—Reviews—

# Renal Sodium Handling for Body Fluid Maintenance and Blood Pressure Regulation

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Renal sodium handling is an essential physiologic function in mammal for body fluid maintenance and blood pressure regulation. Recent advances in molecular biology have led to the identification of kidney-specific sodium transporters in the renal tubule, thereby supplying vast information for renal physiology as well as systemic physiology. Renal urinary concentration for body fluid maintenance is accomplished by counter current multiplication in the distal tubule. Sodium transport in the thick ascending limb of Henle (TAL) is the initial process of this system. We have demonstrated that renal urinary concentration is regulated in part by the expression of the $Na^+$–$K^+$–$2Cl^-$ co-transporter (BSC1) in TAL, by showing two mechanisms of BSC1 expression: pitressin vasopressin (AVP)-dependent and AVP-independent mechanisms. Two additional findings, namely, a lack of the ability to increase BSC1 expression leads to urinary concentrating defect and an enhanced BSC1 expression underlies the edema-forming condition, confirm the close association between sodium handling in TAL and body fluid accumulation. The lines of evidence from our genetic studies of the general Japanese population suggest the importance of mendelian hypertension genes in the genetic investigation of essential hypertension. Because those genes directly or indirectly regulate sodium transport by the Na–Cl co-transporter or the epithelial sodium channel in the distal convoluted tubule to the collecting duct (distal tubular segments after TAL), sodium handling in this part of the renal tubule may be, at least in part, involved in blood pressure regulation. The unveiling of such physiologic roles of sodium handling based on the sodium transporters or on the tubular segments may lead to a better understanding of systemic physiology as well as to the development of novel therapy for body fluid or blood pressure disorders.

**Key words**——sodium transport; counter current multiplication; urinary concentration; mendelian hypertension; essential hypertension

## INTRODUCTION

Body fluid maintenance and blood pressure (BP) regulation are two of the major requisites for the survival of mammals in waterless circumstances. Renal sodium handling is known to be involved in those two physiologic mechanisms, as patients with impaired renal function require medical treatment for body fluid and/or BP disorders. Recent advances in molecular biology have led to the identification of kidney-specific sodium transporters in the renal distal tubule,[1—4] thereby supplying vast information for renal physiology related to the physiologic functions mentioned above. After presenting an overview of sodium transport in the entire renal tubule with the introduction of sodium transport in the proximal tubule, the role of sodium transport in the ascending limb of Henle, an early segment of the distal tubule, is discussed by showing the results of our studies on a kidney-specific sodium co-transporter ($Na^+$–$K^+$–$2Cl^-$ bumetanide-sensitive co-transporter 1; BSC1) expressed in the thick ascending limb of Henle (TAL).[5—10] This discussion is aimed at furthering our understanding of renal sodium handling for body fluid maintenance by regulating renal urinary concentration. Genetic investigations of human hypertension are quickly reviewed and our genetic studies of the general Japanese population are introduced,[11—20] because our results suggest the importance of the genes included in mendelian hypertension (autosomal dominant inheritance of hypertension),[21—24] which influence sodium transport in the distal convoluted tubule to the collecting duct (distal tubular segments after TAL), even for the genetic investigation of essential hypertension. The discussion based on the genetic findings on hypertension reveals the close association between sodium handling in the distal tubular segments after TAL and blood pressure regulation.

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## OVERVIEW OF TUBULAR SODIUM REABSORPTION AND ROLE OF SODIUM TRANSPORT IN PROXIMAL TUBULE

After circulating blood is filtered in the glomerulus, more than 99% of the filtered sodium is reabsorbed, as depicted in Fig. 1. In kidney tubular cells, the sodium pump (Na-K ATPase) is located on the basolateral membrane. The activity of this enzyme and the associated tissue oxygen consumption are high in the early part of the proximal tubule, TAL, and the distal convoluted tubule, as indicated by the shaded areas in Fig. 1. These three tubular segments exhibit the highest rates of sodium transport and are separately indicated in Fig. 1 because of different roles they play in the sodium transport. In the proximal tubule, glucose, amino acid, phosphate, and sulfate are co-transported by the entry of sodium into the cells. On the other hand, $H^+$ is counter-transported against sodium, leading to reabsorption of bicarbonate. Therefore, sodium transport in the proximal tubule, which accounts for 50 to 60% of the total sodium transport (accompanied by almost the same percentage reabsorption of filtered water), is mainly dedicated to solute and bicarbonate reabsorption (Fig. 1).

