HHS Public Access

Author manuscript

Curr Opin Nephrol Hypertens. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Curr Opin Nephrol Hypertens. 2017 March ; 26(2): 67–73. doi:10.1097/MNH.0000000000000297.

Role of corin in the regulation of blood pressure

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Abstract

Purpose of review—Corin is a transmembrane protease that activates atrial natriuretic peptide (ANP), an important hormone in regulating salt-water balance and blood pressure. This review focuses on the regulation of corin function and potential roles of corin defects in hypertensive, heart, and renal diseases.

Recent findings—Proprotein convertase subtilisin/kexin-6 has been identified as a primary enzyme that converts zymogen corin to an active protease. Genetic variants that impair corin intracellular trafficking, cell surface expression, and zymogen activation have been found in patients with hypertension, cardiac hypertrophy, and pre-eclampsia. Reduced corin expression has been detected in animal models of cardiomyopathies and in human failing hearts. Low levels of circulating soluble corin have been reported in patients with heart disease and stroke. Corin, ANP and natriuretic peptide receptor-A mRNAs, and proteins have been colocalized in human renal segments, suggesting a corin-ANP autocrine function in the kidney.

Summary—Corin is a key enzyme in the natriuretic peptide system. The latest findings indicate that corin-mediated ANP production may act in a tissue-specific manner to regulate cardiovascular and renal function. Corin defects may contribute to major diseases such as hypertension, heart failure, pre-eclampsia, and kidney disease

Keywords

atrial natriuretic peptide; corin; hypertension; proprotein convertase subtilisin/kexin-6; sodium homeostasis

INTRODUCTION

The heart acts as a central pump in the circulatory system. The discovery of atrial natriuretic peptide (ANP), also called atrial natriuretic factor, in the 1980s revealed another heart function in maintaining cardiovascular homeostasis [1]. Upon sensing increased blood volume, cardiomyocytes release ANP as a natriuretic hormone to promote renal sodium

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Conflicts of interest

There are no conflicts of interest.

excretion and relaxes peripheral vessels. This cardiac endocrine function is important for sodium homeostasis and normal blood pressure [2,3]. Latest studies show that ANP is also involved in energy metabolism and cardiovascular responses to stress and inflammation [4■■,5–7].

Most peptide hormones are produced as prohormones, which are converted to mature forms by proteolytic cleavage. Such post-translational processing also is required for ANP generation. ANP is synthesized as prepro-ANP, consisting of a signal peptide, a propeptide, and a C-terminal mature peptide [8,9]. The signal peptide is removed by signal peptidase in the endoplasmic reticulum (ER) to yield pro-ANP that is stored in the dense granules. Upon secretion, pro-ANP is converted to mature ANP on the cell surface [10]. The enzyme responsible for pro-ANP processing was a target of intense investigation [11–14], but remained elusive for more than two decades before corin was discovered.

CORIN: A TRANSMEMBRANE SERINE PROTEASE

Corin was identified as a serine protease from human hearts [15]. It consists of 1042 amino acids and includes an N-terminal cytoplasmic tail, a trans-membrane domain, and an extracellular region with two frizzled domains, eight low-density lipoprotein (LDL) receptor repeats, a scavenger receptor domain, and a C-terminal protease domain (Fig. 1). Such an arrangement of diverse domain structures is unique among proteases. Corin is the only serine protease containing frizzled-like domains [16]. Between the scavenger receptor domain and the protease domain is an activation site (Fig. 1). Cleavage at this site converts zymogen corin to an active enzyme. Human corin has 19 *N*-glycosylation sites and is heavily glycosylated [17]. Alternatively spliced mRNAs may exist to encode corin isoforms with different cytoplasmic sequences [18].

The signature catalytic residues and substrate-binding pocket in the protease domain predict corin to be a trypsin-like protease [15]. As a transmembrane protease highly expressed in cardiomyocytes, corin is expected to cleave proteins or peptides in the heart. Indeed, biochemical studies showed that corin activated pro-ANP in a sequence-specific manner [19]. Blocking corin expression inhibited pro-ANP processing in cardiomyocytes [20]. In corin knockout mice, mature ANP was undetectable [21], and the mice had salt-sensitive hypertension and cardiac hypertrophy [21,22]. These results show that corin is the long-sought physiological pro-ANP convertase that is essential for normal blood pressure.

