish. The Guidelines of both European and American heart associations were also reviewed. Abstract and full articles were reviewed according to the necessities.

3. Key words

Genetic hypertension, essential hypertension, monogenic hypertension.

Resumen

Ante una patología tan extensa y cotidiana como la hipertensión, es común que se piense en los factores relativos al estilo de vida como etiología, dejando de lado las etiologías pura o parcialmente genéticas. El objetivo de este trabajo es recopilar información acerca de los ya conocidos pero poco frecuentes síndromes monogénicos, así como informar sobre el estado actual de la investigación en el campo de las formas poligénicas de la hipertension

Métodología: Revisión sistemática de artículos científicos consultando las bases de datos Pubmed, Uptodate y The Cochrane Library Plus, sin restricción de fecha, en los idiomas español e inglés. Se revisaron también guías de las sociedades europea y americana de cardiología. Se revisaron abstracts y en los casos necesarios los artículos completos.

Palabras clave: Hipertensión genética, hipertensión esencial, hipertensión monogénica.

4. Introduction

Arterial hypertension (HT) has a high prevalence and is a major risk factor for the development of cardiovascular diseases. It is a major contributor to worldwide morbidity and mortality and hence poses a huge socioeconomic burden(**1**). There is a direct relationship between the incidence of high blood pressure (HBP) and the complications and diseases attributable to this incidence(**2**). However the threshold to diagnose a patient with HT has shifted during the years. The European Society of Cardiology sets the cutting points for HT diagnose at 140mmHg for systolic arterial pressure and/or at 90mmHg for diastolic arterial pressure(**3)**, while the American Heart Association sets the bar at 130mmHg for systolic arterial pressure and/o at 80mmHg for diastolic arterial pressure(**4)**. Nevertheless, both Associations agree that the threshold to start treatment should be the one the Europeans set for diagnose.

The estimated prevalence of HT in 2015 was of 1.13 billion, which translates into roughly 30% of the adult population worldwide(**5**),(**6**). This prevalence, although with some variations between countries, could be considered global even taking into consideration the economical differences across the globe(**5**). HT prevalence experiments an increase related to ageing, getting more and more common in the older age groups. People above 60 years old have a prevalence of HT larger than 60%(**5**). According to the way the global population is currently ageing, adapting a more sedentary lifestyle and increasing in body mass, future estimations point to a 15-20% increase in the HT prevalence by 2025. Thus, around 1.5 billion people will suffer from HT(**7**).

HBP was the main responsible for premature death in 2015 at a global scale.With almost 10 million premature deaths, and 200 million disability adjusted lost years (DALYs). HBP it is the leading cause in both categories(**8**). Despite the improvements that the fields of diagnose and treatment have experienced in the past 30 years, the DALYs attributable to HT have increased 40% since 1990(**8**). The most important factor when it comes to mortality and disabilities is the increase of the systolic blood pressure over 140mmHg. This factor is accountable for most of the HT related deaths, which include: 4,9 million deaths by ischemic heart disease, 2 million deaths by hemorrhagic stroke and 1,5 million deaths by ischemic stroke(**8**).

Despite being an asymptomatic and easily detectable disease, HT can cause severe and even lethal complications. The HT affected organs are mainly the heart, arteries, the kidneys, the brain and the retinas.

At cardiac level, chronically increased left ventricular workload in hypertensive

patients can result in left ventricular hypertrophy, impaired left ventricle relaxation, left atrial enlargement, an increased risk of arrhythmias, especially atrial fibrillation (AF), and an increased risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction(**3**).

At arterial level, HT can cause harm by altering the blood flow at both macrovascular and microvascular levels, causing endothelial dysfunction and arterial wall remodeling. These changes increase the risk of plaque formation and subsequently the risk of stroke. Thickening of the arterial wall increases the risk of ischemic conditions. In big arteries these changes cause stiffness, which is the pathophysiological basis of isolated systolic hypertension and is also related to multiple cardiovascular complications**(3**).

In the kidney, HT is the second leading cause of chronic kidney disease after diabetes mellitus. Among the injuries that HT can cause in the kidney we can find: tubulointerstitial necrosis, focal and diffuse glomerulosclerosis with loss of nephrons, chronic renal ischemia due to atherosclerosis, renal infarction or embolism; all of them leading to chronic renal failure. The pathophysiology behind renal damage and HT is a vicious circle of Na+ and volume reabsorption (**3**).

The brain on a patient with HBP is more at risk of suffering cerebrovascular diseases such as lacunar infarctions, intracerebral hematomas or thrombotic or embolic strokes. Besides, other HT manifestations at a central nervous system level include hypertensive encephalopathy, vascular dementia or microvascular brain damage(**3**).

In the retina HT can cause optic neuropathy, choroidopathy and most commonly, hypertensive retinopathy. In hypertensive retinopathy the increase of intraarteriolar pressure leads to endothelial disfunction, which causes plasma exudates in the vascular wall, causing greater luminal narrowing, which ends up producing fibrinous necrosis and papilledema that can cause blindness**(3)**.

5. Ethiological Classification

Most HT results from a combination of behavioral and environmental factors as seen in Figure 1**(4)**. However, various genetic mutations have been identified as distinct causes as well. These genetic forms of hypertension stem from gain- or loss-of-function mutations within the mineralocorticoid, glucocorticoid, or sympathetic pathways**(9)**. As a general way of classification, every genetic form of HT can be fitted into one of these 2large groups: primary (or essential) hypertension and secondary hypertension (**10**).

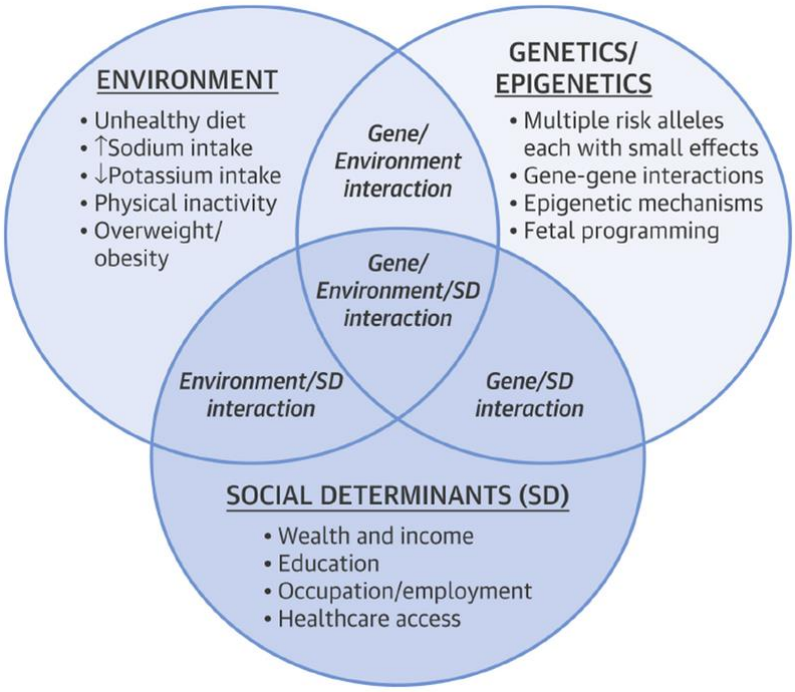

Figure 1. Venn diagram of the different factors associated with HT. Taken from(4).