## SODIUM TRANSPORT IN TAL AND BODY FLUID REGULATION

**Counter Current Multiplication and Urinary Concentration** Renal urinary concentration is performed by counter current multiplication,[25] which is composed of several steps, as indicated in Fig. 2. First, sodium is supplied to the interstitial space of the renal medulla mainly from the early part of TAL (① in Fig. 2), forming an osmotic gradient for water reabsorption from the descending limb of Henle and the collecting duct (②). In mammalian collecting duct, water reabsorption elevates urea concentration in the collecting duct, and then, urea begins to move into the renal medulla via a urea transporter (③). Urea acts as an osmolyte for further water reabsorption (④). In the descending limb of Henle (high water osmotic permeability and low sodium permeability), the two steps of water absorption (② and ④) highly elevate sodium concentration that, in turn, induces sodium movement into the renal medulla in the thin ascending limb that is permeable to sodium and not water. This sodium supply enhances the water absorption mentioned above, leading to a cycle of the above processes (⑤). As the initial sodium move-

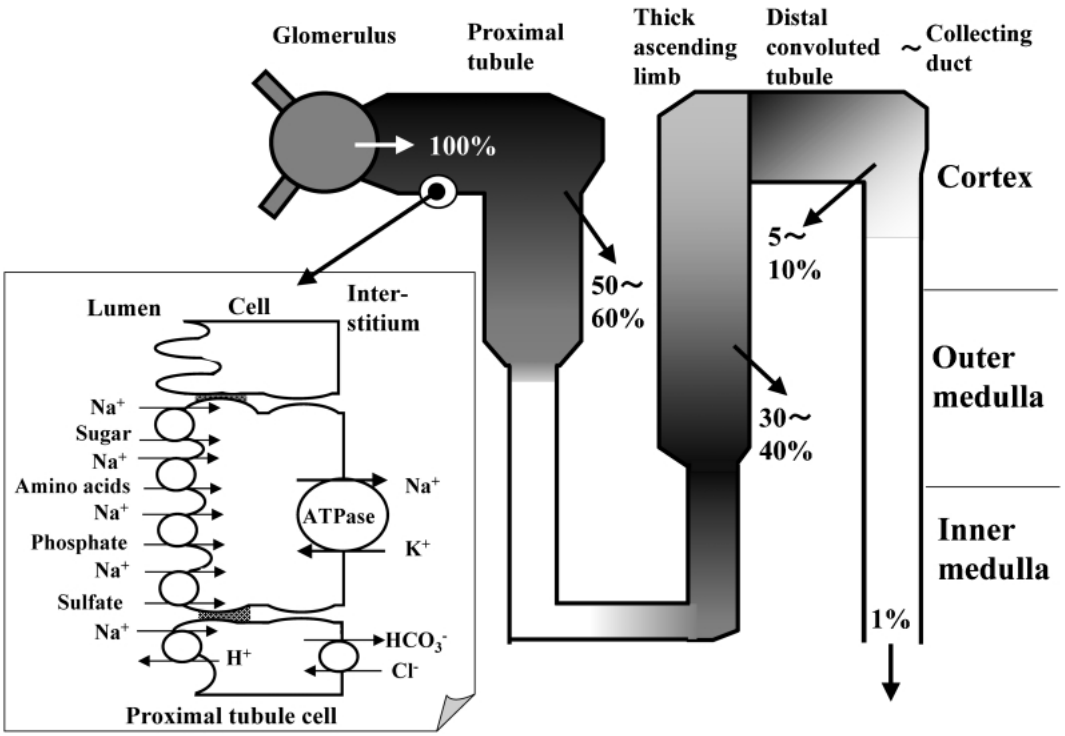


Fig. 1. Overview of Sodium Transport in Renal Tubule and Sodium Transporters in Proximal Tubule
The intensity of shaded areas indicates the activity of Na-K ATPase located in the basoleteral side of the tubular cells.

