Corin is a multiple-domain type II transmembrane serine protease class of the trypsin superfamily composed of multiple structurally distinct domains (1). It contains a cytoplasmic tail at its N terminus, followed by a transmembrane domain, a stem region composed of two frizzled-like cysteine-rich domains, eight low density lipoprotein receptor repeats, a macrophage scavenger receptor-like domain, and a serine protease domain at its C terminus. The overall topology of corin is similar to that of other type II transmembrane serine proteases, including hepsin (2), enterokinase (3), MT-SP1/TPR (4), human airway trypsin-like protease (5), TMPRSS2 (6), TMPRSS3/TADG-12 (7), TMPRSS4 (9), MSPL (10), and Stubble-stubbloid (11). The similar topologies with distinct modular structures suggest that these proteins compose a gene family that evolved by duplication and rearrangement of ancestral exons.

The expression of corin is abundant in tissues where atrial (ANP) or B-type (BNP) natriuretic peptides are produced, predominantly in the atrium and ventricle of the heart (1). In functional studies (12, 13), corin converts pro-ANP into biologically active ANP in a highly sequence-specific manner, indicating that corin is the pro-ANP convertase. In addition, corin processes pro-BNP to BNP (12). ANP and BNP regulate blood volume and pressure by promoting salt excretion, increasing urinary output, and reducing vasomotor tone (14–20). In response to volume overload or a hypertrophic signal, the heart increases its release of these hormones, which in turn reduce blood volume and lower blood pressure. The increased release of ANP and BNP has been attributed to the increased synthesis of pro-ANP and pro-BNP (21). In principle, the level of corin expression would also affect the circulating levels of ANP and BNP because overexpression of corin increases the conversion of pro-ANP to ANP (13). It is possible that the increased synthesis of pro-ANP and pro-BNP is coordinated with the up-regulation of cardiac corin expression.

The molecular mechanisms for cardiac-specific expression of ANP and BNP and their up-regulation in response to volume overload or a hypertrophic signal have been characterized (22, 23). Strikingly, both genes share several common regulatory elements (such as the GATA element) in their promoters. It has been shown that the GATA element is the key regulatory element for cardiac-specific expression and possibly for their up-regulation (24, 25). It is unknown, however, whether the corin gene shares similar regulatory elements with the ANP and BNP genes.

To understand the structural features of corin and its cardiac expression, we isolated the human and murine corin genes, determined their genomic structures, and analyzed the function of their 5′-flanking regions. The conserved feature of their genomic structures supports the concept that corin is assembled from exons encoding structurally distinct domains. The characterization of their promoter regions provides insights into the mechanism that regulates cardiac expression of corin.
GATA-6 (accession NO.74244) were from Santa Cruz Biotechnology (Santa Cruz, CA). Other chemicals were from Sigma.

Cell Culture—HL-5 cells were cultured in Ex-Cell 320 medium (JRH Biosciences, Lenexa, KS) containing 10% fetal bovine serum, 15 μg/ml insulin, 50 μg/ml endothelial cell growth supplement (Upstate Biotechnology, Lake Placid, NY), 10 μg/ml penicillin/streptomycin, 292 μg/ml l-glutamine, and 0.1 mM minimal essential medium nonessential amino acids. HeLa cells were cultured in M199 medium (Invitrogen) supplemented with 10% fetal bovine serum. All cells were cultured at 37 °C in humidified incubators with 5% CO2 and 95% air.

Electrophoretic Mobility Shift Assay (EMSA)—Nuclear extracts were prepared from exponentially growing HL-5 cells (29). The double-stranded oligonucleotide probes containing two consensus GATA sequences or mutated GATA sequences (GATA to CTTA) were originally derived from the T cell receptor enhancer (30, 31) and were purchased from Santa Cruz Biotechnology. The probes were preincubated with antibodies (at a final concentration of 50 μg/ml) at room temperature for 45 min before addition of labeled probes.