Essential hypertension is the HT that by definition has no identifiable cause, while secondary HT is the result of an identifiable cause. The majority of hypertension (90-95%) falls under the definition of essential hypertension**(11**). Essential hypertension has traditionally been categorized as idiopathic, however this is only partially true because we are starting to have more and more information on genetic variations or genes that are overexpressed or underexpressed as well as the intermediary phenotypes that they regulate to cause high BP(**12**). Several environmental factors are known to increase blood pressure, including obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging, sedentary lifestyle, stress, low potassium intake, and low calcium intake, all of them can be purely environmental but they can all also be influenced by genetic predisposition. Furthermore, many of these factors are additive, such as obesity and alcohol intake(**13**), (**14**).

When it comes to the role of genetics in the heritability of HT, there are two main groups, polygenic and monogenic forms of HT.

The term, monogenic hypertension, is used to describe specific genetic hypertensive disorders which inhibit normal renal and/or adrenal blood pressure regulation. It is especially important to keep these rare conditions in mind when diagnosing HT in children, as the younger the child, the more likely that their hypertension is due to a secondary cause. Recent advancements in genetic sequencing methodology have provided further insight into these conditions(**15**). This means that monogenic forms of HT are well established rare syndromes, in which the diagnostic suspicion plays a main role since effective treatment is available. These syndromes are listed on table 1, which also classifies them according to their renin and aldosterone levels(**15**).

Low renin level	Low aldosterone levels	Liddle syndrome Congenital adrenal hyperplasia Apparent mineralocorticoid excess Gellers syndrome
	Normal aldosterone levels	Gordon syndrome (pseudohypoaldosteronism type II)
	High aldosterone levels	Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism) Familial hyperaldosteronism type II Familial hyperaldosteronism type III Familial hyperaldosteronism type IV
Adrenergic/sympathetic excess	High metanephrine and normetanephrine levels	Familial pheochromocytoma
Vascular smooth muscle proliferation		Hypertension and brachydactyly syndrome

TABLE 1. Basic classification scheme for causes of monogenic hypertension. Taken from **(15)**

On the other hand, polygenic HT is still much less clear. It is believed that essential hypertension is really polygenic, but there is still much research to be done. As of today, there are more than 50 different genes that have been linked to an increased risk of HT, and the list is still growing. The implementation of genome-wide association studies (GWAS) is responsible for many of these new findings**(16).**

In secondary HT there is a clear underlying cause that is recognized to be responsible for the HBP. The most common causes of secondary HT are: renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea and drug or alcohol induced HT**(4**). There are even more causes that have been found to cause secondary HT butthey are beyond the scope of this review, which focuses on the genetic aspects of essential HT, both polygenic and monogenic.

6. Genetics in Essential HT

a. Monogenic Hypertension

As seen on table 2(**15**), monogenic forms of hypertension are conformed by 11 well stablished syndromes, which all have the increase of blood Na+ absorption and the early onset of HT in common, but this comes because of different mechanisms. All these syndromes present low renin levels, but they can be further classified regarding aldosterone levels.

Low aldosterone syndromes include Liddle syndrome, congenital adrenal hyperplasia and apparent mineralocorticoid excess. Gordon syndrome or pseudo hypoaldosteronism type II have normal levels of aldosterone. The remaining familial hypoaldosteronisms (types I, II, III and IV) present themselves with high aldosterone levels, while familial pheochromocytoma and hypertension and brachydactyly syndrome fall outside of this classification as their pathophysiological pathways don't involve the renin-angiotensin-aldosterone chain.

All these 10 syndromes are explained more in depth in the following sections.

Condition	Mode of inheritance	OMIM phenotype number(s)	OMIM genotype numbers(s)	Cytogenetic loci
Liddle syndrome	Autosomal dominant	177200	600760 (SCNN1B) 600761 (SCNN1G)	16p12.2
Congenital adrenal hyperplasia	Autosomal recessive	202010 (type IV)	610613 (CYP11B1)	8q24.3
	Autosomal recessive	202110 (type V)	609300 (CYP17A1)	10q24.32
Syndrome of apparent mineralocorticoid excess	Autosomal recessive	218030	614232 (HSD11B2)	16q22.1
Gordon syndrome (pseudohypoaldosteronism type II)	Autosomal dominant	145260 (type IIA)	Unspecified	1q31-1q42
	Autosomal dominant	614491 (type IIB)	601844 (WNK4)	17q21.2
	Autosomal dominant	614492 (type IIC)	605232 (WNK1)	12p13.33
	Autosomal recessive or dominant	614495 (type IID)	605775 (KLHL3)	5q31.2
	Autosomal dominant	614496 (type IIE)	603136 (CUL3)	2q36.2
Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism)	Autosomal dominant	103900	610613 (CYP11B1)	8q24.3
Familial hyperaldosteronism type II	Autosomal dominant	605635	600570 (CLCN2)	3q27.1
Familial hyperaldosteronism type III	Autosomal dominant	613677	600735 (KCNJ5)	11q24.3
Familial hyperaldosteronism type IV	Autosomal dominant	617027	607904 (CACNA1H)	16p13.3
Familial pheochromocytoma	Autosomal dominant	171300	605995 (KIF1B)	1p36.22
			185470 (SDHB)	1p36.13
			613403 (TMEM127)	2q11.2
			608537 (VHL)	3p25.3
			600837 (GDNF)	5p13.2
			164761 (RET)	10q11.21
			602690 (SDHD)	11q23.1
			154950 (MAX)	14q23.3
Hypertension and Brachydactyly Syndrome	Autosomal dominant	112410	123805 (PDE3A)	12p12.2

Gene names are in parentheses next to the genotype number, where applicable. HTN, hypertension; ENaC, epithelial s chloride cotransporter.

TABLE 2 Monogenic forms of hypertension with involved genotypes. Taken from **(15)**

i. Liddle syndrome

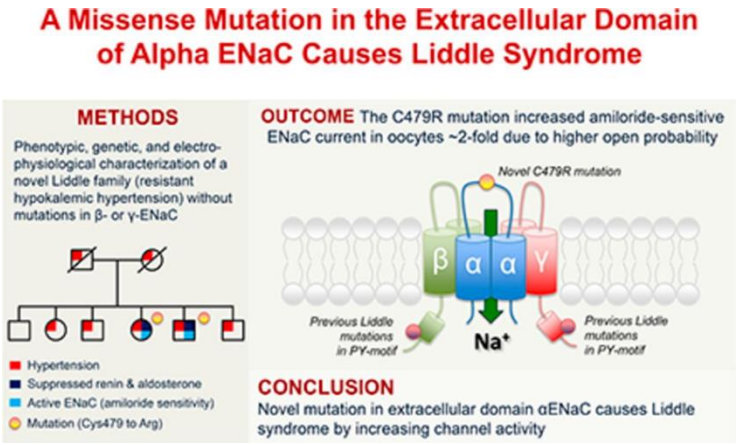

Figure 3: Causes and genetics of Liddle syndrome **(17)**.