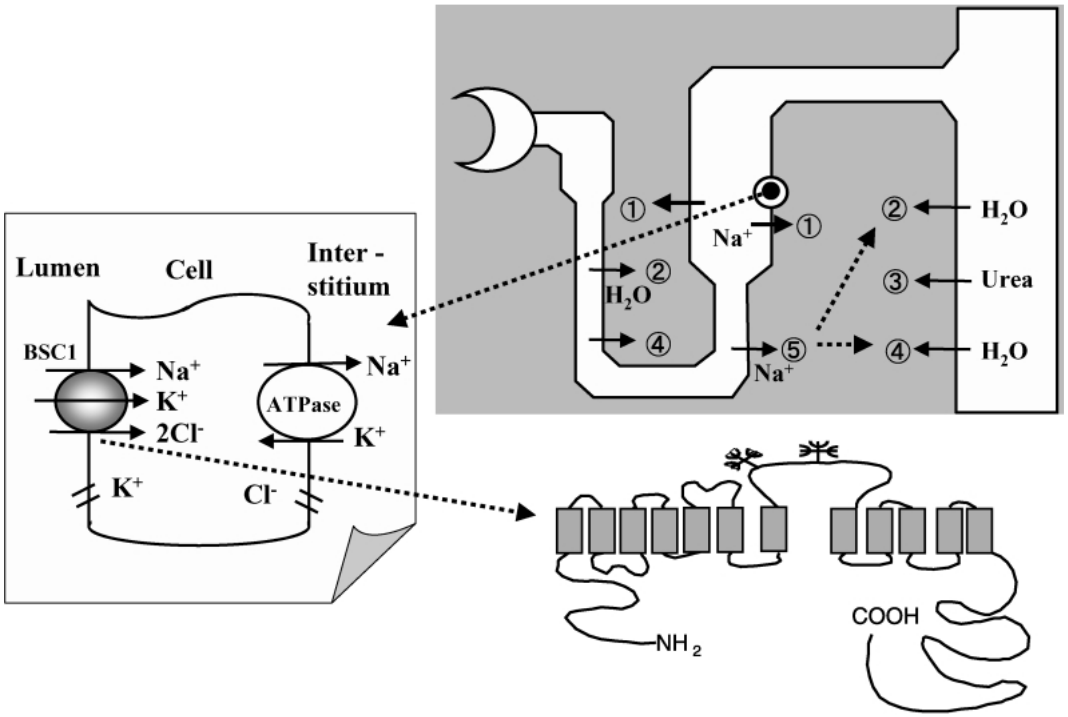


Fig. 2. Counter Current Multiplication in Distal Tubule and Kidney Specific Sodium Transporter in TAL (BSC1)

ment in those processes (①) is mediated by BSC1 in TAL,[26] the functional or expressional regulation of BSC1 is considered to be one of major regulatory mechanisms for the counter current multiplication.