Corin also cleaves pro-brain natriuretic peptide (pro-BNP) *in vitro* [23,24]. In corin knockout mice, however, pro-BNP processing was not abolished [25■■], indicating that corin-mediated pro-BNP cleavage is not essential *in vivo*. Furin is another pro-BNP processing enzyme [23,24], which may act as a primary pro-BNP convertase *in vivo* [26■]. Potential role of corin in activating pro-C-type natriuretic peptide (pro-CNP) has been examined in cell-based studies. The results indicate that furin, but not corin, is a primary pro-CNP convertase [27]. It remains unknown if corin has other physiological substrates, especially in tissues such as skin, brain, and chondrocytes in which corin is expressed.

REGULATION OF CORIN EXPRESSION AND ACTIVITY

Proper regulation of protease activities is important in many physiological processes. Recent studies have shown that corin expression and activity can be regulated at different levels from gene transcription, intracellular trafficking, cell surface expression to post-translational modifications (Fig. 2), which are discussed in the following sections.

Transcription and mRNA stability

Corin is expressed most abundantly in the atrium [15,28]. GATA-4 is a major transcription factor that controls corin expression in cardiomyocytes [29] (Fig. 2). Under pathological conditions such as heart failure [30–32], diabetic cardiomyopathy [33■], and radiation-induced heart injury [34], corin expression and/or activity may be reduced. In heart failure patients, unprocessed natriuretic peptides are abundant in their blood, an indication of limited corin activity in falling hearts. Inositol-requiring enzyme 1 (IRE1) is an ER-stress protein with an endoribonuclease activity. A recent study indicated that increased IRE1 expression in falling hearts may enhance corin mRNA degradation, thereby contributing to corin deficiency [35].

Zymogen activation

Corin is synthesized as a zymogen. Proprotein convertase subtilisin/kexin-6 (PCSK6) has been identified as a primary corin activator [25■■]. In cells, PCSK6 and corin travel separately to the cell surface, wherein PCSK6 cleaves corin at the conserved activation site, converting zymogen corin to an active enzyme (Fig. 2). Blocking PCSK6 expression by small interfering RNAs (siRNAs) inhibits corin activation in cultured cells. PCSK6 knockout mice have no detectable corin activity in the heart and develop salt-sensitive hypertension [25■■]. These results indicate a key role of PCSK6 in regulating corin activity and blood pressure. Among PCSK proteases, PCSK9 is involved in LDL receptor degradation [36]. PCSK9 inhibitors are used to treat patientswith high LDL cholesterol levels [37]. Thus, proteases of the PCSK family may play different roles in cardiovascular biology.

Cell surface targeting

Cell surface expression is essential for corin activation and function. Cytoplasmic sequences regulate corin intracellular trafficking and cell surface targeting [18,38,39]. *N*-glycosylation is also important for the intracellular trafficking of corin. Blocking *N*-glycosylation by tunicamycin inhibits corin surface expression and zymogen activation in cultured cardiomyocytes [17,40]. *N*-glycosylation at Asn-697 in the scavenger receptor domain and Asn-1022 in the protease domain have been shown to promote corin cell surface expression [41]. It remains unknown how *N*-glycans facilitate the trafficking of corin inside the cell.

Ectodomain shedding

Uncontrolled proteolytic activities can be detrimental. As a protection mechanism, many proteases are coevolved with their cognate inhibitors. Remarkably, corin remains active in the presence of human plasma [42], indicating that circulating protease inhibitors do not block corin activity. To date, no physiological corin inhibitors have been identified. How is

its activity controlled once corin is activated on the cell surface? In cultured cardiomyocytes, activated corin undergoes autocleavage and metalloproteinase-mediated shedding, which reduces corin protein and activity on the cell surface [43] (Fig. 2). These proteolytic events may serve as a regulatory mechanism to prevent excessive corin activity in the heart.

