Essential hypertension is a complex multifactorial disease caused by interactions between genetic and environmental factors. Contribution of genes to the pathogenesis of human hypertension is estimated at 30%, and this hereditary component is mediated by at least a few genetic loci. The polygenic nature of essential hypertension is well documented by genomewide scans that identified several independent quantitative trait loci (QTLs) for blood pressure (BP). Although BP QTLs are present on almost every human chromosome, only a few genomic regions were linked to BP in >1 investigation. One of these unique chromosomal segments is the distal portion of the long arm of chromosome 5 (5q23.1 to 5q35.2). Not only was it linked to BP in individual genomic searches, but it also was implicated as 1 of only 5 chromosomal regions with suggestive linkage to hypertension in the meta-analysis of genome scans. In addition, the distal segment of human chromosome 5 is syntenic to a QTL for salt-sensitive hypertension in rats. Finally, 5q23.1 to 5q35.2 is rich in functional candidate genes that encode critical BP regulators including adrenergic receptors, inflammation-related molecules, and growth factors. Collectively, these data show clearly that the distal portion of the long arm of chromosome 5 may indeed harbor gene(s) that contribute to BP regulation and human hypertension.

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Our previous studies revealed that 5q23.1 to 5q35.2 was linked to systolic blood pressure (SBP) in families with clustering of essential hypertension. In addition, we narrowed down this 55-cM region by ≈80% and mapped the BP QTL to a segment flanked by D5s500 and D5s1480. The following family-based single-locus and haplotype analysis...
excluded the role of the $\beta_2$-adrenergic receptor gene (ADRB2) as the mediator of the linkage to BP.\textsuperscript{4} Herein, we dissected the previously identified QTL by fine mapping, comparative genomics, and functional prioritization in silico. The subsequent positional analysis based on linkage disequilibrium (LD) mapping, single-locus and multilocus association testing, and gene expression studies identified fibroblast growth factor 1 gene (FGF1) as a variant that may contribute to human hypertension.

**Methods**

**Subjects**
The Silesian Hypertension Study (SHS) is a cohort of Polish families that were recruited to investigate the genetic predisposition to essential hypertension. The study design, recruitment strategy, family structure, and clinical characteristics of the subjects were described in detail elsewhere.\textsuperscript{4,9} In brief, 629 individuals from 207 families with clustering of essential hypertension were included in the present analysis. Each SHS family consisted of a hypertensive index patient with available parents and/or siblings. In addition, an independent sample of 52 unrelated individuals was recruited from the general population within the same region of Poland as a source of DNA for sequencing analysis.

Phenotyping included taking clinical history by standardized, anonymously coded questionnaires, basic anthropometry, and measuring BP in triplicate by mercury sphygmomanometer, as reported before.\textsuperscript{4,9} Subjects were considered hypertensive if their BP readings on 3 different occasions were $\geq 140/90$ mm Hg or if on enrollment they were taking antihypertensive treatment.\textsuperscript{4,9}

The Silesian Renal Tissue Bank is a collection of tissue that was gathered to investigate renal expression of candidate genes in human cardiovascular disease. Fifty-five patients (33 men and 22 women; median age, 60 years) with noninvasive renal cancer that required elective unilateral nephrectomy were recruited in a center of urology in Poland. Each subject was phenotyped and classified as hypertensive (32 subjects) or normotensive (23 subjects) according to the original BP QTL (D5s500 and D5s1480).\textsuperscript{4} After saturation of the microsatellites were placed between the markers that flanked the within the previously identified QTL for SBP.\textsuperscript{4} These additional genes was assessed individually on the basis of preferential expression in BP-regulating tissues (kidney, heart, and blood vessels), evidence for contribution to hypertension in experimental models, and the overall level of support for association with hypertension in human studies. The gene that showed the highest pathophysiological potential to regulate BP was selected for further positional analysis.