**Regulation of Sodium Transport and BSC1 Expression in TAL** As the functional blockers of BSC1, bumetanide and furosemide, show strong diuretic effect by inhibiting counter current multiplication, the physiologic importance of BSC1 is well established.[27] The molecular cloning of BSC1[14] has enabled us to investigate the expression of this transporter.[5] We examined BSC1 expression in a normal rat kidney that achieved maximal urinary concentration in the dehydrated condition,[5] a kidney isograft (a rat with kidney transplantation),[7] and a remnant kidney after 5/6 nephrectomy (a rat model for chronic renal failure),[8] the latter two of which lost the ability to perform maximal urinary concentration even in the dehydrated condition. A marked increase in BSC1 expression was observed in the normal kidney from the dehydrated rat[5] and not the kidney isograft[7] or the remnant kidney[8] (Fig. 3), indicating a close association between BSC1 expression and renal urinary concentration. Then, we supplied direct evidence of this association by using a rat with a congenital defect of AVP secretion (Brattleboro rat; BB rat).[10] An antidiuretic hormone (pitressin vasopressin: AVP) secreted by the pituitary gland determines the final urinary concentration by inducing water absorption in collecting duct through apical expression water channel (AQP2).[28,29] Because this hormone increases the expression of both BSC1 and AQP2,[28,30] we attempted to determine the condition in which BSC1 expression is enhanced without altering AQP2 expression. When BB rats were dehydrated (water restriction), increased BSC1 expression and significant urinary concentration were noted (Fig. 3) in spite of unaltered AQP2 expression.[10] In this condition, we also noted increased sodium and urea accumulation in the renal medulla, indicating the enhancement of the counter current multiplication mentioned above.[10] These results indicate that renal urinary concentration is regulated in part by BSC1 expressional regulation, the mechanisms of which are classified into two: AVP-dependent and AVP-independent mechanisms, whereas AQP2 expression in the collecting duct is strongly dependent on AVP stimulus.

**BSC1 Expression and Edema-Forming Conditions** Attmane-Elakeb et al. have reported the stimulatory effect of glucocorticoids on both expression and function of BSC1.[31] Angiotensin II may enhance sodium

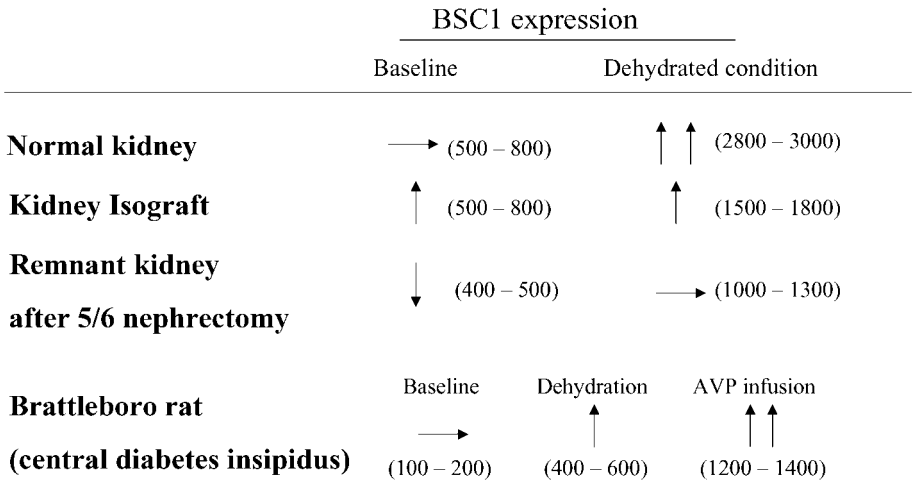


Fig. 3. BSC1 Expressions
Numbers in parentheses indicate urinary osmolality (mOsm/kg·$H_2O$).

transport[32] by increasing BSC1 expression.[33] Taken together, those findings indicate the complexity of the AVP-independent mechanism that regulates BSC1 expression. Although the details of this mechanism remain to be fully determined, studies of BSC1 expression in such edema-forming conditions as congestive heart failure (CHF)[5] and liver cirrhosis[34] indicate the clinical importance of this AVP-independent BSC1 expression. As loop diuretics that inhibit the activity of this transporter exhibit critical effects on excess fluid and sodium retention in CHF, we examined BSC1 expression in rats with myocardial infarction, and found a marked and specific increase in BSC1 expression.[6] Recently, Jonassen et al. showed an increase in BSC1 expression in a rat model for LC, and proposed that renal sympathetic nerve activation promotes BSC1 expression, leading to fluid accumulation.[34] Renal sympathetic nerve activation has also been demonstrated in other serious conditions such as brain diseases, in which the edema-forming condition is absent.[35,36] Therefore, the detailed mechanisms of the AVP-independent regulation of BSC1 expression leading to edema formation are still to be elucidated.

