Serum- and Glucocorticoid-Regulated Kinase (SGK1) Gene and Blood Pressure

Andreas Busjahn, Atakan Aydin, Regina Uhlmann, Christine Krasko, Sylvia Bähring, Tamas Szelestei, Yuxi Feng, Stephan Dahm, Arya M. Sharma, Friedrich C. Luft, Florian Lang

Abstract—The serum- and glucose-regulated kinase (SGK1) gene has recently been identified as an important aldosterone-induced protein kinase that mediates trafficking of the renal epithelial Na\(^+\) channel (ENaC) to the cell membrane. Thus, SGK1 is an appealing candidate for blood pressure regulation and possibly essential hypertension. To test this hypothesis, we recruited monozygotic (126 pairs) and dizygotic (70 pairs) normotensive twin subjects and parents of dizygotic twins. Blood pressure was measured in a controlled fashion: recumbent, sitting, and upright. We documented genetic variance on blood pressure in all positions. We then relied on microsatellite markers at the SGK1 gene locus (D6S472, D6S1038, and D6S270) and 2 single nucleotide polymorphisms within the SGK1 gene. We found significant linkage of the SGK1 gene locus to diastolic blood pressure (P<0.0002) and suggestive evidence for linkage for systolic blood pressure (P<0.04), documenting the locus as a quantitative trait locus for blood pressure. We next performed association, using all dizygotic twins and a monozygotic member from each pair. We found significant associations between both single nucleotide polymorphism variants and blood pressure, as well as a significant interaction between the single nucleotide polymorphisms enhancing the effect. This combined effect of the polymorphisms was confirmed in an independent sample of 260 young normotensive men. We conclude that the SGK1 gene is relevant to blood pressure regulation and probably to hypertension in man. (Hypertension. 2002;40:●●●●●●)

Key Words: genetics ■ twins ■ blood pressure ■ hypertrophy ■ kinase ■ protein kinases ■ polymorphism

The serum- and glucocorticoid-regulated kinase (SGK) was originally cloned from rat mammary tumor cells as a glucocorticoid responsive gene.\(^1\) The human isoform was subsequently cloned as a cell volume–sensitive gene upregulated by both hypertonic and isotonic cell shrinkage.\(^2,3\) Because of the discovery of the 2 isoforms SGK2 and SGK3,\(^4\) the originally cloned kinase is labeled SGK1. SGK1 is expressed in renal tubular epithelial cells,\(^5,6\) and its transcription is strongly stimulated by mineralocorticoids,\(^7\) suggesting a role in renal Na\(^+\) regulation. Indeed, coexpression of SGK1 with the renal epithelial Na\(^+\) channel (ENaC) in Xenopus oocytes markedly upregulates Na\(^+\) channel activity by enhancing channel protein abundance in the cell membrane.\(^5,9\) Furthermore, SGK1 upregulates BSC1, the thick ascending limb Na\(^+\),K\(^+\),2Cl\(^-\) cotransporter similarly important in renal Na\(^+\) reabsorption.\(^10\)

ENaC \(\beta\)- and \(\gamma\)-subunit mutations are responsible for Liddle’s syndrome, an autosomal-dominant form of monogenic hypertension.\(^11\) ENaC subunit variants have generated interest in terms of possibly influencing blood pressure in essential hypertension as well.\(^12,13\) We have studied monozygotic (MZ) and dizygotic (DZ) twins and the parents of DZ twins to gain inference into genetic variance on blood pressure and to map blood pressure quantitative trait loci. In an earlier study, we showed linkage of several gene loci to blood pressure, including ENaC subunit gene loci.\(^14\) The fact that aldosterone regulates cell membrane abundance of ENaC in the renal collecting system, at least in part via SGK1, makes this kinase an attractive candidate gene for blood pressure regulation and possibly hypertension. We addressed this issue by means of a twin study and an independent verification cohort.

