The Role of ACE Gene Polymorphism in Rapidity of Progression of Focal Segmental Glomerulosclerosis

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Abstract:
BACKGROUND: The insertion/deletion (I/D) polymorphism of angiotensin converting enzyme (ACE) gene has been associated with progression of renal diseases. AIMS: We investigated its role in the rate of progression of focal segmental glomerulosclerosis (FSGS). METHODS: Forty-seven patients with end-stage renal disease (ESRD) due to FSGS were evaluated. RESULTS: The distribution of ACE genotype was II-25.5%, ID-55.5%, and DD-19%, as compared to 40 controls with genotype of 7.5%, 60%, and 32.5%, respectively (p = NS). In African Americans (AA) the gene frequencies among patients and controls were I-43%, D-57% vs I-36%, D-64%, respectively. This was different than the gene frequencies in White/Hispanic (W/H) patients I-61.5%, D-38.5% vs I-38.6%, D-61.4%, in controls (P < 0.05). In 22 patients with rapid progression (RP) of FSGS to ESRD the genotype distribution was II-18%, ID -64%, and DD-18%. In 25 patients with FSGS who progressed slowly (SP) the genotype was similar (II-32%, ID-48% and DD-20%, P > 0.05). With respect to rate of progression, D allele frequency was similar in AA patients (RP 64% vs SP 50%) and W/H patients (RP 36% vs SP 40%). CONCLUSION: Our study reveals no association between the I/D polymorphism of the ACE gene and the presence of and rapidity progression of FSGS. (J Postgrad Med 2002;48:266-269)

Key Words: ACE gene polymorphism, end stage renal disease, focal segmental glomerulosclerosis, rapid progression.

Idiopathic focal segmental glomerulosclerosis (FSGS) is one of the most important diseases leading to progressive renal failure in adults and children. A number of observations suggest that genetic factors may play an important role in progression of FSGS. A polymorphism of the angiotensin converting enzyme (ACE) gene consisting of a 287 bp fragment within intron 16 defined by insertion (I) or deletion (D) was reported to be associated with progression of several renal diseases including IgA nephropathy, autosomal dominant polycystic kidney disease and diabetic nephropathy. In a Korean population the double deletion (DD) genotype in FSGS patients has been associated with steroid unresponsiveness and a tendency to progress to renal failure. A strong genetic association has also been found between a DD genotype and increased risk of atherosclerotic cardio-vascular and cerebral diseases. In African Americans (AA) end-stage renal disease (ESRD) due to FSGS occurs much more frequently than in the general population. AA with essential hypertension have a higher frequency of DD genotype than normotensive AA. The rate of progression of FSGS varies among different races. FSGS can be particularly aggressive in AA with the rate of progression to ESRD from the time of diagnosis is significantly less than other racial groups. The purpose of the present study was to determine if I/D polymorphism of intron 16 of the ACE gene is associated with idiopathic focal segmental glomerulosclerosis and with its high rate of progression, particularly in African Americans.

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Patients and Methods
Seventy ESRD patients with biopsy proven FSGS were identified. Twenty-three patients were excluded from the study because of a systemic disease being the most likely etiology of FSGS. The patients were recruited from the dialysis unit or from the Nephrology clinic at Albert Einstein College of Medicine and allied hospitals. Of the 47 patients with primary FSGS included in the study, 21 patients were African-Americans (AA) and 26 were White/Hispanics (W/H). Forty healthy blood donors (18 AA and 22 W/H) served as controls. The controls had normal blood pressure and no history of renal disease at the time of blood donation. Patient charts were reviewed with special emphasis on race, time of biopsy and time of ESRD. The disease was called rapidly progressive (RP) when the time period between initial biopsy and ESRD exceeded two years. The disease was considered to be slowly progressive (SP) when the period from the diagnostic renal biopsy to ESRD was longer than two years. This study was approved by the Institutional Review Board at Albert Einstein College of Medicine and allied hospitals. Written informed consent was obtained.

The purpose of the present study was to determine if I/D polymorphism of intron 16 of the ACE gene is associated with idiopathic focal segmental glomerulosclerosis and with its high rate of progression.
from the patient/guardian and the donor in each case. The study was completed within 12 months from the time of initiation.

Ten ml blood was collected from patients and controls and stored at -20°C pending analysis. DNA was isolated from peripheral leucocytes by the standard protocol. The I/D polymorphism in intron 16 was determined by a PCR based protocol.6 As there may be preferential amplification of the D allele,4 all samples found to have DD after amplification with conventional primers, were re-amplified with an insertion-specific primer pair.6,5 The distribution of genotypes and alleles were compared among patients and controls using χ² tests.

Results
Table 1 lists selected characteristics of the patient and control groups. The time to ESRD from diagnosis of FSGS in AA patients was 2.9 ± 1.9 years as compared to 5.7 ± 4.5 years in W/H group; (p < 0.05).

Majority of patients (41/47) had nephrotic range proteinuria at the time of the kidney biopsy. The age at the time of the study, the male-female ratio, age at presentation, and incidence of nephrotic syndrome were not significantly different between AA and W/H patient groups.