## SODIUM TRANSPORT IN DISTAL TUBULE AFTER TAL AND BLOOD PRESSURE

### Sodium Transport and BP Maintenance

Although the membrane proteins for sodium transport, which are located in the tubular segment after TAL (from the distal convoluted tubule to the collecting duct), have been identified, as demonstrated in Fig. 4,[1—3] the physical and/or clinical implications of sodium handling by those sodium transporters have not been fully determined. Both thiazide, which inhibits the activity of sodium and chloride co-transporter (TSC), and amiloride, which blocks sodium transport through epithelial sodium channel (ENaC), are classified as diuretics. The diuretic effect of those drugs, however, is much weaker than that of loop diuretics, namely, BSC1 blockers, and those drugs are often used as antihypertensives. In addition, the excessive secretion of aldosterone, which enhances the expression of both TSC[37] and ENaC[38] (Fig. 4), leads to the development of hypertension, but not of edema (hyperaldosteronism). These clinical information suggest that sodium transport in this part of the renal tubule is associated with the regulation of blood pressure, rather than that of body fluid. Quite interestingly, genetic investigations of mendelian hypertension (autosomal dominant inheritance of hypertension) conducted over the last decade have led to the identification of the genetic abnormalities in enzymes influencing sodium handling by TSC[39] or ENaC,[22,23] or in ENaC itself,[21] as demonstrated in Fig. 5.

### Genetic Studies of Essential Hypertension

Most of the patients with essential hypertension develop BP elevation relatively late in life, and the heritability of hypertension is low (around 30% of BP variance is attributable to genetic factors). In addition, the physiologic effect of individual molecular variant is weak, and multiple genetic factors might be required to develop hypertension. Thus, it is extremely difficult to clearly identify the genetic factor leading