**FGF1: Sequencing, Single Nucleotide Polymorphism Function Analysis in Silico, Genotyping**

Potentially functional FGF1 segments including the coding exons, the untranslated exons (1A, 1B, 1C, 1D) along with the adjacent promoters, the 3' untranslated region, the intronic segment, and the 7.1-kb 5' flanking region located upstream from the first exon were sequenced directly on 104 chromosomes with the use of capillary-based DNA sequencing technology. In brief, DNA was amplified by PCR with thermal cycling parameters recommended by the manufacturer (Qiagen, Valencia, Calif). PCR product was purified by magnetic bead technology (Agencourt Bioscience Corporation, Beverly, Mass), and the purified DNA was prepared for sequencing with the use of BigDye version 3.1 cycle sequencing (Applied Biosystems). Capillary sequencing was performed with the Applied Biosystems DNA Analyzer 3730, and genetic variants were identified with SeqScape version 2.1 single nucleotide polymorphism (SNP) discovery software (Applied Biosystems). Altogether, 25.6 kb (~25% of the entire FGF1) was sequenced directly in 52 unrelated Polish subjects.

Molecular mechanisms by which the FGF1 SNPs could influence the mRNA or protein function and structure were investigated in silico with the use of SNP Function Portal (http://brainarray.mbni.med.umich.edu/Brainarray/Database/SearchSNP/snpfunc.aspx).\textsuperscript{10} In brief, each of the identified FGF1 SNPs was analyzed with the use of available functional annotations including alternative splicing, CpG islands, DNAse I hypersensitive sites, microRNA target sites, and the possible effect on structure and function of the encoded protein.

Fine Mapping

DNA was extracted from peripheral leukocytes by a previously validated method (MasterPure DNA purification kit, Epicenter Biotechnologies, Madison, Wis), quantified, and diluted to the standard concentration of 5 ng/\mu L. Five microsatellites (D5s2116, D5s1979, D5s2017, D5s1972, D5s207) were selected from the Center for Medical Genetics at Marshfield Medical Research Foundation database (http://research.marshalldclinic.org/genetics/) to tighten the grid of genetic markers within the previously identified QTL for SBP.\textsuperscript{4} These additional microsatellites were placed between the markers that flanked the original BP QTL (D5s500 and D5s1480).\textsuperscript{4} After saturation of the region with additional microsatellites, the average spacing between the markers was 1 cm. Each of the additional markers was genotyped in the SHS according to the protocol described in detail elsewhere.\textsuperscript{4} In brief, after amplification in standard conditions, the polymerase chain reaction (PCR) products were resolved on 5% polyacrylamide gel (ABI 377 sequencer, Applied Biosystems, Foster City, Calif).

Assignment of genotypes was completed with the use of Genescan and Genotyper software (Applied Biosystems).

**Comparative Genomics and In Silico Functional Prioritization**

Genes identified within the region of linkage to BP on human chromosome 5 were aligned against syntenic BP QTLs on rat chromosome 18 with the use of Ensembl (http://www.ensembl.org/Homo_sapiens/multicontigview?s1=Rattus_norvegicus;c =5:142600000;w =3000001). Human genes that were conserved on the syntenic chromosomal region in rat were prioritized with regard to their functional potential to affect BP regulation. Each of these genes was assessed individually on the basis of preferential expression in BP-regulating tissues (kidney, heart, and blood vessels), evidence for contribution to hypertension in experimental models, and the overall level of support for association with hypertension in human studies. The gene that showed the highest pathophysiological potential to regulate BP was selected for further positional analysis.