RESULTS

Isolation and Characterization of the Human and Mouse Corin Genes—Four BAC clones, two each containing the human and murine corin genes, were obtained by PCR-based screening. Three BAC clones were sequenced by a shotgun strategy using dye terminator chemistry. During the course of our studies, partial human and mouse corin genomic sequences became available. Upon combination of the shotgun data and the publicly available trace file information, we assembled a contiguous sequence of 340 kb containing the human corin gene and five contigs for the murine corin gene. The order of five contigs was confirmed by the existence of several mated reading pairs in respective neighboring contigs. The distance of those allowed us to determine the gap size to be <500 bp because the insert size of the public shotgun libraries was well defined. The structures of the human and murine corin genes were then analyzed. However, the 340-kb human genomic sequence did not contain the 5′-flanking region. We isolated an additional 4165-bp HindIII-EcoRI fragment from BAC 262540, which included the first 3919 bp of the 5′-flanking region, all of exon 1, and part of intron 1 (submitted to the GenBank®/EBI Data Bank with the accession number AF521006; Fig. 3 depicts a 1596-bp portion of the sequence).

Fig. 1 depicts the organization of the human corin promoter and the locations of BAC clones, contigs, and plasmid clones containing the corin genes and their promoter regions. Tables I and II indicate the sizes and locations of the exons and introns as well as the nucleotide sequences surrounding the splice donor and acceptor sites. The human and murine corin genes span ~238 and 204 kb, respectively. They consist of 22 exons and 21 introns. The relative sizes of all corresponding exons and introns are very similar. The nucleotide sequences at the 5′-donor and 3′-acceptor sites of all introns conform to the GT/AG rule (33).

Analysis of the genomic organization indicates that most intron/exon junctions are highly conserved between the human (Table I) and murine (Table II) corin genes. However, exon 1 diverges between human and mouse, which is consistent with the divergence in the cDNA sequences coding for the cytoplasmic tails of human and murine corin. Interestingly, the junction sequence (5′-GGTAAAGACCC-3′) between human exon 1 and intron 1 is identical to the mouse sequence (5′-GGTAAAGACCCC-3′), indicating potential alternative RNA splicing in the murine corin gene. Thus, the divergence between the cytoplasmic tails of human and murine corin found in the cDNA sequences could arise from alternative RNA splicing.

The corin cDNA sequence predicts a protein composed of a number of discrete domains. The boundaries between protein domains correspond mostly to the intron/exon boundaries of the genomic structure, as illustrated schematically in Fig. 2. The cytoplasmic tail at the N terminus is encoded by exon 1 and...
Fig. 1. Organization of the human and murine corin genes. Vertical bars indicate exons. The positions of BAC clones, contigs, and a plasmid clone containing the human (A) and murine (B) corin genes and their 5′-flanking regions are indicated. The BAC clones were sequenced by a shotgun strategy, and the sizes of the assembled sequences are indicated. The plasmid clone derived from BAC 26540 is indicated by the restriction enzyme sites HindIII (H) and EcoRI (E), and the insert was sequenced by a primer extension method using automated sequencing.

**TABLE I**

Intron/exon boundaries of the human corin gene

The numbering of cDNA is according to GenBank™/EBI accession number NM_006587. The exon and intron sequences are shown in uppercase and lowercase letters, respectively. Codon phase: 0, no interruption of codon; 1, interruption after the first nucleotide; 2, interruption after the second nucleotide of the codon.