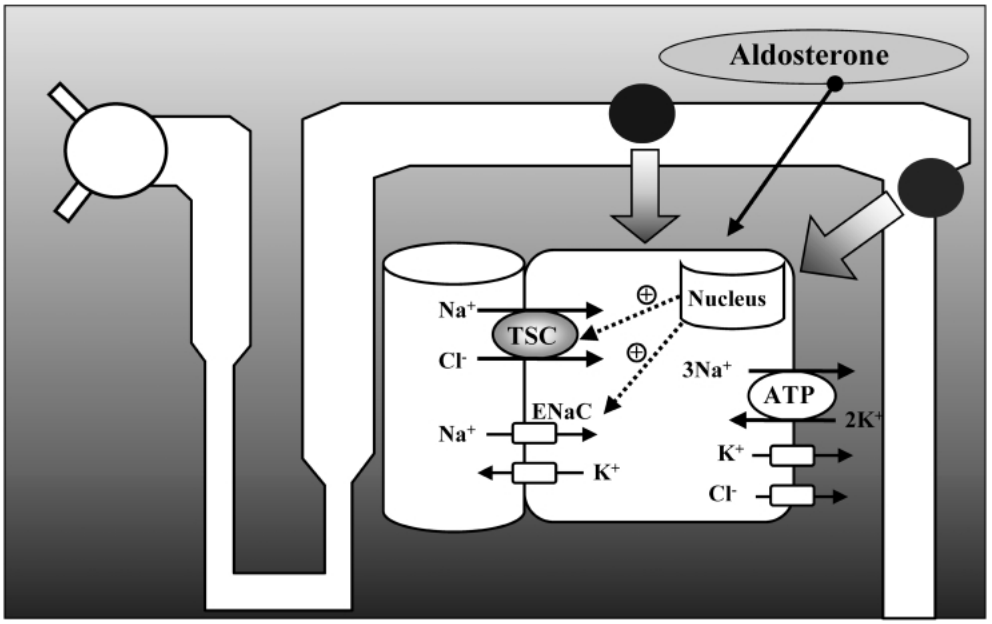


Fig. 4. Sodium Transport in Distal Tubule after TAL

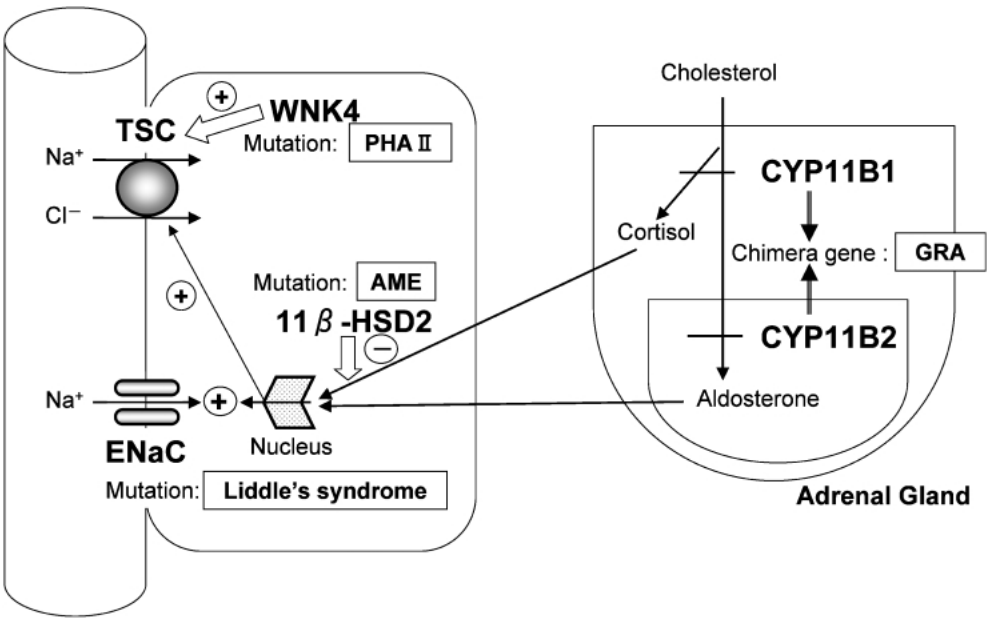


Fig. 5. Genetic Abnormalities in Mendelian Hypertension

to essential hypertension.[11] Most genetic investigations to date have been conducted by means of statistical analyses of a large number of patients (case-control study) or of the general population (population-based association study). The major genetic polymorphisms studied worldwide are depicted in Fig. 6. Although the unveiling of mendelian hypertension has suggested candidate genes influencing renal sodium handling in the distal tubule (Fig. 5), the most famous target (AGT M235T) was selected by linkage analyses (affected sib-pair analysis or genome-wide scan linkage analysis).[40] Extensive studies of the renin-angiotensin system have led to the selection of other major genetic factors in this system, as demonstrated in Fig. 6.[11] Considerable work has been performed worldwide on those four major candidate genes with divergent results; even the AGT gene polymorphism M235T is still under

