SALT AND HYPERTENSION: GENETIC ASPECTS.

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Two major determinants of systolic hypertension is the extracellular fuild volume (ECFV) and renin-angiotensin-aldosterone system (RAAS). The former is determined by the salt content of the body thus is a variable primarily affected by daily average salt intake. This of course differs considerably from one individual from another and from one civilization to other. While ECFV is a variable reflecting salt intake, the activity of RAAS represents a response to a change in ECFV to maintain systemic blood pressure to assure the proper blood supply to deliver adequate quantities of oxygen to each and every cell of the body. All other physiological factors participating blood pressure regulation serve as modifiers of these two primary determinants. The kidney is the principal and sole organ through which salt intake is regulated to maintain a 'normal' ECFV in response to varying salt intake. Thus, any upward alteration in this setting of ECFV-RAAS axis will result in hypertension. Stated in another way, hypertension can be regarded as a shift of a set point of this ECFV-RAAS axis to maintain blood pressure. Two examples of the results of genetic analyses illustrate this point. Liddle syndrome is due to a gain of function mutation in Na channel genes in distal nephron, the primary target of aldosterone action. Thus, the syndrome reflects excess aldosterone action. But, the genetic mutation is a random process, but we rarely see the loss of function of the Na channel. Why? This is because a baby with the loss of function will die soon due to dehydration, thus cannot be transferred to next generation. The gain of function will ensure salt retaining ability, which is advantageous in natural environment of terrestrial life with very limited salt intake, thus has been transmitted over generations. Now with emergence of high salt intake of our modern civilization, this mutation has become disadvantageous, as a pathology called 'essential hypertension'. How about mutations in RAAS? Angiotensinogen 235T mutation is thought to be related to hypertension. However, in natural environment most creatures on land almost exclusively carry 235T and not 235M. Again, in this natural setting with limited salt intake, 235M will be quite of disadvantage of even lower blood pressure, thus is unlikely to survive the competition. In our modern 'civilization'

of high salt intake, 235M may become pretective and 235T is a pathology, ie, hypertension. Thus, when we wish analyse genes in a disease (which is an analytical technique), one must consider what you wish to find and what you wish to learn.