HUMAN CORIN VARIANTS IN HYPERTENSIVE DISEASES

ANP variants are associated withblood pressure levels and heart disease [6,44,45]. To date, corin variants have been reported in patients with hypertension and heart disease. Dries *et al.* [46] identified a corin variant allele (T555I and Q568P) in African Americans, which was associated with hypertension, cardiac hypertrophy, and reduced natriuretic peptide processing [47,48]. The T555I and Q568P substitutions are in the frizzled-2 domain (Fig. 3) and impair corin activation and function *in vitro* [25■■,49]. Transgenic mice expressing this variant allele had high levels of pro-ANP in the heart and developed salt-sensitive hypertension and cardiac hypertrophy [50]. These results indicate that the corin variant, which occurs in ~10%of African Americans, is defective *in vivo* and may contribute to cardiovascular disease in this high-risk population.

R539C is another corin variant identified in a hypertensive family [51] (Fig. 3). The amino acid change creates a mismatched disulfide bond that alters the frizzled-2 domain conformation and causes corin autocleavage and inactivation [51]. Zhang *et al.* [39] also reported an insertion variant, c.102_103insA, which occurs preferentially in hypertensive patients in China (Fig. 3). The insertion shortens the corin cytoplasmic tail and reduces corin trafficking in the Golgi and cell surface expression [39]. These results indicate that genetic variants that impair corin structure and function may contribute to hypertension and heart disease in general populations.

Pre-eclampsia is a major disease characterized by gestational hypertension and proteinuria. Reduced uteroplacental perfusion and placental hypoxia play a central role in the disease [52,53]. Corin expression was detected in human and mouse pregnant uteruses, suggesting a local corin function [54,55]. Pregnant corin and ANP knockout mice were found to have delayed trophoblast invasion and poorly remodeled uterine spiral arteries [54]. The mice developed gestational hypertension and proteinuria [54,56], a phenotype similar to that in pre-eclamptic women. These findings suggest that locally activated ANP by corin in the uterus may promote spiral artery remodeling and that defects in the uterine corin function may cause pre-eclampsia.

To date, two intronic single nucleotide polymorphisms (SNPs) in the corin gene have been identified that are associated with pre-eclampsia in Caucasian women [57]. These SNPs are located next to exon 9 that encodes the LDL receptor-4 repeat and may alter mRNA splicing [57]. Cui *et al.* [54] also found two corin mutations in pre-eclamptic women: K317E in LDL receptor-2 repeat and S472G in the frizzled-2 domain (Fig. 3). In functional studies, the K317E mutation was found to alter LDL receptor-2 conformation, impairing corin activation by PCSK6, whereas the S472G mutation was found to abolish a β-sheet in the frizzled-2 domain, causing protein misfolding and ER retention [58]. These results indicate that

naturally occurring variants may impair corin function by affecting gene expression, protein folding, intracellular trafficking, and post-translational modifications.

PLASMA SOLUBLE CORIN IN HEART DISEASE AND STROKE

Soluble corin has been detected in human blood, indicating that corin fragments cleaved in tissues may enter into the circulation [59,60]. Decreased circulating corin levels have been reported in patients with cardiovascular diseases, including acute myocardial infarction (AMI) [61,62■,63■], coronary artery disease [64,65], heart failure [66,67,68■], and stroke [69■] (Table 1). In heart disease patients, reduced circulating corin levels often correlated with poor clinical outcomes, suggesting that corin deficiency may be an underlying contributing factor. Consistent with this hypothesis, reduced cardiac corin expression was found in animal models of dilated and diabetic cardiomyopathies [33■,70■]. Conversely, overexpression of corin improved cardiac function and survival in a mouse model of dilated cardiomyopathy [71].

Hypertension is a major risk factor for stroke. ANP variant rs5063 is associated with a high risk for stroke [72]. Compared with healthy controls, stroke patients were found to have lower serum corin levels [69■] (Table 1). In men and women, individuals with the lowest quartile corin levels had threefold to five-fold and 8.5–17.5-fold higher risks, respectively, of ischemic and hemorrhagic stroke, compared with individuals with corin levels in the top quartile [69■]. Low levels of serum corin were also associated with a high risk for major disability within 3 months after stroke [73]. Given the role of corin in regulating blood pressure, these new findings should encourage further investigations to understand the potential role of corin in stroke [74].