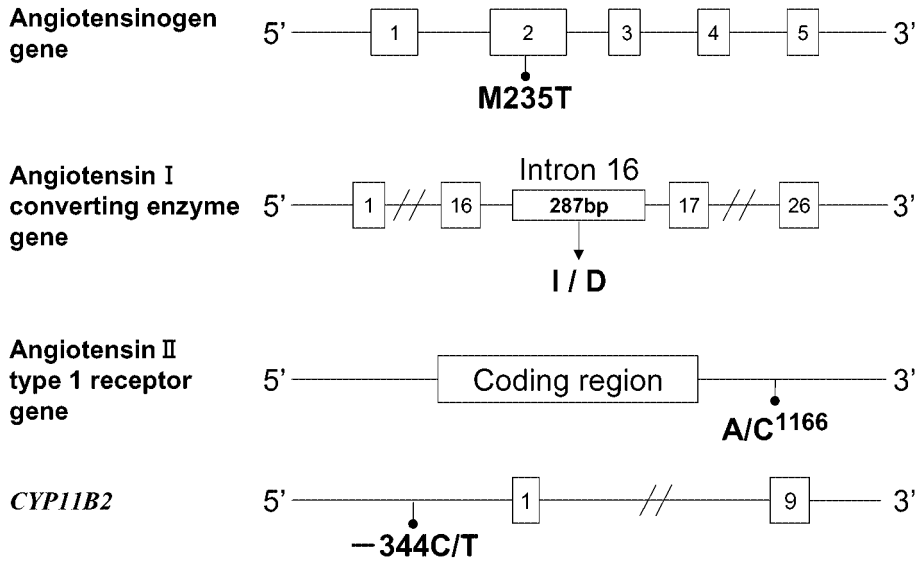


Fig. 6. Major Genetic Polymorphisms in Genetic Investigation of Human Essential Hypertension

investigation.[18,41]

**Our Genetic Investigations in a Population-based Cohort in Japan** The characteristics of our genetic study were as follows: 1) all genetic factors were analyzed in the same set of general Japanese population (age 40 or over), which represents the generality of the Japanese population in which clinical factors contributing to hypertension, such as age, gender difference, obesity, and smoking, have been confirmed; and 2) data obtained from improved blood pressure measurements, such as 24–hour ambulatory BP monitoring (ABP, $n=802$) or measurement at home (home BP, $n=1242$), were used for statistical analyses. In the Japanese population on a high salt diet (13 g/day), the genetic factors influencing the onset or prevalence of hypertension may differ from those in populations with low salt intake. This population-based difference is considered to be one of the main reasons for the inconsistent results of individual genetic factors.[11,41] Therefore, a Japanese-population-based genetic investigation is required to determine the genetic factors contributing to hypertension in Japanese. In the BP measurement, BP values obtained by ABP and home BP are more precise than that obtained by the conventional method of casual BP measurement in the hospital, because the conventional method of casual BP measurement is influenced by several biases.[42] In addition, ABP has the ability to monitor circadian BP variation. A summary of the results obtained from ABP subjects is shown in Fig. 7.[13,14,16,19] Although no direct influence of genetic factors on blood pressure was observed, the *CYP11B2*–344T allele was found to be significantly associated with altered % BP fall during the night time [(daytime BP-night time-BP) $\times$100/daytime BP (%)] and an increased prevalence of cardiovascular disease.[13] Additional analyses of home BP data[14,18,20] revealed that only *CYP11B2*–344T allele is associated with the increased prevalence of hypertension and with the increased incidence of cardiovascular diseases in subjects aged 60 and over.[20] Therefore, the results of our investigations indicate that the genetic factor in aldosterone synthase gene influences the onset of hypertension and circadian BP variation in Japanese, leading to an increase in prevalence of cardiovascular diseases in the aged, as both hypertension and circadian BP variation are clinical risk factors for cardiovascular diseases.[43] These results and clinical implications indicate the importance of genes included in mendelian hypertension in the genetic investigation of essential hypertension.

**Genetic Investigations of ENaC Gene, 11$\beta$HSD2, and WNK Gene** After confirming the importance of the genes included in mendelian hypertension even for the genetic investigation of essential hypertension as mentioned above, we examined $\beta$ENaC gene and *11$\beta$HSD2* by determining the location and incidence of mutations in the Japanese population. In *11$\beta$HSD2*, no specific genetic polymorphisms related to essential hypertension have been reported in any populations, and we have not found any mutations in the whole exons of *11$\beta$HSD2* in the Japanese general

| | (*n*) | Mean BP (systolic/diastolic) (*mmHg*) | % BP fall during the night time (systolic/diastolic) (%) | Prevalence of cardiovascular disease (%) |
|---|---|---|---|---|
| **AGT M235T** | MM(28) | 120/70 | **17/20** | 17.9 |
| | MT(206) | 122/72 | **14/17** | 7.8 |
| | TT(568) | 122/72 | **13/16** | 13.0 |
| **ACE I/D** | I I(376) | 122/72 | 14/16 | 12.5 |
| | ID(348) | 122/72 | 14/16 | 11.2 |
| | DD(79) | 123/72 | 14/17 | 11.4 |
| **AT1 A/C$^{1166}$** | AA(678) | 122/72 | 14/16 | 11.1 |
| | AC(121) | 124/73 | 14/17 | 16.5 |
| | CC(3) | 117/71 | 21/25 | 0 |
| ***CYP11B2* −344C/T** | CC(111) | 122/72 | **15**/18 | **6.3** |
| | TC(354) | 122/72 | **14**/16 | **10.2** |
| | TT(337) | 123/72 | **13**/16 | **15.4** |

Fig. 7. Summary of our Results of Major Genetic Polymorphisms in the General Japanese Population
Thick and underlines figures indicate the statistical significance.

