Angiotensin Converting Enzyme Gene Polymorphism and Hypertension: No Ace Yet in the Pack of Cards

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Systemic hypertension remains an important risk factor for a variety of cardiovascular, renal and neurological diseases. It is well known that elevated blood pressure (BP) of any degree is a precursor to excessive morbidity and premature mortality. Untreated hypertension predisposes to coronary artery disease (CAD), left ventricular hypertrophy (LVH), congestive heart failure (CHF), chronic kidney diseases (CKD), end - stage renal disease (ESRD), transient ischemic attacks (TIA), and cerebrovascular accidents (CVA). Although systemic hypertension is a risk factor for disease burden, the risk is uneven, heterogeneous, and unpredictable. At the present time, there is no way to determine which patient with an elevated blood pressure (BP) level is at risk and which patient is not; therefore, BP level reduction is indicated and recommended for “all” individuals with hypertension irrespective of their “personal risk”. Hence guidelines rightly recommend measures to reduce the BP in all persons with hypertension. Despite successful treatment of hypertension, some patients experience complications whereas other patients remain free of disease even though their hypertension remains untreated or uncontrolled. This clinical scenario, therefore, raises the possibility of “genetics” in the development of hypertension and/or related complications. Various “genetic” hypotheses have been proposed to explain systemic hypertension but none has been clearly identified.

Monogenic explanations have not stood the test of evidence. Hence, it is possible (but not proven) that hypertension may be of polygenic origin. To define hypertension beyond numbers, much work has been done in the areas of genetics, inheritance, and environmental factors.

In the current issue of JAPI, Borah and co-workers¹ show evidence that in the Northeastern state of Assam, India, Angiotensin Converting Enzyme (ACE) gene polymorphism is linked to isolated systolic hypertension (ISH). Renin-Angiotensin-Aldosterone-System (RAAS) is one of the regulatory systems governing circulation, systemic vascular resistance, and kidney function. Thus, it is logical to assume that inappropriate activation of RAAS elevates systemic BP and may be an aetio-pathologic factor in the genesis of hypertension. An upward aberration in the activity of RAAS might lead to an upward shift in the BP level. For the same reason pharmacological measures which block RAAS are widely used to treat hypertension. ACE is a dipeptidyl carboxy-peptidase - I which activates angiotensin - I through cleavage of carboxy-terminal dipeptide into angiotensin II which causes vasoconstriction and subdues the activity of vasodilators such as bradykinin. Imbalance between forces of vasoconstriction over forces of vasodilatation elevates the systemic BP levels, and vascular tone. High (or inappropriate) levels of ACE thus may be associated with hypertension. On the basis of this theory, ACE polymorphism can be considered as a genetic model in the development of hypertension and its complications.

Circulating ACE levels show much variability and are genetically determined. An insertion / deletion (I/D) dimorphism has been shown to co-segregate with tissue and serum ACE function, and D allele is associated with elevated ACE levels.⁴-⁸ Therefore, the ACE gene can be considered as a qualitative trait locus (QTL) modulating ACE levels; ACE I/D dimorphism is a reflection of linkage disequilibrium (LD) with variants located in the ACE gene, implicated in cardiovascular diseases. The study reported in this issue by Borah and co - workers concludes that Del/Del polymorphism of ACE gene correlated only with isolated systolic hypertension (ISH) but not with systolic/diastolic hypertension or diastolic hypertension. This observation raises certain important questions:

- Are there different components of RAAS which control systolic and diastolic BP levels?
- Are there any environmental factors?
- Are there any ethnic/geographic differences?

It is clear that there are inherited and geographical variations in the ACE gene polymorphism which reflect the inconsistency of linking ACE gene to hypertension. For example, even in the Indian subcontinent there is no correlation between ACE gene polymorphism and hypertension in different geographic areas.⁹-¹² Data available at ALFRED (http://alfred.med.yale.edu) reveals that among Indians the frequency of the D allele ranges from 0.141 to 0.462 if the population is segregated on the basis of geographic regions; while it narrows to 0.300 to 0.454 if the population is segregated on the basis of ethnicity. Taking a mixed population thus may yield a value anywhere between 0.221 to 0.357 and therefore observed associations may not be actually true for different populations/ethnic groups.¹³ Even amongst Asians, there is no consistency among the nations about correlating ACE gene polymorphism to hypertension.¹⁴ Added to this variability, is the factor of altitude and oxygen saturation and ACE gene polymorphism in pulmonary edema.¹⁵

The findings of D/D polymorphism in ISH as reported by Borah and co-workers add another interesting facet to the pathogenesis of hypertension since D/D polymorphism of ACE gene has been shown to increase vascular stiffness, a hallmark of ISH. There could be an age factor, particularly with CAD risk. For example, ACE I allele has been linked to CAD only in the younger subjects, but not in the older age group.¹⁶ So, here too, we have an ACE gene age dependent paradox! In addition to CAD, chronic kidney disease (CKD) is emerging rapidly as a dangerous threat to public health in India due to escalating prevalence of diabetes and diabetic nephropathy. There appears to be a link between ACE gene (D allele) and diabetic nephropathy in the South Indian population whereas no such correlation was observed...
in the North Indian population and in Caucasians.\textsuperscript{19}\textsuperscript{,20} So, here we have a possible geographic/ethnic paradox!

Although linkage evidence implicates ACE gene polymorphism in certain subsets of populations and subsets of hypertension, the conclusions are not consistent and therefore, no consensus can or should be achieved at this juncture. Moreover ACE gene polymorphism may be linked to salt intake or salt sensitivity or both raising the complexity in interpreting population studies. Angiotensinogen polymorphisms (A to G substitution at the -6 nucleotide) have also been proposed to explain BP levels but with far greater inconsistency than ACE polymorphisms.\textsuperscript{21}

Plasma levels of ACE are remarkably stable within an individual but with marked differences between individuals and at variance with sodium balance.\textsuperscript{3,22}\textsuperscript{,23} That is why, population studies linking ACE gene to hypertension, CAD and CKD have been inconclusive and even controversial. Owing to the pathogenesis of hypertension related to the activity of RAAS, there might indeed be a role of ACE polymorphism in hypertension. Future studies should be more refined to study ACE gene aberrations in the context of ethnicity, age, gender, environmental and geographic factors, and importantly, to the duration of hypertension. Ultimately, in life, it boils down to survival. Hence, we need to understand the correlation between ACE gene polymorphism and "longevity"! Until these and the above questions are resolved, we are yet to find an Ace triumph card in the pack of ACE genetics and hypertension.

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References