In addition to heart disease and stroke, altered circulating corin levels have been linked to other diseases. In a population study involving 2498 adults of more than 30 years old, increased serum corin levels were associated with hypertension [75], obesity [76], dyslipidemia [77], and hyperglycemia [78]. High levels of plasma corin were found in patients with atrial fibrillation [79]. In pregnant women, increased plasma corin levels were associated with gestational age and hypertension [54,80–82]. Khalil *et al.* [80] reported that plasma corin levels before 20 weeks of gestation were lower in one-third of pre-eclamptic women compared with normotensive controls, suggesting that reduced plasma corin may be a predictor for pre-eclampsia. At this time, the tissue-origin and activity of the circulating corin remain unclear, making it difficult to interpret the data. Recently, Yin *et al.* [83] developed an electrochemical assay that measures corin activity in human plasma. Studies with such an activity assay may help to understand the significance of the circulating corin in disease settings.

RENAL CORIN EXPRESSION AND FUNCTION

Corin was discovered as a cardiac protease [15]. Later studies detected corin expression in noncardiac tissues such as uterus, skin, and brain [54,55,84–86]. Corin is also expressed in mouse, rat, and human kidneys [15,87–89]. In rat models of kidney disease, reduced renal corin expression was reported [89]. Similar results of low renal and urinary corin levels were

found in patients with chronic kidney disease [87]. These data suggest a potential role of corin in kidney biology and disease.

Recently, Dong *et al.* [90■■] reported colocalization of corin, ANP and natriuretic peptide receptor-A mRNA, and protein expression in human renal segments. The highest expression levels were in the proximal convoluted tubules and the inner medullary connecting ducts. These results indicate that corin may produce ANP in the renal segments as an autocrine mechanism to regulate sodium reabsorption [90■■]. These results also point to the proximal convoluted tubule as a major ANP action site. ANP-mediated natriuretic response has been well established as a cardiac endocrine function [91]. The latest findings of corin and ANP coexpression in renal segments suggest that a corin-ANP autocrine function may exist in the kidney to regulate sodium homeostasis.

Sodium retention is common in kidney disease [92]. In rat kidney disease models, reduced renal corin expression contributed to sodium retention [89], indicating that an impaired corin-ANP autocrine function may be an underlying mechanism. The question remains how the renal corin-ANP autocrine function differs from the cardiac corin-ANP endocrine function in regulating sodium homeostasis. In nephrotic patients, sodium and water retention often occurs despite high levels of plasma ANP [93,94]. Is it possible that these patients have an impaired renal corin-ANP autocrine function that is not compensated by circulating ANP of the heart origin? Additional studies will be important to understand the role of corin in renal physiology and disease.

CONCLUSION

Corin is a type II transmembrane serine protease that converts pro-ANP to ANP, thereby regulating sodium homeostasis and blood pressure. Corin variants that impair corin function have been reported in patients with hypertension, heart disease, pre-eclampsia, and kidney disease. In addition to the heart, corin is expressed in non-cardiac tissues. The latest studies indicate that corin and ANP may act in a tissue-specific manner to regulate salt-water balance and cardiovascular homeostasis.

Acknowledgments

The authors thank Dr Ningzheng Dong and other laboratory members for their helpful discussions.

Financial support and sponsorship

This work was supported in part by grants from the National Institutes of Health (HD064634 and HL126697) and the Priority Academic Program Development of Jiangsu Higher Education Institutions in China.

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KEY POINTS

- Corin is synthesized as a zymogen that is activated by PCSK6 on the cell surface.
- Genetic variants impairing corin intracellular trafficking, cell surface expression, and zymogen activation have been identified in hypertensive patients.
- Low levels of circulating soluble corin have been detected in patients with heart disease and stroke.
- Coexpression of corin, ANP, and natriuretic peptide receptor-A in human renal segments suggests a renal corin-ANP autocrine function that may differ from the cardiac corin-ANP endocrine function in regulating sodium and cardiovascular homeostasis.