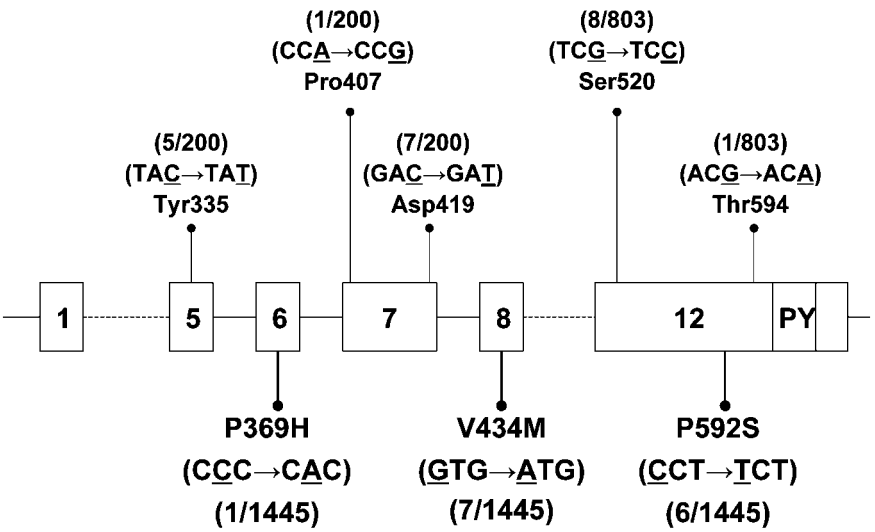


Fig. 8. Mutations in $\beta$ Subunit of ENaC in the Japanese Population

population (data not published). ENaC consists of three units, $\alpha$, $\beta$, and $\gamma$, and most of the mutations causing Liddle's syndrome, one of the mendelian hypertensions, are found in the $\beta$ subunit.[11,12] Our examination of this unit revealed several mutations (three sense and five nonsense mutations), as indicated in Fig. 8.[12,15,17] All mutations except for Val434Met in exon 8 are novel and specific to the Japanese population.[17] Unfortunately, we could not select any specific mutations associated with hypertension due to the low incidence of each of the mutations. Iwai et al., however, reported the possible genetic factors influencing BP in genes for the $\alpha$ and $\gamma$ subunits of ENaC in the Japanese population.[44,45] Quite recently, the WNK4 gene, which regulates sodium transport of TSC in the distal convoluted tubule to the collecting duct,[46] was closely examined in African-American and white populations, and a novel genetic factor related to essential hypertension was suggested.[47] A confirmation study of the Japanese population, however, remains to be performed. Although no specific genetic factor related to essential hypertension has been determined even in the candidate genes selected based on genetic findings in mendelian hypertension, the increasing amount of information provided by genetic investigations on hypertension strongly suggests the close association between sodium handling in the distal tubule after TAL

and BP regulation.

## CONCLUSIONS

The combined implications of physiologic and genetic investigations on renal sodium handling in the distal tubule have revealed the diverse roles of sodium transport depending on the location and the type of transporter in the renal distal tubule. Sodium transport by BSC1 in TAL is mainly designed to maintain body fluid by the reabsorption of water in the thin descending limb of Henle and the collecting duct. The abnormalities of BSC1 expression lead to renal urinary concentrating defect or an edema-forming condition. Sodium handling in the distal tubular segments after TAL is involved in blood pressure regulation, although the detailed mechanisms have yet to be elucidated.

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