Genetics of Hypertension

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Hypertension genetics is of interest to different health care professionals: The clinician is often embarrassed by patient questioning on the origins of the blood pressure (BP) elevation in the absence of risk factors and in the clinic, signs indicating the presence of a rare monogenic hypertensive syndrome are important to be recognized. The clinical-trialist can find proof for causality between BP and for example, target organ damage in Mendelian randomization studies.\(^1\) BP is of interest to the scientist in genetic or genomic medicine as it is a classic quantitative trait in the population\(^2\) and monogenic disease in rare families.\(^3\)

Hypertension (HTN) or BP genetics has been proceeding at two separate paces for primary hypertension and the rare familial forms of monogenic hypertension. The former requires genotyping of hundreds of thousands of variants that only became practical with microarrays and the implementation of genome-wide association studies (GWAS).\(^4\) Genes underlying monogenic family traits can be identified with a few hundred genetic markers, and the identification of causal genes was therefore feasible much earlier. Both types of experiments have largely contributed to our understanding of the architecture of BP genetics.

## THE CONTRIBUTION OF GENETICS TO THE BLOOD PRESSURE DISTRIBUTION

The contribution of genetics to the BP distribution is of two types: Rare mutations segregating in families drive up BP substantially in many cases and make affected individuals outliers in the BP distribution. This is secondary hypertension caused by single genes and is discussed in more detail in the first part of this chapter. The first such defect was described in 1991\(^5\) and the latest was described in 2015,\(^6\) such monogenic hypertension is a typical example of classic medical genetics.

On the other hand, the distribution of systolic BP (SBP) and diastolic BP (DBP) in the general population has a skewed, but otherwise close to normal distribution, and is a classic quantitative trait.\(^2\) BP in the general population has surprising high heritability at 30% to 50%,\(^7,8\) opening an opportunity to an improved understanding of the interindividual differences in BP levels by understanding the origins of the heritability observed. The nature of the genetic architecture of primary HTN has been the subject of the combative controversy between Robert Platt and George Pickering around 1950, where Dr. Platt advocated a monogenic dominant disease and Dr. Pickering multigenic inheritance and a continuous trait.\(^9\) Today Dr. Pickering’s model of primary hypertension is clearly documented by a large body of data. Because HTN is defined as an arbitrary threshold of BP, causes that explain the interindividual variability of BP values also explain HTN (or primary hypertension when other specific causes of HTN are excluded).\(^10\) BP (continuous phenotype) is prefered over HTN (dichotomous phenotype) in many genetic experiments because the use of a continuous phenotype has greater precision and therefore greater statistical power. The second part of this chapter will describe in more detail the advances made over the last decade to better describe the genetic architecture of primary hypertension.

## MONOGENIC (SECONDARY) HYPERTENSION

Monogenic hypertension should be considered secondary hypertension because an underlying genetic defect is clearly identifiable. The genetic defects that are necessary and sufficient for monogenic hypertension have distinctive characteristics that make them different from genetic variants underlying primary hypertension (Table 6.1). Eight different monogenic hypertensive syndromes (MHS) have been described and are summarized in Table 6.2. Three MHS have typically elevated aldosterone levels and are listed above the two MHS with typically low aldosterone. Three additional MHS have special features (occurring in pregnancy, brachydactyly, or virilization features). Among the three groups there is considerable overlap.

Even collectively, monogenic familial hypertension is thought to be rare with an incidence of likely below 1/5000 in the general population.\(^11\) But these estimations have been challenged and pathologic mutations might occur more frequently than previously thought.\(^12\) Definite proof of significance of these genes for the general population is outstanding. Even though likely rare, the genetic variants underlying MHS are important in two respects:

1. For the occasional patient with hypertension who carries a pathogenic monogenic hypertension variant, the recognition of the syndrome is important because in some cases, specific treatment approaches exist that can have spectacular treatment effects and because the recognition of the familiarity makes cascade screening possible. In MHS, untreated hypertension is often very elevated and can be severe with target organ damage occurring early in life, precocious death by stroke is observed in some cases.\(^13\)

2. It is without question that the pathways and mechanisms illuminated by the defects induced by monogenic hypertension have permitted great advances in the understanding of general BP pathways. All but one monogenic hypertension gene act either in the kidney or in the steroid metabolism or at the mineralocorticoid receptor (Fig. 6.1). The one exception is the latest identified member of the monogenic hypertension genes, PDE3A, a phosphodiesterase that

### TABLE 6.1 Key Features of the Genetics of Monogenic Hypertension in Rare Families and Common Primary Hypertension in the General Population

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>MONOGENIC HYPERTENSION</th>
<th>PRIMARY HYPERTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele frequency in the population</td>
<td>rare (&lt;1/1000)</td>
<td>~30%</td>
</tr>
<tr>
<td>Effect size per genetic variant</td>
<td>Large (likely average 20 mm Hg)</td>
<td>Small (average ~0.5-1 mm Hg so far)</td>
</tr>
<tr>
<td>Total number of known genes (loci) involved</td>
<td>13</td>
<td>~90</td>
</tr>
<tr>
<td>Estimated number of all genes (loci) involved</td>
<td>Likely ~15-20</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>