Liddle syndrome was thought to only be caused by an autosomal dominant (AD) mutation which consists of a gain-of-function mutation β- or γ-subunit of the epithelial sodium channel present in the collecting duct, however, recent studies confirmed that a mutation in the α-subunit (while β- and γ-subunits were nonmutated) has also been found to cause this syndrome, this mutation is a missense mutation, as depicted on Figure 3**(17)**. The cytogenetic locus of this mutation is 12p13.31 for SCNN1A(OMIM 600228), 16p12.2 (OMIM 177200) for SCNN1B and SCNN1G (OMIM 600761). The epithelial sodium channel´s alpha, beta and gamma subunits,SCNNA1 SCNN1B and SCNN1G, respectively, are most commonly affected **(18)**. The disfunction of SCNN1B and SCNN1G results in disruption of the regulation of the process necessary to break down epithelial sodium channels (via disruption of expression of proline-rich regions of the cytoplasmic carboxyl terminus and results in loss of regulatory binding sites for Nedd4-2, a ubiquitin ligase that is in charge of the epithelial sodium channel breakdown)**(19)**. This leads to an excess of sodium reabsorption (gain of function) which ultimately leads to this form of genetic monogenic hypertension.

The excess of Na+ reabsorption responds only to the mutation of the epithelial Na channel, so the renin aldosterone hormonal axis tries to correct this, thus, both renin and aldosterone present low levels in this syndrome in an attempt to lower the blood Na+ concentration**(20)**. The continuous reabsorption of Na+ is also responsible for the hypokalemia, as the Na+ carries the K+ extrusion with it via the Na+/K-ATPase pump on the alpha-intercalated cells**(18)**. This exact mechanism is also the key to explain the mild metabolic alkalosis that appears in Liddle Syndrome, as the increased Na+ reabsorption increases the net negativity of the lumen, causing an increase in H+ extrusion via the renal outer medullary potassium channel and H+-ATPase pump, also located on alpha-intercalated cells**(21)**.

Liddle syndrome is an extremely rare disease, with only 31 new formal diagnoses registered since 2008. However it is considered as an underrecognized, and thus underdiagnosed, cause of HT by many nephrologists**(22)**. The age of onset of the HT in Liddle syndrome patients varies between late childhood and adolescence**(23)**. Some of those 30 cases have appeared without a family history, indicating a possible spontaneous mutation which lead to the syndrome, this supports the advice of including Liddle´s syndrome in every early onset HT´s differential diagnosis**(23)**. Even though Liddle´s can be suspected in a patient with story of familiar HT with low renin and

aldosterone levels, the definitive diagnosis requires genetic testing for SCNN1B, SCNN1A and SCNN1G**(24)**. Liddle syndrome is alternatively known as pseudohyperaldosteronism due to its similarity to hyperaldosteronism with hypertension, hypokalemia, and metabolic alkalosis**(25)**.

To treat Liddle´s syndrome, diuretics that target the renin-aldosterone axis, such as spironolactone, have proven to be ineffective because in Liddle´s the effect of this axis is not responsible for the augmented Na reabsorption**(26)**. Instead potassium sparring diuretics such as amiloride (only option during pregnancy) or triamterene show great results in keeping the HT in Liddle´s under control-These types of diuretics specifically target the epithelial Na+ channels, inhibiting them, thus counteracting the effect of the mutation of SCNN1B and SCNN1G, which is the pathophysiological basis of HT in Liddle´s syndrome**(27)**. A low Na+ intake is also part of the treatment and management of Liddle´s, as is it in most cases of HT**(23)**. The mechanism of the treatment is shown in Figure 4**(15)**.

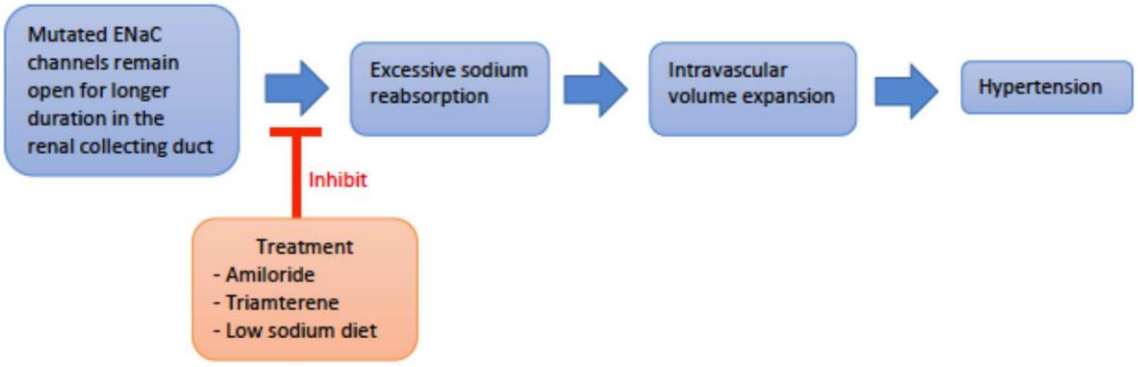

Figure 4: Treatment of Liddle´s syndrome**(15)**.

ii.Congenital adrenal hyperplasia

Congenital adrenal hyperplasia or CAH encompasses several autosomal recessive diseases that result from gene mutations for enzymes that mediate the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands**(28)**. Though 21a-hydroxylase deficiency is the most common, 11b-hydroxylase deficiency (11OHD or CAH type IV) and 17a-hydroxylase deficiency (17OHD or CAH type V), are two subtypes of CAH known to cause monogenic hypertension, so they will be reviewed more in depth than the others**(29)**. The respective enzymes regulate different steps in steroid synthesis, but 11OHD and 17OHD deficiency both cause elevated deoxycortisol and deoxycorticosterone levels. These intermediates have activity at the mineralocorticoid receptors. The overactivation of these receptors leads to HT and hyperkalemia. Both 11b-hydroxylase deficiency and 17a-hydroxylase deficiency are inherited in autosomal recessive fashion, which come from inactivating mutations that prevent the expression of these respective enzymes**(30)**. In the Figure 5**(15)** the normal synthesis of mineralocorticoids is depicted to visualize where the mentioned enzymes take part. These metabolites are active at

the mineralocorticoid receptor and are important in generating hypertension(15).

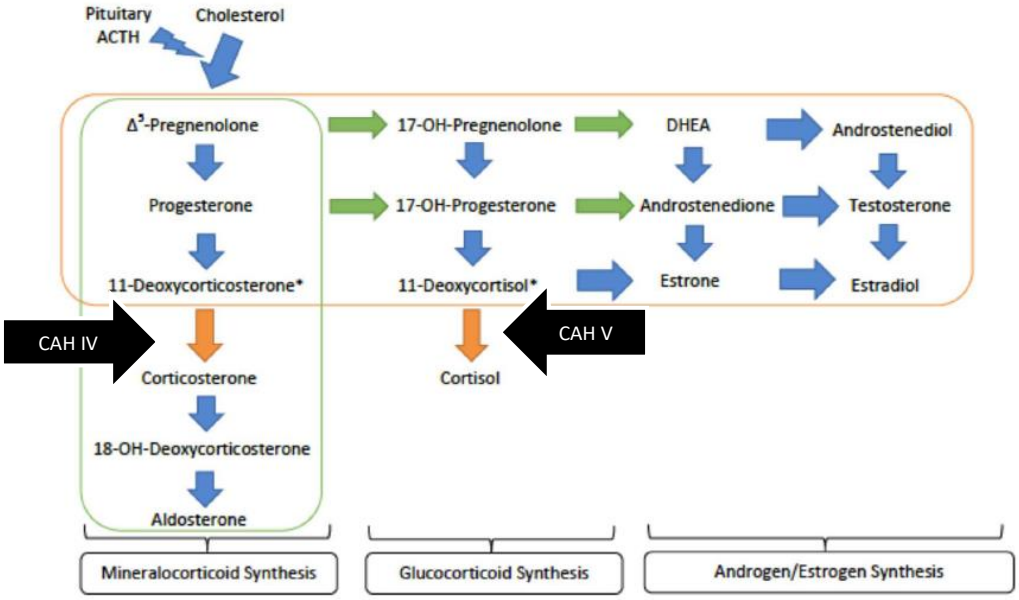

Figure 5: Steroidogenesis Pathways. The orange arrows show the activity of 11b-hydroxylase (deficient 1 in type IV) while the orange rectangle surrounds the steroid hormones still produced in CAH type IV. The green arrows denote the activity of 17a-hydroxylase (deficient in type V) while the green rectangle encircles those hormones produced in CAH type V. ACTH - adrenocorticotropic hormone; DHEA - dihydroepiandrosterone. **(15)**.