Methods: We recruited 126 pairs of MZ and 70 pairs of DZ twins to participate in studies involving blood pressure regulation and cardiovascular phenotypes.\(^14\) We also recruited the parents of the DZ twins. The subjects were all white Germans recruited from various parts of Germany. The University’s committee on the protection of human subjects approved the protocol, and written informed consent was obtained from all participants. Blood was obtained for the determination of zygosity and other molecular genetic studies from all the twins and the parents of the DZ twins. Each participant underwent a medical history and physical examination. None had a family history of chronic medical illness. Blood pressure was measured after 5 minutes (2 measurements, 1 minute apart) with a standardized...
mercury sphygmomanometer in the recumbent, sitting, and standing positions by a trained physician. Blood pressure was defined as the mean of the 2 measurements. Echocardiography was performed as described earlier.14

We included a confirmation sample consisting of 260 normal healthy male volunteers (mean age, 25±2 years; resting BP, 111±8/58±6 mm Hg) who participated in a protocol to delineate salt sensitivity and resistance of blood pressure.15 The subjects received a 20-mmol/d or 220-mmol/d sodium diet for 7 days in random order. Blood pressure was measured on the seventh day under standardized resting conditions with an oscillometric device as outlined earlier.13

Linkage
Heritability was calculated based on maximum likelihood estimation by structural equation modeling by use of the MX program. For the linkage study, the DZ pairs and their parents were genotyped to permit an identity-by-descent analysis. The DZ twins were used as ordinary sib-pairs, but with the advantage of perfect age matching and reduced environmental variation affecting the phenotype. The zygosity was verified with the use of 5 polymerase chain reaction (PCR)–amplified microsatellite markers.14 We examined 3 microsatellite markers at the SGK1 gene locus: D6S472, D6S1038, and D6S270. We assessed linkage for blood pressure as a continuous trait. Sib-pair analysis to determine linkage does not require the specification of a genetic model. The underlying trait can follow either mendelian or nonmendelian modes of inheritance. Analysis was performed by use of a structural equation modeling (SEM) approach. This approach is based on variance-covariance matrices of sibs weighted by the probability of sharing 0, 1, or 2 alleles identical by descent. Phenotypic variance (VAR) is decomposed into variance due to genetic background (A2), variance due to the quantitative trait loci effect (Q2), and environmental variance (E2):

\[
VAR = A^2 + Q^2 + E^2
\]

For the 3 possible identical-by-descent states (sharing 0, 1, or 2 alleles), covariance of a sib pair is then defined by the following:

\[
\text{COV}_{\text{IBD}0} = 0.5A^2; \quad \text{COV}_{\text{IBD}1} = 0.5A^2 + 0.5Q^2;
\]

and

\[
\text{COV}_{\text{IBD}2} = 0.5A^2 + Q^2
\]

For each sib pair and each locus, the proportion of alleles identical by descent, based on parental genotypes and independent allele frequency estimates, is calculated using a multipoint approach as implemented in MAPMAKER/SIBS. From these identical-by-descent estimates, the significance of the quantitative trait loci effect was tested by the difference in model fit for models with and without a quantitative trait loci effect, calculated as a chi-square statistic. For this analysis, we used the MX package. The probability values for these tests are given in the Results section. The higher power of the variance-covariance–based analysis, compared with the squared trait differences–based approach by the Haseman-Elston method has been documented in simulation studies.10,17 Because we used a candidate gene approach, we accepted P<0.05 to test for significant linkage in accordance with the criteria defined by Lander and Kruglyak.18 The definition of a candidate gene may rely on prior evidence from genome scans (positional candidate) and on physiological evidence from functional studies based on the gene product.

Association
The genomic organization of SGK1 has been described earlier.19 Information can be obtained at gene No. 00000118515 (wwwensembl.org). We first searched public databases to identify single nucleotide polymorphisms (SNPs) in SGK1; however, most SNPs either were erroneous or were not sufficiently polymorphic for our purposes. An SNP in exon 8 (C→T) that we identified from the National Center for Biotechnological Information SNP database proved satisfactory (rs1057293). We eventually relied on direct sequencing and found a second SNP (C→T) in exon 6 (T→C). These 2 SNPs, intron 6 (T→C) and exon 8 (C→T), were analyzed.