**RNA Extraction, cDNA Synthesis, and Real-Time PCR**

Total RNA was extracted from 55 human renal samples with the use of a commercially available assay (RNeasy, Qiagen) according to the
manufacturer’s protocol. The extracted RNA was treated to remove contaminating DNA with the use of a DNase treatment and removal kit (DNA-free, Ambion). First-strand cDNA was synthesized with the use of 1 μg of total RNA and random hexamer primers (Advantage RT-for-PCR, Clontech Laboratories, Inc, Mountain View, Calif). Expression of FGF1 mRNA was determined with the use of an Applied Biosystems 7900HT Sequence Detection System and normalized to expression of β-actin housekeeping control gene. TaqMan primers and probes were obtained from Applied Biosystems and had the following sequences: FGF-1 forward GAAGTTATTA-ATCTGCCTCCAGGGAAAT, reverse CCCCGTGCTGATGTA- GAG, probe CAAGAGCCCCAATCT. Real-time PCR was performed in 5-μL volumes, in a reaction buffer containing 1× TaqMan Universal PCR Master Mix, 2 μL of cDNA, and 0.25 μL of TaqMan probe/primer mix. Reactions were as follows: 50°C for 2 minutes, 95°C for 10 minutes, and then 40 cycles of 95°C for 15 seconds followed by 60°C for 1 minute. Data were expressed as cycle threshold (Ct) and used to determine the dissociation (∆Ct values) (FGF1 Ct – β-actin Ct). The fold difference in gene expression between hypertensive and normotensive subjects was calculated as follows: fold difference = 2^(-∆Ct).

Western Blotting and Immunohistochemistry

Given that mRNA levels do not always correlate with changes in protein because of posttranscriptional and posttranslational regulation, a parallel comparative analysis of protein expression with the use of Western blot and immunohistochemistry was performed on 11 available samples. The tissue samples were homogenized and diluted to the same protein concentration, applied to 12% acrylamide gels, and electroblotted to nitrocellulose membranes. The membranes were incubated with specific FGF1 antibody (rabbit, polyclonal anti-human, Abcam). After they were rinsed, membranes were incubated with the secondary peroxidase-labeled IgG anti-rabbit antibody and proteins visualized by enhanced chemiluminescence (KPL, Gaithersburg, Md).

The densities of specific bands were normalized to the total amount of protein loaded in each well after densitometric analysis of gels stained with Coomassie blue. The densities of specific bands were quantified by densitometry with the use of Scion Image beta (version 4.02) software. Primary antibody for FGF1 was highly specific; it did not cross-react with FGF2 protein, which shares a significant structural homology with FGF1.

Paraffin sections were cut at 4 μm, and nonspecific immunolabeling was blocked with 10% nonimmune goat serum. After incubation with the primary antibody against FGF1, the sections were incubated with biotinylated anti-rabbit IgG for 1 hour at room temperature. The sections were washed with PBS and incubated with the avidin-biotin complex. A positive reaction was identified after a 10-minute treatment with 3, 3′-diaminobenzidine containing 3% H2O2 and counterstaining with Mayer’s hematoxylin.

Statistical Analysis

Consistent with our previous studies,5 the linkage analysis was based on adjusted SBP and pulse pressure (PP) as quantitative traits. Before linkage analysis, BPs of patients treated pharmacologically for hypertension were corrected nonparametrically for therapy-induced BP-lowering effect according to the formula used in our previous studies.4 These values were then adjusted for age, sex, and body mass index by linear regression. Joint nonparametric multipoint analysis of linkage of the candidate region, after saturation with additional markers, to adjusted SBP and PP was performed with the use of the MERLIN program.12 Single-point linkage of microsatellite markers to adjusted BP was examined by standard Haseman-Elston regression.

Construction of LD map and haplotype blocks within FGF1 was based on genotypes of the SHS families and a method of solid spine of LD (D' coefficient threshold of 0.8) available in Haploviz software (version 3.2) (http://www.broad.mit.edu/mpg/haploviz/).13 A graphic image of LD within FGF1 was created with the use of the LocusView program (T. Petryshen, A. Kirby, M. Ainscow, unpublished software) (http://www.broad.mit.edu/mpg/locusview). Deviation from Hardy-Weinberg equilibrium (HWE) was assessed on the basis of genotypes of the founders of the SHS families and unrelated Silesian Renal Tissue Bank subjects with the use of Pearson χ2 test available in the SIB-PAIR software.14 Consistent with the previous studies,5,10 a conservative cutoff value (P = 0.01) was used as a threshold of the HWE test. SNPs with HWE χ2 statistics corresponding to the probability value of < 0.01 were excluded from the association analysis.