a. 11β-Hydroxylase deficiency (CAH-IV)

Absence or malfunction of 11b-Hydroxylase prevents the conversion of deoxycortisone and deoxycortisol into corticosterone and cortisol, respectively (Figure 5). Both deoxycortisone and deoxycortisol accumulate and even though they have weak activity at the mineralocorticoid receptor, the amount of metabolite ends up being enough to cause to produce a significant mineralocorticoid activity that leads to HT. As the conversion to glucocorticoids, androgens and estrogens are preserved, patients present high levels of deoxycorticosterone, deoxycoritsol and androgens, mainly androstenedione and dehydroepiandrosterone, which is key for diagnostic purposes. The diagnostic test used for this is stimulation of the axis with ACTH (adrenocorticotropic hormone) as high levels of the androgens coupled with HTN prove helpful in differentiating 11b-Hydroxylase deficiency from other causes of CAH and monogenic hypertension**(31)**. Prenatal diagnose is available by measuring 11b-Hydroxilase activity in amniotic urine**(32)**, but the confirmatory diagnose is made by a sequencing test for the CYP11B1 gene (cytogenetic locus 8q24.3)**(31)**.

11bHydroxylase deficiency is a rare condition that accounts for 5-8%of the CAH

cases**(33)**. Its prevalence rises to a 15% of CAH cases in certain populations such as Muslim Jewish or middle eastern populations**(34)**.

As the key step to form sexual hormones is also affected in this syndrome, CAH-IV patients present sexual development disorders, which can be found at birth. If the patient is a female the androgen accumulation will provoke a virilization, presenting ambiguous genitalia with enlarged clitoral fold at rest.(9) Both females and males will experience precocious puberty and hypertension onset at young ages.

Treatment consists of glucocorticoids in sufficient doses to lower ACTH secretion, inhibiting stimulation of steroid synthesis and accumulation of mineralocorticoid receptor agonists. Spironolactone, amiloride, and calcium channel blockers may be further used to treat hypertension. Further considerations include individualized therapy to accommodate sexual development, specifically in patients with genital malformations, it is more often females the ones who may need surgical correction**(35)**.

b. 17α-Hydroxylase deficiency (CAH-V)

Also known as P450C17a deficiency, is caused by a mutation on gene CYP17A1, on cytogenetic locus 10q24.32 which encodes the said enzyme. This enzyme has two key actions: 17α-hydroxylase and 17,20-lyase activity **(31)**. Its 17α-hydroxylase function generates 17α-hydroxypregnenolone and 17α-Hydroxyprogesterone, which can be converted to cortisol. These products of the 17α-Hydroxylase are also substrates for the

17,20-Lyase activity, which generates DHEA and androstenedione to serve as precursors for androgen and estrogen synthesis. This rare disorder thus blocks the production of cortisol as its direct precursors are not synthesized, shifting steroid production toward the mineralocorticoids (Figure 5). Since the blockage is so early in the pathway, there is very little production of sex hormones**(34)**. Clinically it manifests as hypogonadism, hypokalemia and HT. In males CAH-V causes ambiguity of the external genitalia and might even present a female phenotype in the external sexual organs. In females it causes primary amenorrhea and delayed sexual development or it may present solely as infertility**(36)**,**(37)**.

As a diagnostic approach, patients with early onset HT and hypogonadism should be tested using ACTH stimulation, which to be positive for 17α-Hydroxylase deficiency would need to show atypically elevated levels of pregnenolone and progesterone relative to their next metabolites in the mineralocorticoid synthesis chain (17α-pregnenolone and 17α progesterone respectively). It was believed to be a very rare condition, representing less than 1% of CAH but recent studies suggest that it might be an underdiagnosed disease**(38)**.

The target when treating this disease is the same as for 11βHydroxylase deficiency: glucocorticoids in sufficient doses to lower ACTH secretion, inhibiting stimulation of steroid synthesis and accumulation of mineralocorticoid receptor agonists. Spironolactone, amiloride, and calcium channel blockers may be further used

to treat hypertension. Addition of sex hormone therapy is also needed, depending of the degree of production shown by the serum levels of those hormones**(36)**.

iii. Syndrome of apparent mineralcorticoid excess

The syndrome of apparent mineralocorticoid excess (AME) is inherited in an autosomal recessive fashion. The genetic cause of this syndrome is an inactivating mutation of 11β-Hydroxysteroid dehydrogenase type 2 (HSF11B2), which inactivates cortisol to the less active metabolite cortisone. This gene is located on the chromosomal locus 16q22.1**(39)**. In physiological conditions the mineralocorticoid receptor´s prototypical ligand is aldosterone, but in AME the excess of cortisol is the one that activates this non-selective receptor. In individuals without pathology cortisol is expressed at much higher physiologic levels than aldosterone, HSD11B2 function is critical to maintaining proper control over mineralocorticoid receptor activation. With this mutation, cortisol is not metabolized and is able to bind to the mineralocorticoid receptor, leading to aldosterone like effects in the kidney**(40)**, as depicted on Figure6**(36)**. Excessive consumption of licore of Carbenoxolone may also induce AME, as they have the ability of activating the same receptor as cortisol does.

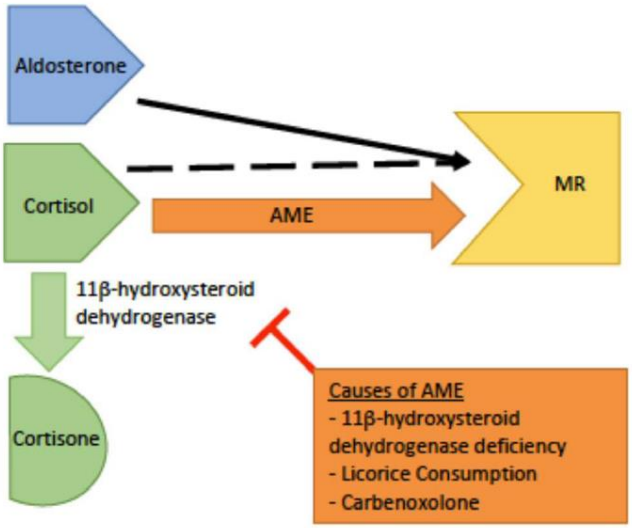

Figure 6: schematic of the pathophysiology of AME. Dashed arrow indicates normal binding of cortisol to the mineralocorticoid receptor. Orange arrow indicates AME, where due to 11b-dehydrogenase deficiency leads to increased levels of cortisol-mineralocorticoid receptor binding, causing hyperactivity **(15)**.

