Mapping genes for hypertension using experimental models: a challenging and unanticipated very long journey

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QUANTITATIVE TRAIT LOCUS (QTL) mapping is a powerful tool to identify genetic determinants of complex phenotypes. Experimental hypertension is one condition in which this strategy was expected to succeed, since the hypertension phenotype in currently used genetic models was experimentally “assembled” in the late 1950s by several laboratories. Presumably, a handful of hypertension genes were fixed in rat outbred populations by consecutive selection of individual pairs with the highest blood pressure levels used for subsequent breeding until new strains of “spontaneous hypertensive rats” reached genetic homogeneity. Therefore, we expected these tools to be effective to disassemble this complex phenotype.

Since then, these strains have been instrumental for the understanding of what happens when hypertension gradually ensues and how antihypertensive drugs influence blood pressure and affect end organ damage. In the last 15 years these rat strains have been used to dissect the genetic determinants of hypertension (1, 4, 5). Unfortunately, there is no example of a single study where a set of mapped QTLs have all been validated (e.g., congenic lines) and then the underlying culprit locus identified. Instead, these findings revealed that a more sophisticated genetic architecture may underlie the genesis of hypertension, prompting some to consider the progress in the area a half-glass empty, while others, including myself, a half-glass full (1).

Similar strategy can now be used for human samples regardless of the genetic variation amongst the individual samples. One human DNA sample can be interrogated for millions of genetic variants simultaneously and soon the whole genome will be sequenced and unanticipated very long journey understanding the whole picture. In this regard, the magnitude of blood pressure variation reported between the control strain (Dahl salt sensitive), and each of the congenic substrains was within the same magnitude of the differences reported for the control strain over time (data presented in that article’s Table 1) suggesting that nongenetic influences may also be influencing the phenotype, further complicating matters.

Sorting out these issues and taking advantage of novel approaches that enable the genetic modification of the rat genome shall be important to identify the determinants of high blood pressure, a challenge that has been more difficult than anticipated years ago (2).

DISCLOSURES

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REFERENCES