Single-locus analysis of associations between hypertension and FGF1 SNPs was performed with the empirical variance option17 of the family-based association test (FBAT) under the null hypothesis of linkage but no association. In brief, the FBAT uses conditioning on trait information and genotypes from available parents or offspring (if the parental data are missing) in deriving the distribution for the S statistic and the corresponding level of statistical significance. In conditioning on the trait and the parental genotypes, the FBAT is similar to the original transmission disequilibrium test but has an advantage over the classic transmission disequilibrium test by extinguishing genetic polymorphism, we used Schaid’s genotypic risk ratio test for familial association23 available in the SIB-PAIR software.14 Independence of parental transmissions to affected offspring in this analysis was secured by inclusion of only 1 affected offspring per family. The calculations were based on the likelihood method appropriate when HWE is not violated.

To control for multiple testing, we used a SNP spectral decomposition method proposed by Nyholt25 in modification by Li and Ji.24 In brief, the correction was based on the spectral decomposition of matrices of pairwise LD between SNPs and calculation of the effective number of independent genetic marker loci along with the significance threshold required to keep the type I error rate at 5%. The SNP spectral decomposition approach is preferred to a conservative Šidák’s correction, which does not account for LD-driven dependence among markers and thus may overestimate the level of type I error and reduce the power to detect associations.23 After spectral decomposition of the LD matrices of FGF1 SNPs, the corrected threshold of statistical significance in the single-locus association study was estimated at P = 0.0028.

The statistical power of this study to detect an association between hypertension and candidate gene polymorphisms was explored with the use of version 3.2 of the PBAT program.23 The analysis was performed under the following assumptions: (1) allele frequency from 0.1 to 0.4; (2) penetrance of AA, AB, and BB genotypes (0.6, 0, and 0.2, respectively); and (3) calculation based on numerical integration. At a nominal significance level (P = 0.05), the study had 88.35%, 97.24%, 98.46%, and 98.54% power to detect an association between hypertension and a variant with minor allele frequency of 0.1, 0.2, 0.3, and 0.4, respectively. At the level of significance implicated by the correction of multiple testing in single-locus association analysis (P = 0.0028) and under the same statistical assumptions related to allele frequency, genotypes penetrances, and the type of power calculation, the SHS had power of ~54.36%.
79.34%, 85.64%, and 85.8% to provide evidence for association between hypertension and a variant occurring with a frequency of 0.1, 0.2, 0.3, and 0.4, respectively. Student t test and Mann-Whitney test were used in comparison of the quantitative phenotypes between 2 contrasting groups of genotypes or phenotypes.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Quantitative Trait Locus for SBP on Human Chromosome 5: Fine Mapping, Comparative Genomics, and Functional Prioritization**

Multipoint analysis based on the tightened grid of genetic markers within the QTL showed increased linkage of this chromosomal region to both adjusted SBP and PP (Figure 1). The maximal linkage to SBP and PP was detected in close proximity to D5s1480 ($Z=2.86$, $P=0.002$ and $Z=3.51$, $P=0.0002$, respectively). Single-point analysis confirmed linkage of BP phenotypes to 4 additional microsatellite markers (D5s207 through D5s1979) located between D5s1480 and centromere (Figure 1).

In silico examination revealed that the region linked to BP in both multipoint and single analysis spanned ≈3 Mbp and contained 13 human genes (Figure 1). Of those, 2 genes (GNPDA1, HMHB1) were not conserved on the syntenic QTL on rat chromosome 18. Five other human genes (PCDH1, SPRY4, ARHGAP26, KIAA0141, KCTD16) corresponded either to predicted rat genes or annotated ex-
pressed sequence tags on the corresponding portion of the rodent BP QTL. Functional prioritization of the 6 remaining human genes that had unambiguous orthologs within the BP QTL on rat chromosome 18 (Figure 1) implicated FGF1 as the locus with the highest pathophysiological potential to influence BP.