The spectrum of cortisol-mediated mineralocorticoid activation includes the classical AME syndrome, with 1 in a million affected, to less severe (nonclassic) forms of AME, the latter with a much higher prevalence (7.1%) than classic AME but different phenotype and genotype. Nonclassic AME (NC-AME) is mainly related to partial 11βHSD2 deficiency associated with genetic variations and epigenetic modifications (first hit) and potential additive actions of endogenous or exogenous inhibitors and other factors (ie, age, high sodium intake) (second hit).**(41)**

Diagnose is suspected when hypokalemia, metabolic alkalosis, hypoaldosteronemia with hyporeninemia and elevated cortisol to cortisone ratio (in 24h urine sample) are found. It is important to discard excess licorice or carbenoloxone consumption, as they may mimic the pseudohyperaldosteronism and are easily correctable.

Treatment consists of mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, along with potential potassium supplements and dietary sodium restriction **(42)**. Elevated cortisol levels may further warrant glucorticoid therapy to reduce ACTH-stimulated cortisol production and subsequent mineralocorticoid receptor stimulation **(43)**. Renal transplantation may be curative in some cases. NC-AME condition should benefit from low-sodium and potassium diet recommendations and monotherapy with MR antagonists**(44)**.

iv. Gordon syndrome

Gordon syndrome, also known as pseudohypoaldosteronism type 2 (PHA2), is a rare monogenic form of HT characterized by hyperkalemia, hyperchloremic metabolic acidosis and normal or elevated aldosterone levels**(45)**. Four families of genes are involved in the pathophysiology of Gordon syndrome: WNK1, WNK4, KLHL3, and CUL3, in loci 12p12.3, 17q21.2, 5q31.2, 2q36.2 respectively**(46)**. The first two mutations affect the Na+Cl- co-transporter. In WNK1 or WNK4 PHA2 patients, this transporter is not properly endocytosed by mediation of the ubiquitination, so it degrades, causing its upregulation, which leads to hyperchloremic metabolic acidosis and an increased Na+ absorption, responsible for HT. This PAH2 phenotype can be reached through a gain of function mutation on WNK4 or through a loss of function mutation in WNK1, this is explained because the WNK4 causes Na+ Cl- channel downregulation, an effect inhibited by WNK1. KHLHL3 and CUL3 mutations aid WNK4 When stimulating the serum and glucocorticoid inducible protein kinase by modifying the E3 ubiquitin ligases and thus altering the Na+ Cl- cotransporter ubiquitination, causing proteosomal degradation of the channel which further activates the Sodium Chloride cotransporter**(47)**.

Molecular effects mentioned above cause and excessive Cl- reabsorption by the Sodium- Chloride cotransporter, which adds to increased Sodium reabsorption further by the epithelial Sodium channel, causing hyperkalemia, hyperchloremic metabolic acidosis, and normal-to-elevated levels of aldosterone, which are the most common clinical features in Gordon syndrome. HT tends to manifest in adolescence or early adulthood, even if cases involving younger patients have been reported. Global prevalence is unknown, but it is believed to be larger than the 180 cases that have been reported up to this point**(48)**.

Diagnosis is made using genetic testing after the clinical features help to suspect any monogenic HT. To treat Gordon syndrome, thiazide type diuretics have shown promising results, as they inhibit the overactive Sodium-Chloride cotransporter, as shown in figure7. As in previous syndromes low Sodium intake is beneficial (15).

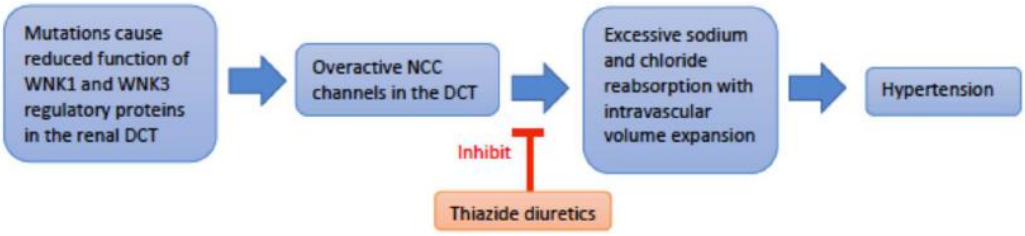

Figure 7: Schematic overview of Gordon Syndrome pathophysiology and treatment. NCC: Na+ Cl- Cotransporter. DCT: Distal Convoluted Tubule **(15)**.

v. Familial hyperaldosteronism type I

Familial hyperaldosteronism type 1 (FHT1), also called glucocorticoid remediable aldosteronism, is inherited in autosomal dominant fashion and was the first to be discovered out of the familial hyperaldosteronisms**(30)**. The genetic basis of FHT1 lies on the 8q24.3, where to adjacent genes are mutated: CYP11B1 and CYP11B2, which encode 11β-Hydroxylase and aldosterone synthase, respectively. This particular mutation consists on an unequal crossover between the 2 mentioned genes, resulting in a chimeric variant of both that renders them so that the gene ends up being regulated by ACTH instead of by angiotensin 2, while still controlling aldosterone secretion**(49)**. The place of aldosterone secretion shifts, because of the mutation from the zona glomerulosa to the adrenal zona fasciculata, thus resulting in an ectopic secretion**(50)**.

Clinically the ectopic and excessive aldosterone production causes HT and hypokalemia, which go along with suppressed renin levels**(51)**. FHT1 typically presents during childhood, in the form of severe HT with mild hypokalemia. FHT1 also increases the risk of intracerebral hemorrhage, which has a mortality rate of 60%**(52)**. The aldosterone/renin activity relation in plasma is higher than 30 in FHT1 (normal <20), which orients the diagnosis in young patients with HT and hypokalemia towards this syndrome, although the definite diagnose requires genetic testing**(53)**.

Treatment of FHT1 consists of inhibiting ACTH, which in this syndrome will suppress the ectopic aldosterone secretion, making blood pressure and Potassium levels return back to normal. The drugs that achieve this effect are glucocorticoids at low doses, dexamethasone (0.25mg/day) and prednisolone (5mg/day) being the most used**(49)**.

vi. Familial hyperaldosteronism type II

Familial hyperaldosteronism type II or FHT2 is also called non glucocorticoid remediable hyperaldosteronism, which is one of the main differences with FHT1**(54)**. The mutation responsible for FHT2 is believed to occur in chromosomal locus 3p.27.1, in the CLCN2 gene, which encodes chloride channel ClC2, and is inherited in an autosomal dominant fashion with variable penetrance**(55)**. This mutated channel has been seen to increase aldosterone synthase production and aldosterone production in in vitro studies. There is also a correlation between FHT2 and bilateral adrenocortical disease or adenomas**(56)**.