For the mini-sequencing reaction, the 2 different loci were amplified with the following forward and reverse primers: for SGK exon 8 C→T, 5′-ATA GAT GAG CAG AAC AAG GCC and 5′-CTG GAC TTT TTG AGG GTG ACT; for exon 8 T→C, 5′-GCC TGC TTT GTT TTA GTT TGA and 5′-GCT ACG GGA TCT GTT ATT AGG. The total PCR reaction volume was 15 μL. The PCR reaction mix contained the following: 10 nmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, 2.5 mmol/L MgCl₂, 250 μmol/L of each dNTP (dATP, dCTP, dGTP, and dTTP from Pharmacia), 333 nmol/L of forward and reverse primer, 50 ng of genomic DNA, and 0.6 U of Ampli Taq gold DNA polymerase (Applied Biosystems). After PCR amplification, we used 1 U alkaline phosphatase/1 U exonuclease I (Amersham) to degenerate the PCR primers and dephosphorylate the samples, dNTPs. The PCR was conducted at 95°C for 10 minutes and for 35 cycles at 95°C for 15 seconds, followed by 62°C for 15 seconds and 72°C for 30 seconds, and an extension step at 72°C for 10 minutes. The PCR amplifications were performed in a 9600 thermal cycler (Applied Biosystems). The sequences for the mini-sequencing primer were as follows: for the SNP in intron 6 C→T, 5′-CTC CTT GCA GAG TCA GCC; for the intron 6 SNP T→C, 5′-ACC AAG TCA TTC TGG GTG GC. The reaction conditions were in a 10 μL reaction volume, 2.5 μL ready-reaction premix buffer, containing (F)-ddNTP, Taq-polymerase, ABI prism SnipShot ddNTP (Primer Extension Kit II, Applied Biosystems), 10 nmol/L mini-sequencing primer, and 0.15 pmol purified PCR product as template. The mini-sequencing conditions were for both loci were as follows: 25 cycles consisting of a heat-denaturation step of 10 seconds at 96°C, an annealing step of 10 seconds at 50°C, and an extension step of 30 seconds at 60°C. The mini-sequencing reactions were performed in a 9600 thermocycler (Applied Biosystems). To remove the 5′ phosphoryl groups from the unincorporated fluorescence marker ddNTP, we added 2 U shrimp alkaline phosphatase (Boehringer) to the mini-sequencing reaction and incubated it at 37°C for 1 hour. The separation was performed on the ABI Prism 3100 with POP4 polymer 36-cm capillary and with GS STR POP4 E5 module. The signals were analyzed using Collection software version 1.0 and the GeneScan Analysis software version 3.6.3.

Descriptive statistics for both SNPs showed a recessive mode of action. Thus, association analysis was based on 2 group comparisons of homozygous carriers of the variant versus heterozygous/noncarriers. Independence of the 2 SNPs was tested by χ² test. The relation between SNPs and phenotypes was tested by a univariate ANOVA incorporating both polymorphisms at the same time. This analysis included both members of DZ pairs and 1 randomly selected member of the MZ pairs. We relied on this test rather than the χ² test to simultaneously analyze both polymorphisms, including their interaction, as well as to reduce the number of tests performed. As both members of a DZ pair are not independent, family effects were included in the ANOVA, as well as age and sex as covariates. A significance level of 0.05 was set. In the confirmation group, we tested the association effect by univariate ANOVA with both SNPs at the same time.

Results
Table 1 shows the demographic twin data, the genetic influence on blood pressure, and the linkage results. The twins were young, nonobese, normotensive men and women. A strong genetic effect was found on blood pressure in all positions. Heritability estimates from twin studies are usually higher than those obtained from parent-offspring correlation. This state-of-affairs is because twins share nonadditive genetic effects (dominance and epistasis) in addition to the additive genetic effects shared by all first-degree relatives. Further increase in heritability estimates may come from gene-environment interaction. A theoretical bias in twin-based estimates may arise from a greater extent of shared prenatal influences in MZ twins. The linkage analysis showed significant or suggestive linkage of the SGK1

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gene locus to systolic and diastolic blood pressure in all positions. These data provide evidence implicating the SGK1 gene locus in blood pressure regulation.

Table 2 shows the results for systolic and diastolic blood pressure in the recumbent, sitting, and standing positions and the SNP genotypes. The allele frequencies for the exon 8 SNP C were 91%; for T, 9%. Those for the intron 6 SNP T were 79%; for C, 21%. Hardy-Weinberg equilibrium was maintained for both polymorphisms. The blood pressure values in all positions were very similar. Homozygous and heterozygous carriers of the exon 8 alleles (CC or CT) did not differ from each other while showing higher systolic and diastolic blood pressure values than those of the homozygous exon 8 TT subjects. The results for the intron 6 SNP were less consistent; however, homozygous CC subjects showed the lowest blood pressure, despite being homozygous for the blood pressure–increasing intron 6 C allele (Figure). These results indicate the presence of an interaction between the polymorphisms themselves or other genetic variants in different linkage dysequilibrium.