FGF1: Direct Sequencing and In Silico Functional Examination of SNPs
No genetic variation existed within the coding or untranslated exons of FGF1. The 7.1-kb 5’ flanking region adjacent to exon 1, the intronic segment, and the 3’ untranslated region contained 21, 78, and 6 SNPs, respectively. Of these, 9, 18, and 6 had a minor allele frequency >10%. Only 1 common genetic variant in the 3’ untranslated region (rs33999) was implicated as a functional microRNA target site in the SNP Function Portal.10

FGF1 Locus: LD Map
The LD map based on SNPs genotyped in the SHS revealed 3 major, independent haploblocks within the FGF1 (Figure 2). Analysis of high-density haploblock structure denoted the borders of LD across the entire FGF1 locus and confirmed that the adjacent extragenic polymorphisms did not overlap with the haploblocks identified in FGF1 (Figure 2).

FGF1 and Hypertension: Single-Locus and Multimarker Family-Based Association Analysis
Of 45 FGF1 SNPs, 3 (rs2278688, rs11167783, rs9324892) showed deviation from HWE (probability values from HWE $\chi^2$ test of 0.0094, 0.0031, and 0.0036, respectively) and were excluded from further association analysis.

Family-based analysis revealed that genetic variations within both haploblock 1 and haploblock 3 of FGF1 were...
associated with hypertension. Specifically, 6 alleles in haploblock 1 and 1 variant in haploblock 3 were transmitted from parents to hypertensive offspring more frequently than expected by chance at the nominal level of significance (Table). However, only 1 FGF1 SNP (rs152524 in haploblock 1) retained its significant association with hypertension after correction for multiple testing ($P=0.0026$).

The multimarker test (FBAT T1c) based on all 20 SNPs of FGF1 haploblock 1 confirmed its association with hypertension ($P=0.0301$). The subsequent elimination of rs152524 from this multimarker analysis reduced the statistical significance of the

**Table. FGF1 SNPs and Hypertension: Single-Locus Family-Based Association Analysis**

<table>
<thead>
<tr>
<th>Internal SNP ID</th>
<th>db SNP rs No.</th>
<th>Chromosomal Location</th>
<th>Alleles</th>
<th>Minor Allele Frequency</th>
<th>FGF1 Haploblock</th>
<th>Gene Region</th>
<th>Hypertensive Variant</th>
<th>$P$ in HWE</th>
<th>No of Families</th>
<th>$P$ in FBAT</th>
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<td>3'</td>
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</table>

$P$ in HWE indicates $P$ corresponding to HWE $\chi^2$ test; $P$ in FBAT, level of nominal statistical significance in the single-locus empirical variance FBAT; 3', 3' untranslated region of FGF1; 5', 5' flanking region of FGF1; int, intronic segments of FGF1; and No. of families, No. of informative families in FBAT.
association between hypertension and FGF1 haploblock 1 ($P=0.0457$).

**rs152524 and Relative Risk of Hypertension**
The genotypic risk ratio test for familial association showed that relative risk of hypertension increased with an increase in number of copies of the rs152524 A allele ($P=0.016$). Compared with reference (GG genotype of rs152524), the relative risk of hypertension increased to 2.2 (95% CI, 1.19 to 4.05) and 2.84 (95% CI, 1.32 to 6.12) in heterozygotes and homozygotes with 2 copies of rs152524 A allele, respectively.

**FGF1 and Hypertension: Renal Expression Analysis**
FGF1 mRNA expression was $1.7$-fold higher in kidneys of hypertensive patients than in normotensive controls (Figure 3). Consistently, FGF1 protein was more abundant in the renal tissue from hypertensives than normotensives (Figure 3). In addition, the magnitude of the difference in renal expression of FGF1 between hypertensive patients and normotensive controls was comparable at both levels of gene expression (Figure 3). Immunohistochemical studies (Figure 4) showed that FGF1 was immunolocalized exclusively to glomerular endothelial and mesangial cells. Consistent with the findings from Western analysis, intensity of glomerular FGF1 immunostaining was higher in hypertensive subjects than in normotensive controls (Figure 4).

**Association Between rs152524 Polymorphism and FGF1 mRNA Expression**
The distribution of rs152524 genotypes in subjects from the Silesian Renal Tissue Bank was in concordance with HWE (25, AA; 20, AG; and 10, GG; $P=0.2829$ in $\chi^2$ test).