The onset of HT in FHT2 happens during adulthood, and it is clinically indistinguishable from non-hereditary primary aldosteronisms**(29)**. Definite diagnose is not possible to achieve yet as testing for CLCN2 still needs more work before it can be strongly recommended**(55)**. No clear treatment has yet been purposed, but it is known that glucocorticoids are not able to revert the syndrome like it happens with FHT1.Instead, the mainstream treatment of FHT2 is mineralocorticoid inhibitor therapy, with adrenalectomy as a rescue treatment(9).

vii. Familial hyperaldosteronism type III

FHT3 or familial hyperaldosteronism type III is inherited in the same autosomal dominant fashion as the previous two FHTs, however in this syndrome the responsible mutation lies on chromosomal locus 11q.24.3, where it affects the KCNJ5 gene, which encodes a potassium channel in the nephron**(57)**. The mutation affects part of the gene which encodes an inward rectifier of the Potassium channel, which loses its ion specificity and allows Sodium to pass through causing HT**(58)**. The mutation also provokes an increased depolarization of the adrenal cortical cells, which translates into more expression of aldosterone synthase, which leads to more aldosterone. Consequently, and as in both previous forms of FHT renin is low**(56)**. IN epidemiology and treatment FHT2 and 3 are practically identical, both provoking maturity onset HT and the treatment ranging from mineralocorticoid inhibitors to adrenalectomy depending on the severity of the HT.

viii. Familial hyperaldosteronism type IV

FHT4 is inherited in the same autosomal dominant fashion as the other FHT syndromes. In this particular variant the mutation lies in locus 16p13.3, where the gene CACNA1H, which in non-pathological conditions encodes a transient Calcium channel located on the zona glomerulosa suffers a gin of function mutation, which makes it more likely to open at baseline electrochemical activity and to remain open longer once that activation takes place**(59)**. The increased inward Calcium flow stimulates adrenocortical cells, subsequently activating aldosterone synthase. Treatment has been the same as for both previous subtypes of FHT, however new studies suggest a promising clinical response to T-Type Calcium channel blocker Mibefradil**(60)**.

ix. Familial pheochromocytoma

Unlike previous syndromes, HT in familial pheochromocytoma is caused by adrenergic or sympathetic excess. Pheochromocytoma is susceptible to be heritable alone or within the context of syndromes as Von Hippel-Lindau, Multiple endocrine Neoplasia syndrome type 2 or type 1 Neurofibromatosis among others**(61)**. Pheochromocytomas are tumors that arise on the adrenal glands, coming from chromaffin cells. They synthesize norepinephrine and epinephrine in paroxysmal fashion, causing episodes of severe HT along with symptoms associated with sympathetic nervous hyperactivity**(62)**. Each of the aforementioned syndromes is caused by a different mutation; Von Hippel Lindau is caused by a mutation on 3p25.3, where a tumor suppressor gene undergoes a loss of function mutation, causing not only bilateral pheochromocytomas to appear more often, but also increasing the prevalence of other tumors such as retinal and cerebellar angiomas, renal and pancreatic cysts, and renal cell carcinomas**(63)**. Multyple Endocrine Neoplasia type II is caused by a suppressing mutation of proto-oncogene RET, which is located on chromosomal locus 10.11.21. The loss of function of the tumor suppressing gene causes not only pheochromocytoma, but it also causes medullary carcinoma of the thyroid gland and hyperparathyroidism on its 2A subtype, and increase of medullary carcinoma of the thyroid gland along with mucosal neuromas on the 2B subtype**(64)**. In type I neurofibromatosis the mutation responsible for pheochromocytoma happens in gene NF1, located on 17q11.2 where information to synthesize neurofibromin is encoded. Neurofibromin is a negative regulator for the Ras oncogene pathway, and when the mutation causes it to loose function, the oncogene proliferates freely**(65)**.

50% of pheochromocytomas are caused by sporadic mutations, leaving the other 50% to autosomal dominant inheritance that takes place in the above mentioned syndromes**(66)**.

The diagnostic process of a pheochromocytoma consists on clinical suspicion, which may vary from the 3 classic symptoms(diaphoresis, headaches and elevated heart rate) to any consequence of sympathetic hyperactivity, followed by catecholamine and metanephrine measure in 24h urine. If positive computer tomography or magnetic resonance imaging are used to locate the tumor, the finding of a pheochromocytoma requires genetic testing for the syndromes that may cause it**(67)**.

Treatment starts with antihypertensive therapy until removal surgery is programmed. The pre-operative medical management consists of alpha-adrenergic antagonists as first line, with the option to use beta adrenergic antagonists and/or dihydropyridines as supplements. The prognosis is very different for single pheochromocytomas and for those in the context of one of the aforementioned neoplasic syndromes, being much worse on the later**(68)**.

x. HT and Brachydactyly syndrome

HT and brachydactyly syndrome, also known as Bilginturan syndrome and brachydactyly typeE, is a rare autosomal dominant disorder which causes severe salt independent, age dependent HT, brachydactyly, increased fibroblast growth rate, altered baroreflex and an increased incidence of stroke before the age of 50. The cause of these symptoms is a mutated PDE3A gene, located on chromosomal locus 12p12.2. This gene encodes a cAMP hydrolyzing phosphodiesterase, which suffers a gain of function provoked by the mutation and subsequently causes a decrease of cAMP in vascular smooth muscle cells, which triggers proliferation**(69)**. The excess of intravascular smooth muscle proliferation causes the lumen to narrow, raising blood pressure and thus being responsible for the HT. When treating this syndrome the aim is to lower cAMP concentration and this is done using Milrinone in high concentrations**(70)**.

B. Polygenic Hypertension

Polygenic hypertension may be the cause of a much greater percentage of hypertension than it is thought to be today. Most cases of hypertension are classified as essential because the etiologies and underlaying mechanisms remain unknown. A major challenge in hypertension investigation is to identify underlaying mechanisms and genes, which would allow for personalized medicine regarding diagnosis, treatment and prognosis (**71**).

i. GWAS generalities

The most promising technique for this purpose is genome-wide association studies or GWAS. GWAS is an observational study of the whole genetic variants of different individuals, in association with a concrete trait, which, in this case is hypertension. In GWAS, the focus lies on the variation of single-nucleotide polymorphisms (SNPs) and studies links between the different polymorphisms and the consequent phenotype. In short, GWAS asks if a certain SNP is found more often than expected in individuals with a phenotype of interest. The final objective of GWAS is to use genetic risk factors to make predictions about who is or will be at risk of suffering HT and to identify the biological underpinnings of susceptibility for developing new prevention and treatment strategies. Figure 9 shows the clinical implications of GWAS(**16**).

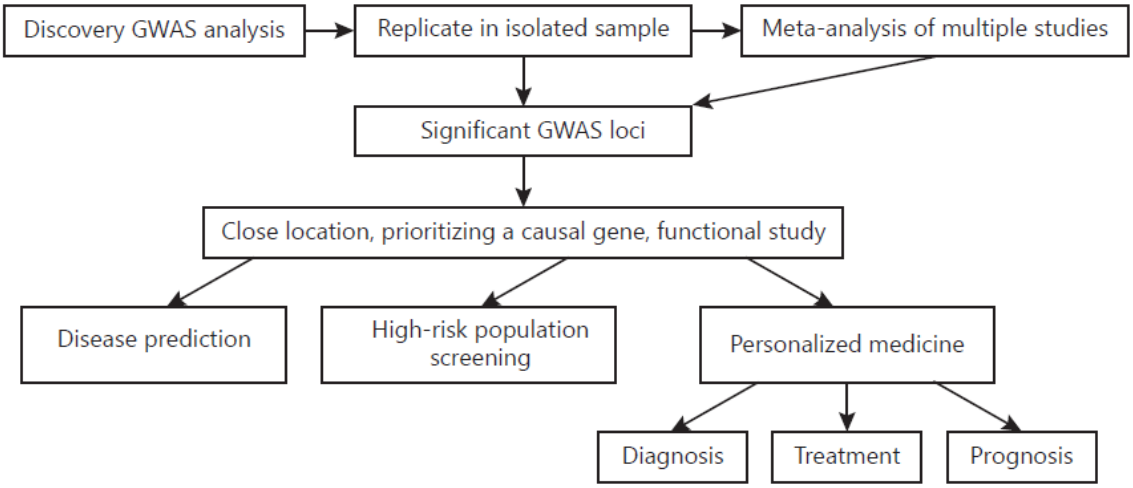

Figure 9: clinical implications of GWAS **(16)**

The most basic unit of analysis in GWAS are SNPs. SNPs are changes in the DNA sequence composed by a single base-pair, they occur with high frequency in the human genome(**72**). For genetic studies purposes, SNP are used as markers of a genomic region, as most of them have a minimal impact on biological systems. However this minimal impact sometimes does have functional consequences on the form of amino acid changes, could affect to mRNA transcript stability or could have an effect on transcription factor binding affinity. Being SNPs the most abundant genetic variation in the human genome, many SNPs are present in a large proportion of the human population(**73**).