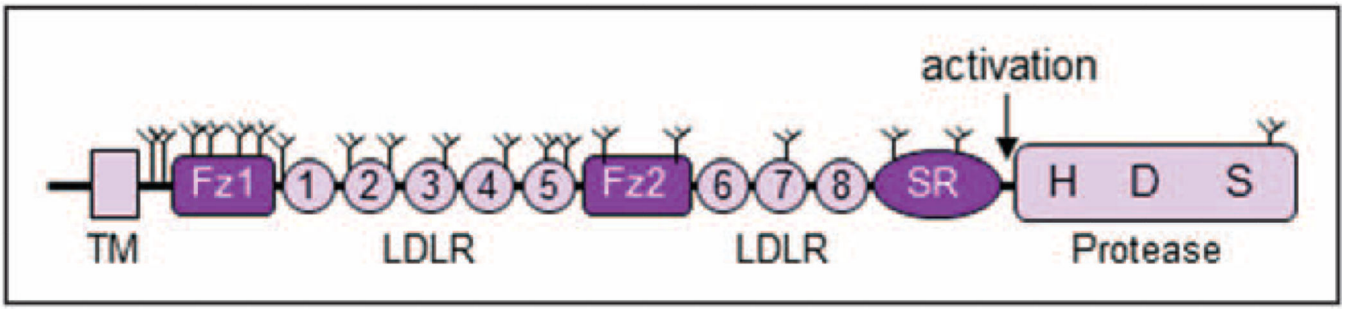

FIGURE 1.

Corin protein domain structure. Human corin consists of an N-terminal cytoplasmic tail, a transmembrane domain (TM), and an extracellular region that contains two frizzled (Fz) domains, eight LDL receptor (LDLR) repeats, a scavenger receptor (SR) domain, and a C-terminal serine protease domain. The catalytic residues His (H), Asp (D), and Ser (S) are shown. The activation cleavage site is located between the scavenger receptor domain and the protease domain. The predicted *N*-glycosylation sites are indicated by Y shaped symbols.