| Exon | Location in cDNA | Size (bp) | 3′-Splice site | 5′-Splice site | Codon phase | Size (bp) |
|------|------------------|----------|----------------|----------------|-------------|----------|
| 1    | 1–156            | 156      | AAATCA         | ---            | 0           | 30,847   |
| 2    | 157–301          | 145      | ctttagGTCTTG   | ---            | 1           | 19,976   |
| 3    | 302–510          | 208      | ttttagGAACAT   | ---            | 1           | 20,044   |
| 4    | 503–710          | 208      | eccaattGCTGCTT| ---            | 2           | 18,795   |
| 5    | 711–892          | 182      | ttttagTCATGG   | ---            | 2           | 51,665   |
| 6    | 893–1006         | 114      | ttttagTGCTCT   | ---            | 1           | 8776     |
| 7    | 1007–1114        | 108      | ttgtagACTCGA   | ---            | 1           | 3479     |
| 8    | 1115–1225        | 111      | ttcctagATTGCA  | ---            | 1           | 2086     |
| 9    | 1226–1342        | 117      | tctctagGCTGCC  | ---            | 1           | 3437     |
| 10   | 1334–1450        | 108      | tctgttagTTCAGA| ---            | 1           | 6877     |
| 11   | 1451–1682        | 232      | ttttagGTCAAT   | ---            | 2           | 3175     |
| 12   | 1683–1828        | 146      | atctagGGATT    | ---            | 1           | 8050     |
| 13   | 1829–1936        | 108      | taatagAATGCT   | ---            | 1           | 8362     |
| 14   | 1937–2050        | 114      | tctgttagTTCAGA| ---            | 1           | 1824     |
| 15   | 2051–2161        | 111      | tctgttagTTCAGA| ---            | 1           | 1096     |
| 16   | 2162–2291        | 130      | cctctagTGCACC  | ---            | 2           | 15,412   |
| 17   | 2292–2408        | 117      | tatctagGAACC   | ---            | 1           | 8456     |
| 18   | 2409–2458        | 50       | atctctagGCAC   | ---            | 1           | 153      |
| 19   | 2459–2633        | 175      | ttgtagACCTGG   | ---            | 2           | 19,914   |
| 20   | 2634–2905        | 272      | ttttagGAGAGA   | ---            | 2           | 3050     |
| 21   | 2906–3039        | 134      | attctacGGAT    | ---            | 0           | 4311     |
| 22   | 3040–4933        | 1894     | ttgctaggGAT    | ---            | ---         | ---      |

The alignment of the 5′-flanking sequences and the first exons of the human and murine corin genes. There is 62% sequence identity in the first 1 kb of the 5′-flanking regions. This degree of similarity is typical for the murine and human orthologs of a gene (34). Both genes share several putative regulatory regions, including two TBX5-binding sites (35), two GATA elements (24), two “GT” boxes for the Kruppel-like factors (36), an NKX2.5-binding site (NKX2) (37), and a TATA box (38). These elements are conserved not only in sequence, but also in relative spacing. We also found nonconserved putative binding sites for NF-AT (nuclear factor of activated T cells) and TBX5 transcription factors in the human and murine corin genes.

Functional Analysis of the 5′-Flanking Regions—To test whether the 5′-flanking regions of the corin genes have promoter activity, we prepared reporter constructs in which serially truncated fragments of the 5′-flanking sequence of the half of exon 2, followed by the transmembrane domain that is encoded by the other half of exon 2. The region between the transmembrane domain and the first frizzled domain is encoded by exon 3. Each of the frizzled domains is encoded by two exons, each of the eight low density lipoprotein receptors by a single exon, and the scavenger receptor cysteine-rich domain by three exons. The protease domain at the C terminus is encoded by exons 19–22, with exon 19 coding for the sequence that includes the proteolytic activation site and the catalytic histidine residue. Exons 20 and 22 code for the sequences that include the other two catalytic residues aspartic acid and serine, respectively. The intron/exon splice junctions are split between all of the three codon phases (phases 0, 1, and 2) (Tables I and II). This feature is conserved between human and mouse.

Comparison of the Structural Features of the 5′-Flanking Regions of the Human and Marine Corin Genes—Fig. 3 shows
human or murine corin gene were linked to a promoterless luciferase gene (Fig. 4A). These constructs were transiently transfected into murine cardiomyocytic HL-5 cells, which express corin mRNA and protein (13). Luciferase activities of the transfected cells were then measured. As shown in Fig. 4B, human constructs hCp1297LUC and hCp405LUC promoted luciferase activity that was significantly higher than the background in cells in these experiments. These results indicate that these regions contain regulatory elements responsible for cardiomyocyte-specific expression. This suggests that these regions contain regulatory elements responsible for cardiomyocyte-specific expression. Inspection of these regions revealed a conserved consensus GATA sequence (designated as the proximal GATA sequence), and the GATA element has previously been implicated in cardiac-specific expression (24).