SNPs typically have two alleles, which means that within a population there are two commonly occurring base-pair possibilities for each SNP location. The frequency of a SNP is given in terms of the minor allele frequency or the frequency of the less common allele. For example, a SNP with a minor allele frequency of 0.40 would imply that 40% of a population has allele versus the more common allele (the major allele), which is found in 60% of the population. In the genetic literature, the term SNP is generally applied to single base-pair changes that are common in the population (at least 1%), while the term mutation is used to describe rarer genetic variants, even though at pure genetic level they may be the same.The determinant of the nomenclature these changes receive is based on the frequency(**74**).

When it comes to matching interpreting the minor allele frequency there are many possible scenarios and those scenarios are explained by the common disease/common variant hypothesis. This hypothesis states that common diseases like HT are likely influenced by genetic variation that is also common in the population, and contrarily rare diseases are likely to be influenced by rare genetic variation. Thus allele frequency and prevalence are correlated. However, this hypothesis has various nuances, one of them relates to penetrance or genetic effect. If an allele would have small genetic effect or penetrance in a common disorder such as HT, but this common disorder showed heritability it must mean that multiple common alleles influence the disease in a small degree each(**75**).

Taking this hypothesis as true, diseases with genetic basis can be put on a continuous scale that takes into account both allele frequency and effect size, as seen on figure 9(76). HT would be located on the bottom right, next to prostate cancer, because it has a lot of common variants with small genetic effect, as opposed to Mendelian disorders, for example cystic fibrosis, where the causing mutation is well known.

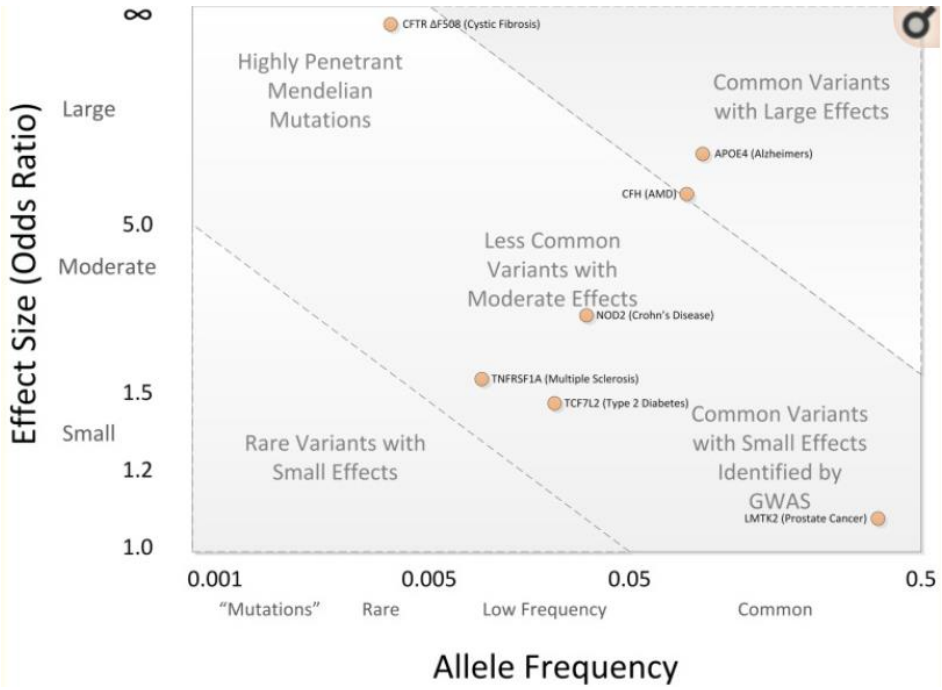

Figure 9: Disease association conceptualized in the dimensions of allele frequency and effect ratio **(76)**.

ii. GWAS in HT

The most recent study "Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk"(77) dates from 2017.It shows over 120 loci that have been identified to have weak effect on blood pressure. This study was made based on a 140,886 sample of European ancestry, extracted from the UK Biobank.

The analyses carried on that sample included GWAS of Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and pulse pressure (PP) for 9.8 million different SNPs on 240 different loci. Out of those 240, 107 were validated by *in silico* investigations and other posterior studies(**78**). 75 of those 107 loci were new findings, validated in this study with a P<0.01. The remaining 13 loci thought to have impact haven't been confirmed nor unvalidated to this date.

24 out of the 107 validated loci were reported for association with SBP, 41 for DBP and 42 for PP as their main trait of association, however many loci were associated with more than 1 blood pressure trait. Figure 10(**77**) shows how 24 validated loci are associated with both SBP and DBP, 11 with SBP and PP, one locus with DBP and PP and four loci (NADK-CPSF3L, GTF2B, METTL21A-AC079767.3 and PAX2) with all three traits at genome-wide significance.

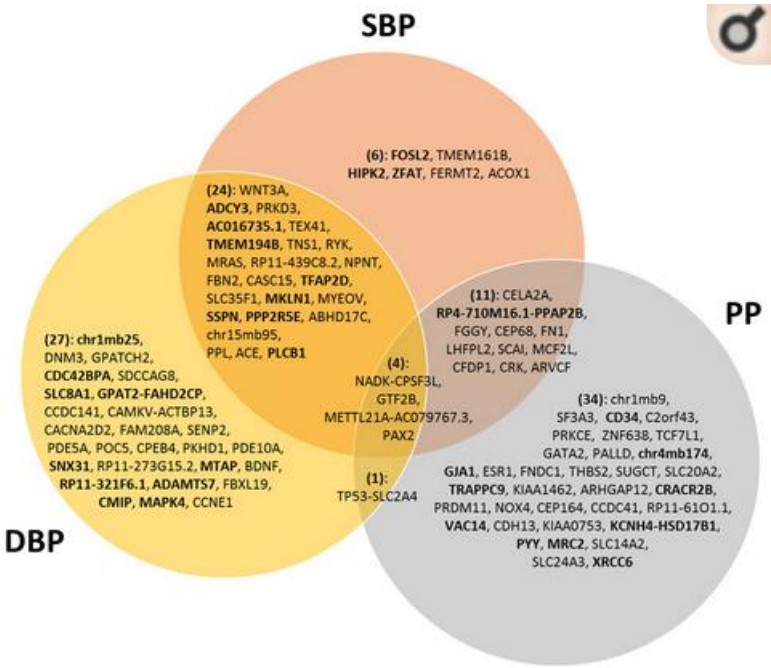

Figure 10: Venn diagram of the 107 validated loci in concordance to which blood pressure trait they relate to. Loci in bold were previously discovered, but validated by this study (**77**).