Renal expression of FGF1 mRNA was $1.8$-fold higher in carriers of the prohypertensive A allele (AA homozygous and AG heterozygous individuals) compared with the subjects with GG genotype (mean±SD dCt, 5.3±1.5 versus 6.1±1.5 in A carriers and GG subjects, respectively), but this difference did not reach the threshold of statistical significance ($P=0.1010$).

**Discussion**
This study provides the first reported evidence for associations between FGF1 and human hypertension. Specifically, our data demonstrated that genetic variation in FGF1 cosegregated with elevated BP in hypertensive families, and this association was likely to be mediated by upregulation of FGF1 within renal glomeruli. Most importantly, the support for the role of FGF1 in human hypertension was consistent across multiple levels of molecular biology including chromosomal, genetic, transcriptomic, and proteomic analysis. In this context, the association between FGF1 and hypertension is functionally integrated and biologically meaningful.

Tightening the grid of genetic markers under the QTL in the current analysis provided enhanced support for linkage of this chromosomal region to BP in the multipoint analysis. This type of fine mapping is fundamental in validation of positive linkage findings and narrowing down the QTL but is critically dependent on accuracy of microsatellite chromosomal locations. Therefore, to exclude spurious linkage that may be driven by arbitrary definition of distances between microsatellite markers, we confirmed the multipoint findings in the complementary single-point analysis. Most importantly, the studies based on single microsatellite markers contributed to narrowing down the QTL to an extent that was dissectible in positional analysis.

Positional potential of FGF1 as a candidate gene is supported by data from in silico comparative genomics and experimental models. First, it is located centrally within the
BP QTL on human chromosome 5. Second, it is conserved on the chromosomal region linked to multiple BP phenotypes in rodent models of hypertension\(^8,27\) (Figure 1). Indeed, it was proposed as a potential driver of the linkage to salt-sensitive hypertension in rodents.\(^8\) FGF1 protein is expressed in target organs involved in BP regulation, including the kidney, heart, and blood vessels.\(^28-30\) In addition, FGF1 was shown to stimulate endothelin-1 release,\(^31\) upregulate expression of endothelin-A receptor,\(^32\) and increase plasma levels of catecholamines as well as corticosteroids.\(^33\) Collectively, these data indicate that FGF1 is a clinically important, multifunctional molecule that may contribute to the pathophysiology of hypertension and cardiovascular disease.

The results from our family-based tests mapped the most significant association signal to the common intronic variant (rs152524) within haplобlock 1 of FGF1. The rs152524 is the first common polymorphism in intron 1, located 1146 bp from the exon-intron junction. Although no obvious molecular functions were annotated to this SNP in silico,\(^10\) we suggest that it may act as a putative coregulator of transcription. In support of this hypothesis, previous studies showed that other common intronic variants could contribute to cardiovascular disorders by regulation of mRNA metabolism.\(^34\) The potential functional relevance of the genetic sequence that contains rs152524 (human FGF1 intron 1) is also supported by its high conservation when aligned against the corresponding genomic segment of the murine, rat, and canine FGF1 (59%, 60%, and 76%, respectively). Finally, our studies on correlation between rs152524 and FGF1 expression showed a trend toward higher renal abundance of FGF1 mRNA in carriers of prohypertensive A allele compared with subjects with GG genotype. Future studies in larger cohorts of subjects will be needed to verify this observation.

Mechanistically, overexpression of FGF1 within glomerular endothelial and mesangial cells represents a putative functional mechanism for BP elevation. Both endothelial and mesangial cells contribute to regulation of glomerular microcirculation,\(^35\) which in turn influences systemic BP.\(^36\) Consequently, dysregulation of glomerular hemodynamics was shown as a key causative mechanism in both experimental as well as essential hypertension.\(^37\) Most importantly, overexpression of growth factors within mesangial cells correlates with genetic predisposition to hypertension\(^38\) and may result in activation of the renin-angiotensin-aldosterone system.\(^39\) In light of these data, upregulation of FGF1 in glomerular mesangial and endothelial cells may represent a genetically dependent mechanism that contributes to BP elevation.