To determine whether the proximal GATA sequences indeed bind to GATA proteins, we performed an EMSA using a well characterized consensus GATA oligonucleotide probe (30, 31) and probes encompassing each of the proximal GATA sequences (Fig. 6A). As expected, the labeled consensus GATA probe formed a sequence-specific DNA-protein complex when incubated with nuclear extracts of HL-5 cells (Fig. 6B). The formation of this complex was prevented by addition of a 100-fold excess of the unlabeled probe, but not of an unrelated interferon activation sequence element. The complex formation was dependent on the intact GATA sequence because the mutated proximal GATA sequences had a minimal effect on formation of this complex was prevented by addition of a 100-fold excess of the unlabeled probe, but not of an unrelated interferon activation sequence element. The complex formation was dependent on the intact GATA sequence because the mutated proximal GATA elements indeed bind to GATA proteins, we performed an EMSA using a well characterized consensus GATA oligonucleotide probe (30, 31) and probes encompassing each of the proximal GATA sequences (Fig. 6A). As expected, the labeled consensus GATA probe formed a sequence-specific DNA-protein complex when incubated with nuclear extracts of HL-5 cells (Fig. 6B). The formation of this complex was prevented by addition of a 100-fold excess of the unlabeled probe, but not of an unrelated interferon activation sequence element. The complex formation was dependent on the intact GATA sequence because the mutated proximal GATA sequences had a minimal effect on the formation of the complex. Furthermore, the complex was not detected in the presence of a 100-fold excess of the unlabeled probe containing either the human or murine proximal GATA sequence. In contrast, a 100-fold excess of the unlabeled probes encompassing the mutated proximal GATA sequences had a minimal effect on the complex formation. These data indicate that the corin proximal GATA sequences and the consensus GATA probe bind to a common GATA protein(s).
To determine which GATA protein(s) was involved in the complex, we performed EMSA with the labeled consensus GATA probe in the presence of antibodies against members of the GATA family. As shown in Fig. 6C, an antibody against GATA-4 markedly inhibited the complex formation, whereas antibodies against GATA-1, -3, and -6 had little effect. To directly demonstrate the binding of GATA-4 to the proximal GATA sequence, we used the labeled human proximal GATA probe in the absence or presence of the same antibody against GATA-4. As shown in Fig. 6D, the antibody against GATA-4 completely inhibited the formation of a DNA-protein complex with a similar mobility to that of the complex formed with the consensus GATA probe. These data indicate that GATA-4 bound to the proximal GATA sequences, suggesting that the binding of GATA-4 to the proximal GATA sequences may contribute to the gene expression of corin in cardiac myocytes.

To corroborate whether the proximal GATA elements are actually required for the promoter activity, we mutated the wild-type sequence AGATAA to ACTTAA in the human and murine constructs with the highest promoter activity (Fig. 7). The mutations in the GATA element were the same as those made in the mutant GATA probes, which eliminated the binding to GATA-4 in the EMSAs. When transfected into HL-5 cells, the human and murine mutant constructs had 10 and 42% of promoter activities compared with their respective wild-type sequences. These results show that the proximal GATA elements are actually required for the promoter activity, corroborating the conclusions from the EMSA experiments.
ments are required for constitutive expression of the human and murine corin genes in cultured cardiac myocytes.

**DISCUSSION**

We cloned the human and murine corin genes, determined their genomic structures, and analyzed the structure and function of their 5′-flanking regions. The conserved intron/exon boundaries and their correspondence to the boundaries of protein structural domains support the idea that corin arose from exon duplication and rearrangement. The comparison and functional analysis of the 5′-flanking regions reveal several conserved sequences, including a functional GATA element, providing a molecular basis for understanding the mechanism that regulates tissue-specific expression of corin.