Once validated and associated with different BP traits, those 107 were further investigated, trying to uncover the functional mechanism of action that lead each of them to increase blood pressure. Those investigations were carried out using the main methods to uncover gene-phenotype associations: gene enrichment set analysis method, knockout mouse method and concordance with previously reported loci in the genetic bibliography databases.

Gene enrichment set analysis is a way of extracting the biological insight of RNA and DNA, allowing to interpret the expression of genetic data. The method derives its power by focusing on gene sets, that is, groups of genes that share common biological function, chromosomal location, or regulation and identifies genes that are over-represented in a large group of genes or proteins, thus stablishing an association(**79**).

The knockout mouse method is an animal model for research that consists of genetically modifying a mouse replacing or disrupting the gene that is meant to be studied so it

loses its function. By causing the gene to study (locus in this case) to be inactive, observing the changes in phenotype that this may produce, the function of said gene can be inferred(**80**).

In the aforementioned studies, after conducting gene enrichment set analysis, the 107 validated loci were found to impact in various different targets in the organism, all of them causing an increase in blood pressure. Some loci were found to be associated using all 3 different methods, but some loci could only be associated to the phenotype using 1 o 2 of the purposed methods.

After conducting said studies, 78 of the 107 loci were linked with cardiovascular expression, which was the main area of study. Out of those 78 only in 10 loci were all 3 of the analyzing methods positive. 18 loci were associated to the suspected function by 2 different methods, 23 were positive for only one method and the remaining 27 couldn't be proved to be linked by any of the three methods, however there is an strong suspicion based on computer generated simulations.

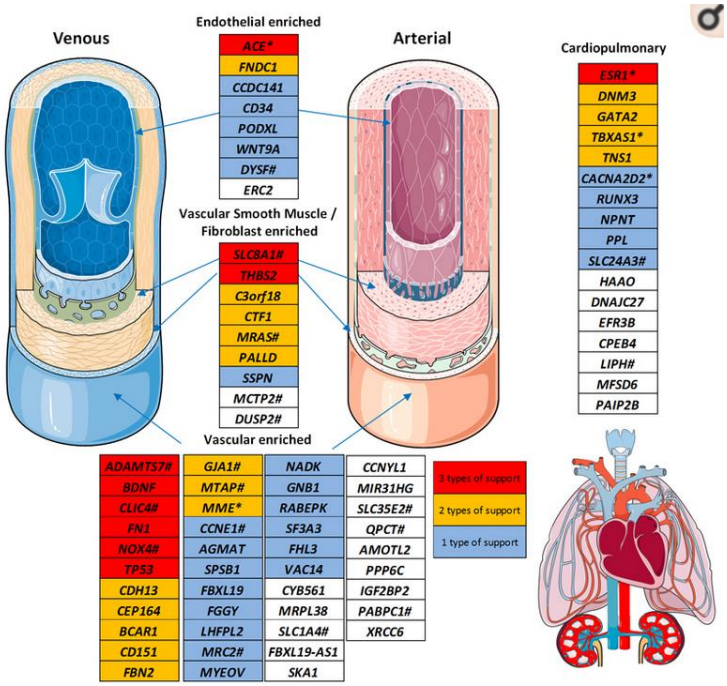

Figure 11: Summary of the 78 validated loci, to which phenotype they were linked and how many types of confirmation supported this evidence.**(77)**

The 78 loci that could be linked to a phenotype were classified in 2 main groups, cardiopulmonary and vascular, the last one being the most common. In the vascular section, loci were split up according to the layer on which they were found to have impact. The found loci, the affected tissue and number of methods via which they were linked to that impact are summarized on figure 11(**77**).

This study is the most recent up to date and the one with the broader sample. Even with those characteristics the authors recognize that it is still underpowered.

Other GWAS studies that have contributed to the incorporation of new loci for the polygenic HT research include "Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians"(81), which was conducted on a sample of 19,608 with an east Asian heritage, this study found four new loci (ST7L-CAPZA1, FIGN-GRB14, ENPEP and NPR3). "A Genome-Wide

Association Study of Hypertension and Blood Pressure in African Americans"(**82**) only has a sample of 1,017, which found two new loci SLC24A4 and CACNA1H. However, this study is still relevant because it was performed on subjects of African American heritage and there are less studies, and in consequence, discovered loci, for African population.

Those are the main studies in which the latest GWAS in HT review (Wang, **16**) bases itself. This review recognizes the Warren et al.(**77**) study as the biggest one up to date in the field. Clues for future personalized prevention and treatment of HT were also hinted in this review (**16**), like for example the Uromodulin gene (UMOD), which was identified in a case control study.

The UMOD gene showed a strong association with lower risk of HT(**83**). Uromodulin, also known as Tamm–Horsfall glycoprotein, is a protein that is expressed in the thick portion of the ascending Henle loop, among its many functions (crystallization inhibitor, defense against uropathogenic bacteria, down regulation of inflamation), that are not yet completely understood, lies one in the field of sodium homeostasis, which is the one that has been hypothesized to have an effect on HT. A study on mice using the knockout method, Uromodulin KO mice had significant upregulation of Na-coupled urate transporters Slc5a8 and Slc22a12 as well as sodium-hydrogen exchanger 3 in the proximal tubule and elevated serum uric acid and allantoin, this lead to an overall increasen of Na+ reabsorption, leading to HT(**84**). These findings are one the most promising among those showed in the latest study recompilation on polygenic HT.

8. Conclusion

There is a considerable difference between available knowledge for monogenic and polygenic hypertension. While monogenic causes of HT have been fully uncovered and their pathophysiological mechanisms are well understood, polygenic is still in a much earlier stage of research, even if promising studies have already been published and more are underway.

Monogenic genetic hypertension should be suspected in in early onset HT and in refractory HT after secondary causes have been ruled out. When it comes to monogenic HT, all of the syndromes it englobes have low renin, but to reach an accurate diagnosis, along with high clinical suspicion additional hormonal and genetic tests are required. Appropriate treatment for these syndromes is available and effective, so an early diagnose has a huge impact in lowering disease progression and minimizing both morbidity and mortality. Emphasis must be made in the area of diagnostic improvement, as these conditions are largely underdiagnosed and many patients with monogenic HT are catalogued as non-genetic (classic) HT, thus not receiving appropriate treatment. Future research in the field of monogenic HT aims to improve diagnosis rate, which relays largely on clinical suspicion by the practitioners.

Polygenic HT however has proven to be more complex than the monogenic one, as it is hypothesized that effects on this case are multiple and additive. Advances in the field of GWAS have shone some light to many different pathophysiological pathways and the interaction among them. The full understanding of these pathways doesn't seem possible in the near future, but research is ever advancing. The discovery of more and more significant loci and their function will enable creation of individual risk profiles and allow to identify concrete variants which would beneficiate from specific treatments. Findings up to today are believed to only represent less than 5% of blood pressure heritability by themselves, even if this percentage rises as we take into account learnt habits like or modifiable lifestyle factors such as alcohol consumption body mass index, smoking and educational level; it is still believed that huge progress can still be made in this field of research. The prospect for polygenic hypertension lies in identification of new loci, and application of known and yet know loci to identify individuals at risk of disease, for clinical guidance and management, causing a direct improvement in prognosis.

Even though traditionally the etiology of essential hypertension has been attributed mostly to lifestyle and environmental factors, in the last decades the paradigm is shifting to a more genetic based approach, mostly thanks to advances in the field of GWAS. This represents one of the many pathways in which medicine could evolve to a more personalized and gene-based approach.

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