We tested this association in an independent 260-subject confirmation sample as shown in Table 4 and found a significant effect of both polymorphisms on resting systolic blood pressure (Figure). Again, the blood pressure–increasing effect of intron 6 CC was compensated by the lowering effect of exon 8 TT in the exon 8 SNP was invariably significant except for diastolic blood pressure in the recumbent position. The results for intron 6 SNP were similar for systolic blood pressure. The SNPs were in strong linkage dysequilibrium, as shown in Table 3. Everyone homozygous for exon 8 TT was also homozygous for intron 6 CC; however, the converse was not invariably the case. The highest blood pressure values were observed for subjects carrying increasing alleles for both SNPs. Homozygous exon 8 TT subjects showed the lowest blood pressure despite being homozgyous for the blood pressure–increasing intron 6 C allele (Figure). These results indicate the presence of an interaction between the polymorphisms themselves or other genetic variants in different linkage dysequilibrium.

Table 2 gives the association statistics for the twin subjects. For the systolic and diastolic blood pressure of the phenotypes, the exon 8 SNP was invariably significant except for diastolic blood pressure in the recumbent position. The results for intron 6 SNP were similar for systolic blood pressure. The SNPs were in strong linkage dysequilibrium, as shown in Table 3. Everyone homozygous for exon 8 TT was also homozygous for intron 6 CC; however, the converse was not invariably the case. The highest blood pressure values were observed for subjects carrying increasing alleles for both SNPs. Homozygous exon 8 TT subjects showed the lowest blood pressure despite being homozgyous for the blood pressure–increasing intron 6 C allele (Figure). These results indicate the presence of an interaction between the polymorphisms themselves or other genetic variants in different linkage dysequilibrium.

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Effect of the polymorphisms on blood pressure in the twin sample and the replication sample. Intron 6 CC has an increasing effect that is compensated by the blood pressure-lowering effect of exon 8 TT.

### TABLE 3. Linkage Disequilibrium Between the 2 Polymorphisms in the Twin Sample

<table>
<thead>
<tr>
<th>SNP</th>
<th>Intron 6 TT</th>
<th>Intron 6 CT</th>
<th>Intron 6 CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 8 CC</td>
<td>172 (64)</td>
<td>48 (19)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Exon 8 CT</td>
<td>2 (1)</td>
<td>24 (10)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Exon 8 TT</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

Values are n (%); \( \chi^2 \) test, \( P<0.01 \).

Subjects homozygous for both polymorphisms. For diastolic blood pressure, no association could be detected. This association was detectable not only for untreated blood pressure but also during the high salt intake period. During a low salt intake period, the effect was weaker (\( P<0.1 \)). The blood pressure difference between high and low salt intakes showed suggestive trend for association (\( P<0.1 \)) for systolic and diastolic blood pressure. However, no clear-cut association for the salt-sensitive or salt-resistance phenotypes was demonstrated.

### Discussion

We used 2 genetic strategies to test the hypothesis that SGK1 is relevant to blood pressure in man. First, we used microsatellite markers and performed an identity-by-descent linkage analysis in DZ twins and their parents. The results were supportive, indicating that the SGK1 gene locus is linked to systolic and diastolic blood pressure, irrespective of body position. We then applied a second independent strategy. We performed an association study in the DZ twins and 1 person from each MZ twin pair, ie, a total of 232 people. We found a significant association for variants in the exon 8 SNP and systolic and diastolic blood pressure, irrespective of body position. This SNP was in close, but not complete, linkage disequilibrium with a second SNP 551 bp away in intron 6 that also generally showed significant associations. An interaction was observed between the SNPs. Finally, we called on a third independent approach, ie, an independent cohort analysis of normotensive young men supporting the findings accrued from the twin subjects. Our findings support a role for SGK1 in blood pressure regulation.

