Circulation

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# Missing Heritability of Hypertension and Our Microbiome

## Have We Been Searching in the Wrong Place?

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Essential hypertension is a complex trait, traditionally considered to have a medium genetic component that interacts with environmental risk factors such as diet. Of all of the common complex polygenetic traits that afflict humans, unraveling the genetic basis of essential hypertension has proven to be the most challenging. The latest genome-wide association study in a large cohort from the UK Biobank identified >100 single genetic variants linked to blood pressure (BP) that doubled the risk for the development of hypertension.[1] Each variant, however, had a small contribution to BP (<1 mm Hg). Even combined, these variants explained only a small proportion (9.3 mm Hg) of the interindividual variation in systolic BP.[1] So where is the missing inherited component of essential hypertension?

A recent body of evidence supports that the gut microbiota are associated with the development of hypertension in experimental and human hypertension (reviewed in Ref 2). Subjects with untreated hypertension, for example, have a different gut microbiota composition, and when their fecal material was transplanted into mice without any microorganisms (ie, gnotobiotic), these mice developed higher BP compared with mice that received a fecal transplant from a normotensive subject. Moreover, the gut microbiota are essential for the development of experimental hypertension: gnotobiotic mice have a blunted response to angiotensin II. The most studied genetic model of hypertension, the spontaneously hypertensive rat, also has a different gut microbiota to its sister control strain, the Wistar Kyoto rat. In addition, systolic BP increased when antibiotic-treated Wistar Kyoto rats received a fecal transplant from a stroke-prone spontaneously hypertensive rat. Our own studies support the existence of communication among the gut, the kidney, and the heart, whereas others have shown that the gut interacts directly with the central sympathetic nervous system in both spontaneously hypertensive rat and angiotensin II models. Therapies that target gut dysbiosis, including the use of fiber and the gut metabolite acetate, decrease BP and improve cardiovascular health. Together these studies support that the gut microbiota are an important, but so far poorly acknowledged, component of the development of hypertension. Although the exact mechanisms are still being determined, a plausible hypothesis is that gut microbes modulate numerous cells of the immune system and could be involved in the exaggerated inflammatory responses known to play a role in BP regulation.

The exact moment when the first microbial colonization to the human body takes place is still to be unraveled. Some believe that the human fetus has a (minor) colonization while it is still in utero, whereas the most traditional line of thought supports the fetus is sterile until birth. Undoubtedly, during birth, the newborn is exposed to a wide variety of microbes from the environment but especially from the mother during a vaginal delivery. The newborn will also acquire new microbes (and their metabolites, such as short-chain fatty acids) through breastfeeding and contact with relevant others such as the father. Although the long-term effects



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of this early colonization on health are not yet understood, the individual human gut microbiota is thought to be mostly (60%) stable over a period of at least 5 years and, potentially, for decades.[3] Not only that, but the gut microbiome of monozygotic twins is more similar than that of dizygotic twins, and several taxa were recently shown to be heritable. These taxa were also found to be particularly stable over >3 years, suggesting that the environment might have a smaller effect on their abundance than previously believed (reviewed in Ref 3). It is important to note that these taxa are mostly abundant in disease states, and some are present at higher rates in subjects with hypertension.

The relevance of these findings to essential hypertension is that we might have been approaching the inherited origins of hypertension the wrong way (Figure). Perhaps the human genome on its own is not as important in the development of hypertension as we were led to believe. Instead, other components such as the human epigenome and the microbiome, which is also transmitted from parents and can be (at least partially) inherited, might have a bigger role than we previously thought. It is possible that the microbiota acquired early in life have a long-lasting founder effect, potentially predisposing us to develop essential hypertension as we age. In support of this hypothesis, studies that determined maternal contribution to essential hypertension, previously attributed to mitochondrial DNA mutations, found that a large percentage (>35%) of the pedigrees with hypertension were because of maternal inheritance.[4] This included a longitudinal analysis of 6421 subjects from 1593 family pedigrees from the Framingham Heart study.[4] Moreover, maternal history of hypertension has been associated with greater lifetime risk of having hypertension than paternal history.[5] Although not all studies in the literature might support a higher maternal effect, paternal microbes acquired early in life may also be involved. So far, no studies have investigated the long-term or transgenerational effects of the gut microbiota in essential hypertension. The lack of fecal samples in already recruited and well-characterized family cohorts will pose a significant limitation to test this theory and to determine what percentage of BP variability is explained by the gut microbiota.

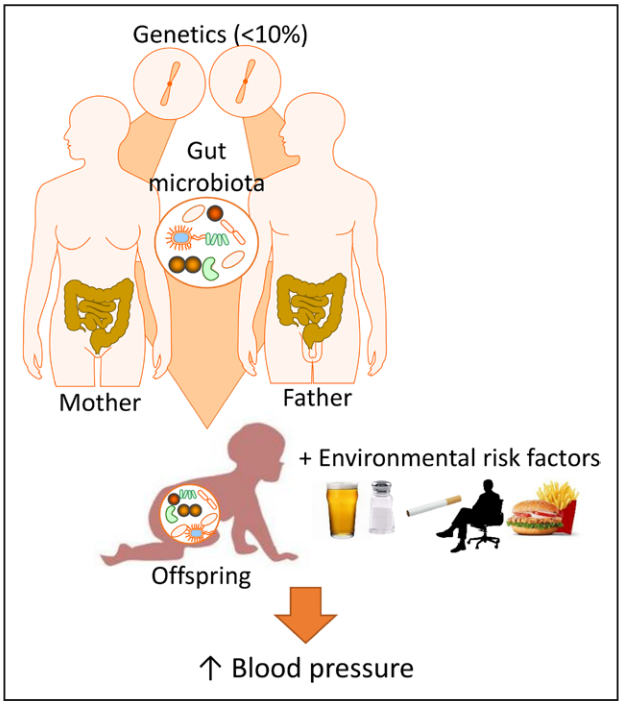


**Figure. The origins of essential hypertension is likely to include the gut microbiota.**
Essential hypertension is likely to be a complex multifactorial disease that includes a small genetic component, combined with gut microbiota that are either transmitted or inherited from parents early in life, and the interaction of both the host genome and epigenome and the gut microbiome with environmental risk factors.

Nevertheless, exciting but challenging times are ahead. For the first time, we have tools to determine the composition of the gut microbiota and models such as gnotobiotic mice to investigate whether specific (communities of) microbes contribute to essential hypertension, but we lack relevant human samples. Blood markers of microbiota are starting to emerge and might facilitate this search. For now, a joint global effort to recruit and collect fecal samples from well-characterized hypertensive participants, especially families, will be the only way we can assert the contribution of the microbiota to essential hypertension relative to genetic, epigenetic, and environmental risk factors. This will be fundamental for the development of new gut-based therapies in an effort to decrease the burden of hypertension in our communities.

## ARTICLE INFORMATION

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None.

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