Both human and murine corin genes span at least 200 kb and contain 22 exons interrupted by some large introns up to 50 kb. The corin genes are the largest genes identified so far among the trypsin-like serine protease superfamily. All but one of the intron/exon junctions are highly conserved between human and mouse. The exception is the first intron/exon, whose divergence leads to the different cytoplasmic domains of the predicted human and murine corin proteins. However, sequence analysis of the human and murine genomic structures indicates potential alternative RNA splicing of the first exon, suggesting the existence of splice variants.

The intron/exon junctions of the corin genomic structures correspond mostly to the boundaries between their protein structural domains. The codon phases used to split the junctions of their structural domains are conserved between human and mouse. The same types of codon phases are also used to split the same types of structural domains within the protein. For example, each of the two frizzled domains is encoded by two exons, and each of the eight low density lipoprotein repeats is encoded by a single exon; the codon phases used to split these domains are the same.

The protease domain of all members of the type II transmembrane serine protease class consists of ~240 amino acid residues. In each gene, however, the number of exons coding for the protease domain may vary. For example, the protease domain is encoded by four exons in the corin, *MT-SP1*, and human airway trypsin-like protease genes; five exons in the enterokinase gene; and six exons in the human and murine hepsin (39) and the human *TMPRSS2*, -3, -4, and -5 genes (analysis of data from the NCBI Human Genome Database). Presumably, some of these exons have been fused (or interrupted) during the course of evolution. It is well established that exon shuffling and fusion have been a major driving force for generation of the multiplicity of domains in protein (40). The available data from the human and mouse corin genes, together with data from other members of the type II transmembrane serine protease family, support the concept that this class of proteins arose from duplication and rearrangement of preexisting exons encoding structurally distinct domains.
To understand the mechanism of cardiac expression of the corin gene, we isolated the 5'-flanking regions of the human and murine genes. Transfection of serially truncated segments of the 5'-flanking region linked to a luciferase reporter gene indicated that the sequences from 646 to 77 in mouse and from 405 to 15 in human supported high level expression of luciferase, similar to longer constructs, in cardiomyocytes. In contrast, these sequences directed only minimal expression in HeLa cells. These findings suggest that these short 5'-flanking regions contain sufficient information to promote specific expression in cardiomyocytes. It remains to be determined whether these regions can mediate tissue-specific expression in vivo.

Within these short 5'-flanking regions, a number of conserved regulatory sequences were identified, including binding sites for TBX5 (35, 41, 42), GATA (24), NKX2.5 (37), Krüppel-like transcription factors (36, 43), and an AT-rich sequence. These binding sites are conserved not only in sequence, but also in relative spacing in the context of the promoters. Furthermore, they are also present in the promoters of the ANP and/or BNP genes, as summarized in Fig. 8 (22, 35, 44, 45).

The AT-rich sequences (-211 to -205 in human and -426 to -426 in mouse) fit well a typical TATA box (38). Interestingly, the TATA box is embedded in the conserved CAAAATATGG sequence, which resembles a serum response element (CC-(A/T)6GG) (46). The serum response element is present in many

![Fig. 6. Binding of nuclear proteins to the regulatory sequence encompassing the proximal GATA element.](image)

A, shown are the sequences of the upper strand oligonucleotides used as probes and competitors. The GATA motifs in each sequence are in boldface, and the mutated nucleotides are in italics. The human and murine proximal GATA elements are from the indicated regions of the corin 5'-flanking sequences. The consensus GATA probe containing two GATA motifs was derived from the human T cell receptor-specific enhancer region (30, 31). B, the labeled consensus GATA probe or its mutant probe (Mut.) was incubated with nuclear extracts from HL-5 cells in the presence or absence of a 100-fold excess of the indicated unlabeled oligonucleotides. The arrow indicates a GATA sequence-dependent DNA-protein complex. C, the labeled consensus GATA probe was incubated with nuclear extracts from HL-5 cells in the presence of antibodies against GATA proteins. The arrow indicates a DNA-protein complex whose formation was blocked by an antibody (Ab) against GATA-4, but not by antibodies against GATA-1, -3, and -6. D, the labeled human corin GATA probe was incubated with nuclear extracts from HL-5 cells in the presence or absence of an antibody against GATA-4. The arrow indicates the DNA-protein complex whose formation was completely blocked in the presence of the anti-GATA-4 antibody.