Our findings also underscore the usefulness of studying multiple contiguous SNPs. Had we relied only on 1 SNP, our analysis would have been less informative. By analyzing 2 SNPs, we were able to document an interaction that solidifies our results. A similar but more comprehensive study was recently reported by Zhu et al.\(^2\) They performed linkage and association analysis of ACE gene polymorphisms with ACE concentrations and blood pressure in 1343 Nigerians from 332 families. Most of the polymorphisms in the ACE gene were significantly associated with ACE levels. The 2 most highly associated polymorphisms accounted for 6% and 19% of the variance in ACE. The authors then used a 2-loci additive model and, with an additive-additive interaction of these polymorphisms, were able to explain most of the ACE variation in this region. They also showed an association with systolic and diastolic blood pressure when the 2-loci additive model was used. We have not yet performed a comprehensive functional analysis of the SGK1 gene, although such an analysis is clearly warranted.

SGK1 and, indeed, all of the aldosterone-induced gene transcripts are attractive candidate genes for blood pressure regulation and particularly for hypertension. The small G protein K-Ras2A and the aldosterone-inducible protein SGK1 both appear to increase ENaC activity. K-Ras2A is a channel-activating aldosterone-induced protein that is involved in GTP-induced increases in channel activity and requires prenylation.\(^2\)

Unpublished observations from our laboratory indicate that activation of Ras upregulates and that disruption of Ras prenylation downregulates SGK1 transcription, pointing to interaction of the 2 signaling molecules (S. Waldegger and F. Lang, unpublished data, 2002). Once expressed, SGK1 requires activation that can be accomplished by insulin and insulin-like growth factor (IGF1).\(^2\) The signaling of insulin and IGF1 to SGK1 involves PI3-kinase and subsequent activation of the serine/threonine kinases PDK1 or PDK2.\(^2\) ENaC upregulation by mineralocorticoids requires activation through the PI3 kinase pathway, which mediates the stimulation of renal Na\(^+\) excretion by insulin and IGF1.\(^4\) Thus, SGK1 may participate in the signaling of IGF1-induced alterations of renal Na\(^+\) transport and blood pressure. Acromegaly, which leads to enhanced release of IGF1, is a well-known cause of hypertension, and the IGF1 gene locus demonstrates linkage to blood pressure in twins.\(^2\) Only a subpopulation of acromegalic patients develop hypertension. In view of the present data, it is tempting to speculate that the acromegalic patients who remain normoten-
sive express low levels of SGK1 and are thus less responsive to the hypertensive effects of IGFI.

The function of SGK1 is not limited to regulation of renal ENaC activity. The kinase is expressed in all human tissues studied, including pancreas, liver, heart, lung, skeletal muscle, placenta, kidney, and brain. In addition to glucocorticoids and mineralocorticoids, cell shrinkage, excessive glucose concentrations, increased cytosolic Ca\(^{2+}\) activity, phorbol esters, serum, and several inflammatory mediators (including granulocyte-macrophage colony-stimulating factor, lipopolysaccharides, N-formyl-Met-Leu-Phe, tumor necrosis factor-\(\alpha\), and tumor necrosis factor-\(\beta\)) stimulate SGK1 transcription. The kinase has also been implicated in the regulation of cell proliferation, apoptosis, and fibrosing disease. Conceivably, SGK1 could also have a bearing on hypertension-induced vascular injury. Thus, further understanding of SGK signaling may clarify the increasing spectrum of aldosterone-mediated effects.

We believe that the SGK1 gene is an excellent candidate gene for blood pressure regulation and hypertension. Limitations of our study are the fact that the linkage data are derived from a relatively small number of DZ twins and their parents, and that the gene locus has not been robustly linked to blood pressure regulation and hypertension in an earlier study. An example for the reproducibility of positive linkage findings in relatively small samples would be the gene(s) responsible for Liddle’s syndrome.

The locus was linked to blood pressure in the general population in parallel on the basis of family studies and an earlier twin study from our group. Careful physiological hypotheses, replication, and concordant evidence from linkage and association can add credibility to genetic studies. We provide evidence for linkage between the SGK1 gene locus and systolic and diastolic blood pressure under several different conditions. We performed an association analysis of 2 SNPs in the SGK1 gene and found that both were associated with systolic and diastolic blood pressure. We were then able to show a significant interaction, which enhanced the effect. We conclude that SGK1 may be important to blood pressure regulation and hypertension.

Acknowledgments

F.C.L. and F.L. were supported by grants-in-aid from the Deutsche Forschungsgemeinschaft. This project also received support from the German Human Genome Project and the European Community, EurHyGen (F.C.L.).

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27. Busjahn et al. SGK1 and Blood Pressure.
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Hypertension. published online August 12, 2002;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
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