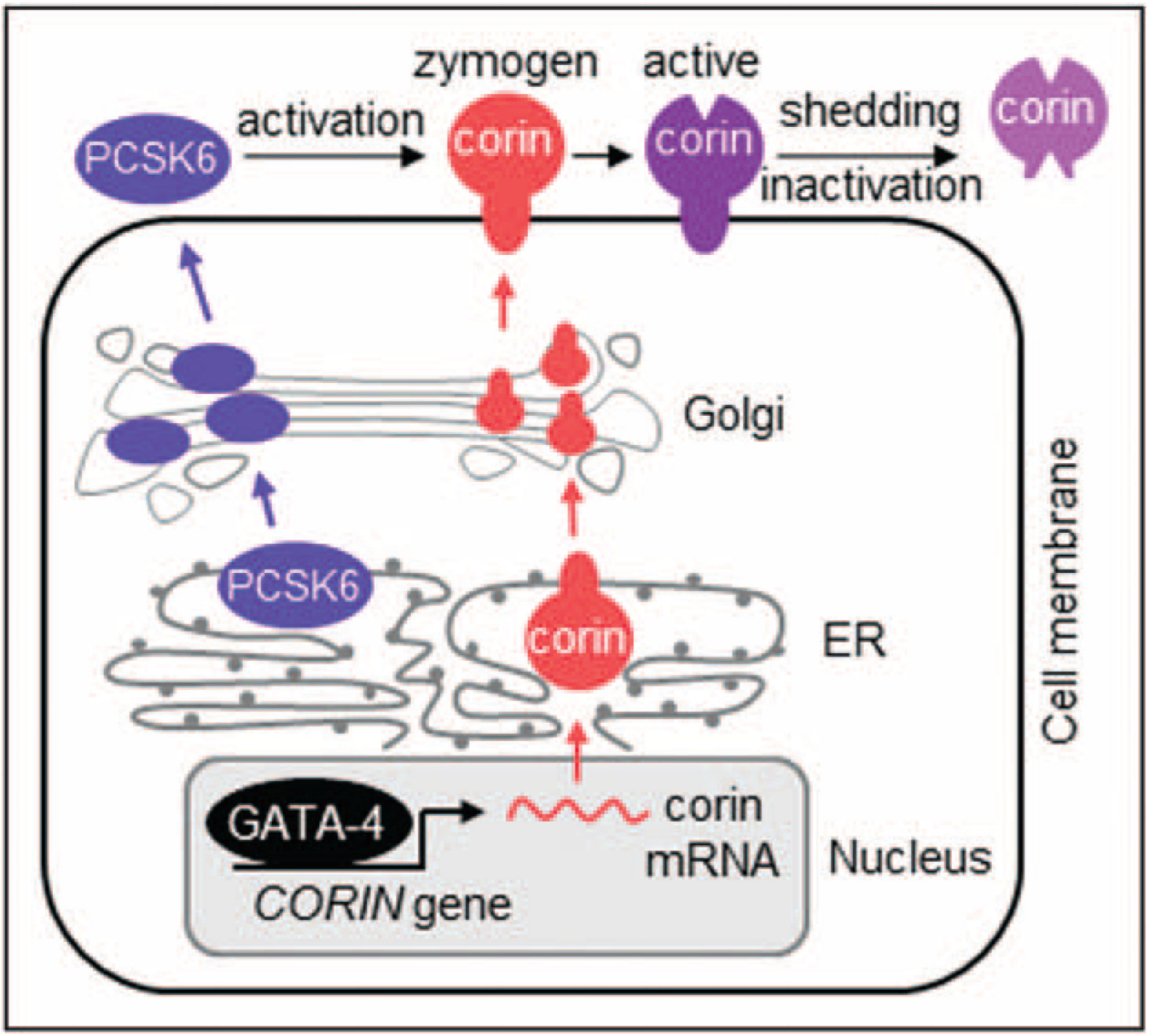

FIGURE 2.

Corin biosynthesis, intracellular trafficking, and post-translational modifications. The transcription factor GATA-4 regulates corin expression in cardiomyocytes. Newly synthesized corin and PCSK6 travel separately to the cell surface, wherein PCSK6 converts zymogen corin to an active enzyme. Protease-mediated shedding and inactivation remove corin from the cell surface and reduce corin activity.

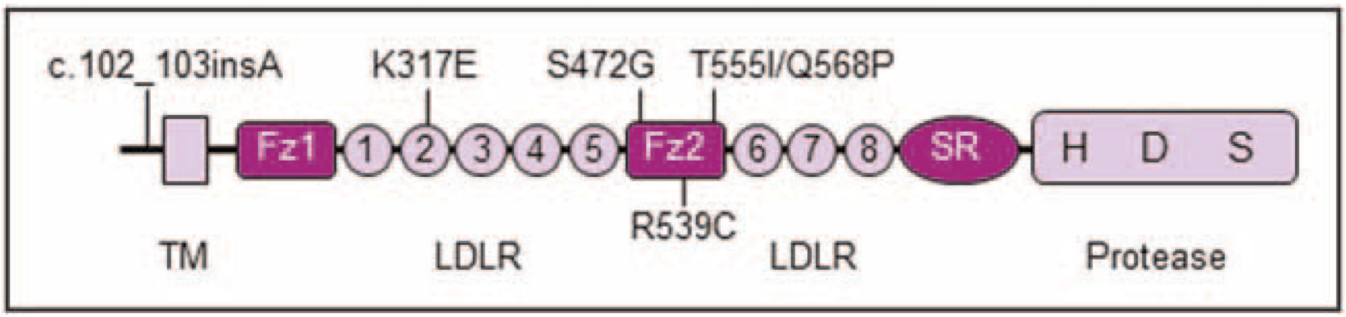

FIGURE 3.

Corin variants associated with hypertension. The locations of corin variants that have been identified in hypertensive patients are indicated.

Table 1

Plasma and serum soluble corin levels in heart disease and stroke

Disease	Sample (*n*)	Finding	Reference
AMI (ST-elevation)	Plasma (50)	Correlated with myocardial necrotic markers and 4-month infarct size	[61]
AMI	Serum (856)	Lower vs. healthy controls; inversely associated with STE/NSTEMI	[62■]
AMI	Plasma (1382)	Low corin level as a predictor for MACE	[63■]
CABG (with CPB)	Plasma (99)	Low corin associated with postoperative HF	[64]
ACS (non-ST-elevation)	Serum (152)	Lower vs. healthy controls; a predictor for MACE	[65]
CHF	Plasma (291)	Lower vs. healthy controls inversely associated with NYHA class	[66]
ADHF	Plasma (14)	Lower vs. healthy controls	[67]
CHF	Plasma (1148)	Low corin inversely associated with NYHA class; a predictor for MACE	[68■]
Stroke	Serum (597)	Lower vs. healthy controls; a risk factor for ischemic and hemorrhagic stroke	[69■]

ACS: acute coronary syndrome; ADHF: acute decompensated heart failure; AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CHF: chronic heart failure; CPB: cardiopulmonary bypass; HF: heart failure; MACE: major adverse cardiac events; *n*: sample number; NYHA: New York Heart Association; STE/NSTEMI: ST-elevation and non-ST elevation myocardial infarction.