![Fig. 7. Mutational analysis of the conserved proximal GATA elements.](image)

The same mutation (GATA to CTAA) that abolished binding to the GATA-4 protein in EMSA was introduced into luciferase (LUC) reporter constructs driven by the 5'-flanking regions from -642 to -77 in mouse and from -405 to -15 in human supported high level expression of luciferase, similar to longer constructs, in cardiomyocytes. In contrast, these sequences directed only minimal expression in HeLa cells. These findings suggest that these short 5'-flanking regions contain sufficient information to promote specific expression in cardiomyocytes. It remains to be determined whether these regions can mediate tissue-specific expression in vivo.
cardiac-expressed genes, including the ANP gene, and is one of
the key regulatory elements for cardiac-specific expression
(47, 48).

The presence of the putative binding sites for TBX5, GATA,
and NKX2.5 in the human and murine corin promoters sug-
gests that the corin gene may be a downstream target gene
regulated by these transcription factors. Intriguingly, muta-
tions in the TBX5 gene cause heart and limb malformations in
Holt-Oram syndrome (35), suggesting that TBX5 regulates not
only cardiac-expressed genes, but also bone-expressed genes.
In fact, the corin gene is also expressed in the long bones of
developing limbs (1).

Unlike GATA elements in the ANP and BNP genes, the corin
GATA sequence (~40 to ~35 in human and ~318 to ~313 in
mouse) is located in the first exon, proximal to the TATA box.
This GATA sequence also overlapped with a putative NKKX2.5-
binding site. The GATA sequence is critical for gene expression
of corin because mutation of this GATA sequence in the human
and murine reporter constructs significantly reduced the pro-
moter activity in transfected cardiomyocytes. The same muta-
tion in this GATA element also eliminated binding to GATA
proteins in EMSAs. We further showed that this GATA ele-
ment bound to GATA-4, but not to GATA-1, -3, and -6, in
cultured cardiomyocytes, indicating that GATA-4 is a major
transcriptional activator for corin gene expression. This is con-
trasted with the fact that GATA-4 expression starts at 7–7.5
days post-conception, preceding the earliest expression of corin
at 9.5 days post-conception in mice (49). Moreover, GATA-4
expression is maintained throughout cardiac development in
both the atrium and ventricle, concurrent with the expression
of the corin gene.

The role of GATA-4 in transcription of the corin gene may
have physiological and pathological implications in the regula-
tion of blood pressure and volume. It has been demonstrated
that GATA-4 serves as a pivotal regulator for expression of
the ANP and BNP genes (22, 24, 45, 50). In response to fluid
volume overload or a hypertrophic signal, the heart produces
more ANP and BNP to reduce blood volume and lower blood
pressure. One of the mechanisms for such increased production
has been shown to be mediated through signaling pathways
converging onto GATA elements and/or NF-AT-binding sites
in the ANP and BNP promoters (50–53). It has been proposed
that myocyte stretch elevates intracellular concentrations of
calcium, leading to activation of calccineurin and hence dephos-
phorylation of the transcription factor NF-AT-3 in the cyto-
plasm. Upon dephosphorylation, NF-AT-3 translocates to the
nucleus, where it binds to NF-AT sites and/or directly interacts
with the GATA-4 protein, thereby promoting expression of the
ANP and BNP genes. There are at least three putative NF-AT
sites in the human and murine corin promoters, although these
sites are not located in the conserved regions.

The presence of several common regulatory elements in the
ANP, BNP, and corin genes suggests that these genes could be
regulated by similar mechanisms. It is likely that expression
of the corin gene is up-regulated in response to excessive blood
volume or a hypertrophic signal. The cloning of the 5′-flanking
regions of human and murine corin genes should help us un-
derstand their tissue-specific expression and regulation.

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Junliang Pan, Bernd Hinzmann, Wei Yan, Faye Wu, John Morser and Qingyu Wu

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