Our study has a number of limitations. First, our findings are based on the data from 1 cohort of hypertensive families. Additional samples, in particular those with evidence for linkage of this chromosomal region to BP, will be needed to replicate our results. Although not immune to the confounding influence of population stratification, cohorts of well-matched cases and controls will be particularly helpful because they usually provide a better power to detect and replicate associations between genetic variants and common diseases compared with family-based studies of similar size.\(^40\)

Second, our expression analysis was based only on human renal tissue. The kidney is the major BP regulator and 1 of the predominant sites of FGF1 expression.\(^41\) Indeed, 1 of the major alternate promoter regions of FGF1 is activated exclusively within the kidney.\(^42\) And our preliminary comparative analysis confirmed that renal expression of FGF1 was higher than vascular tissue from human renal artery (data not shown). Although these data fully justify using the renal tissue as the major platform for gene expression studies on FGF1, its upregulation in hypertensive heart or blood vessels cannot be excluded.

Third, classification of patients with renal cancer as essentially hypertensive or normotensive may be problematic. Indeed, hypertension in such patients may be secondary to fibromuscular dysplasia of the renal artery. Conversely, young subjects with a genetic predisposition to hypertension could be misclassified as normotensive if they were diag-

**Figure 4.** FGF1 and the human hypertensive kidney: immunohistochemistry. FGF1 was expressed almost exclusively within mesangial and endothelial cells of human glomeruli. Intensity of glomerular FGF1 immunostaining was higher in the hypertensive kidney than in normotensive control. C indicates capillaries.
nosed with a renal neoplasm at a young age. However, ≈94% of our patients were diagnosed as essentially hypertensive long before renal cancer (on average 8 years before the diagnosis of kidney tumor). In addition, none of the hypertensive patients had any clinical features of secondary hypertension, and normotensive subjects with renal cancer were mostly middle-aged or elderly (median age, 57.5 years), and none of them were diagnosed with renal cancer before the age of 30 years. Collectively, these data suggest that misclassification of subjects recruited in the Silesian Renal Tissue Bank is very unlikely.

Finally, although higher renal FGF1 expression in hypertensive than in normotensive subjects could be mediated, at least in part, by genetic factors, contribution of secondary mechanisms (such as pressure load) to upregulation of FGF1 in the kidney also cannot be excluded. Future studies on the comparison of renal FGF1 expression between essentially hypertensive patients and subjects with secondary hypertension are warranted to dissect the mechanisms underlying FGF1 upregulation in hypertensive kidney.

In summary, our data provide compelling evidence for the association between FGF1 and human hypertension. Most importantly, our studies show that a combination of linkage analysis, LD mapping, single-locus, and haplotype FBAT as well as gene expression studies may contribute to discovery of a novel genetic determinant of hypertension. Clinically, our results provide insight into the genetics of fibroblast growth factors, a new, therapeutic option for cardiovascular disease. Finally, these data highlight a novel biologically plausible pathway of BP regulation and hold the promise of further studies on fibroblast growth factors as early diagnostic markers of cardiovascular risk.

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Disclosures

None.

References

Essential hypertension is one of the most common cardiovascular disorders. Environmental factors and at least several genes contribute to the pathogenesis of hypertension. Identification of the genetic variants associated with blood pressure elevation is one of the most important challenges of cardiovascular medicine and has a potential to improve diagnostic and therapeutic strategies. In search of genes related to hypertension, we performed a detailed analysis of the blood gene-expression profiles of hypertensive patients and normotensive controls. Our data implicates FGF1 as a novel, potentially causative gene of essential hypertension and the fibroblast growth factor signaling cascade as a new plausible pathway of blood pressure regulation. Further investigations on FGF1 may aid in early prediction and diagnosis of hypertension and its complications.
Fibroblast Growth Factor 1 Gene and Hypertension: From the Quantitative Trait Locus to Positional Analysis


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