The distribution of ACE genotype in 47 patients with FSGS was as follows: II 25.5%, ID 55.5%, and DD 19%, as compared to 40 controls, in whom the genotype was 7.5%, 60%, and 32.5%, respectively (P > 0.05) (Table 2). The ACE genotype amongst the AA and W/H groups was similar. The gene frequencies in the AA group were similar between patients and controls (I 43%, D 57% vs I 36%, D 64%, respectively). However, there were significant differences in gene frequencies between the two groups of W/H individuals I 61.5%, D 38.5% vs I 38.6%, D 61.4%, in controls (P < 0.05).

Eleven AA and eleven W/H patients progressed rapidly (RP) (Table 3). In the RP group the genotype distribution was II 18%, ID 64%, and DD 18%. Among the 25 patients who progressed slowly (SP) the genotype was II 32%, ID 48% and DD 20% (P > 0.05). But in the RP group 4/11 AA had a DD genotype as compared to 0/11 in W/H patients (P > 0.05). With respect to the rate of progression, D allele frequency was similar between AA (RP 64% vs SP 50%, P > 0.05) and W/H (RP 36% vs SP 40%, P > 0.05).

Discussion
This study was undertaken to determine whether I/D polymorphism of intron 16 of the ACE gene is associated with ESRD due to FSGS. The result failed to support such an association. This is in agreement with study conducted by Burg et al who were unable to detect an association of the ACE genotype with primary glomerulonephritis including 17 patients with FSGS.14 In contrast, Lee reported that DD genotype in a Korean sample population was associated with poor response to steroids and tendency to progression.6 This may be the result of genetic differences between the populations or due to relatively small numbers of patients studied. The DD genotype has been associated with accelerated progression in a variety of renal diseases such as IgA nephropathy,4,5 and polycystic kidney disease.3 Marre and co-workers reported that the I/D polymorphism is associated with development of diabetic nephropathy,15 whereas others did not confirm this relationship.16 AA patients with essential hypertension have a significantly higher frequency of a DD genotype as compared to

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**Table 1: Age and Sex Demographics**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (yrs)</th>
<th>M:F</th>
<th>Age at diagnosis (yrs)</th>
<th>Diagnosis to ESRD (yrs)</th>
<th>Nephrotic FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>21</td>
<td>22.1 (8-40)</td>
<td>13:8</td>
<td>23.9 ± 12.4</td>
<td>2.9 ± 1.9*</td>
<td>18:21</td>
</tr>
<tr>
<td>White/Hispanic</td>
<td>25</td>
<td>25.4 (4-52)</td>
<td>13:13</td>
<td>17.3 ± 11</td>
<td>5.7 ± 4.5*</td>
<td>23:26</td>
</tr>
</tbody>
</table>

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**Table 2: Distribution of I/D Genotype and Allele Frequencies**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Genotype Frequency</th>
<th>II</th>
<th>ID</th>
<th>DD</th>
<th>FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>21</td>
<td>3 (14.3)</td>
<td>12 (57.1)</td>
<td>6 (28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Hispanic</td>
<td>26</td>
<td>9 (34.6)</td>
<td>14 (53.8)</td>
<td>3 (11.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>12 (25.5)</td>
<td>26 (55.5)</td>
<td>9 (19.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3: Distribution of I/D Genotype and Allele Frequencies**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Genotype Frequency</th>
<th>II</th>
<th>ID</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly Progressive</td>
<td>11</td>
<td>1 (9.1)</td>
<td>6 (54.5)</td>
<td>4 (36.4)</td>
<td></td>
</tr>
<tr>
<td>White/Hispanic</td>
<td>11</td>
<td>3 (27.0)</td>
<td>8 (73.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>4 (18.0)</td>
<td>14 (64.0)</td>
<td>4 (18.0)</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Genotype Frequency</th>
<th>II</th>
<th>ID</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowly Progressive</td>
<td>25</td>
<td>5 (20.0)</td>
<td>12 (48.0)</td>
<td>10 (40.0)</td>
<td></td>
</tr>
</tbody>
</table>

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Figures in parentheses are percentages. I Insertion, D Deletion.
normotensive AA individuals. However, the linkage analysis between loci in the renin-angiotensin axis and ESRD in AA population failed to suggest an association. If the linkage between the disease locus and the ID polymorphism varies among populations, positive association will be found in populations with tighter linkage but not in populations with weaker linkage. The frequency of DD genotype among dialysis patients is not increased as compared to general population.

Renal survival is worst in FSGS with nephrotic syndrome (NS). 41/47 of our patients had NS. Genetic background also influences prognosis. FSGS tends to progress more rapidly in AA patients especially in the New York area. Ingulli described 38 AA children in whom the time of progression to ESRD from the time of biopsy was 2.8 ± 1.3 year. Detwiler described 14 patients, five of whom were on dialysis and three of whom had died of complications of renal failure within 15 months of diagnosis. Valeri et al described 43 predominantly AA patients with idiopathic collapsing FSGS, in whom median time from diagnosis to ESRD was 13 months. Though, we did not attempt to analyze our data on the basis of biopsy appearances in our study, the rate of progression to ESRD in AA patients was 2.9 ± 1.9 yrs as compared to 5.7 ± 4.5 yrs in W/H patients (p < 0.05). Based on the above information defining the RP patients as those who reached ESRD in less than two years from the time of biopsy, though somewhat arbitrary, seems justified. We did not find differences in the ACE genotype between the RP and SP groups. In fact, when we compared the RP group to patients who took longer than five years to reach ESRD there was no difference in genotype (data not shown). Yet, the higher frequency of the DD genotype among the AA RP than the W/H patients (4/11 vs 0/11) did not reach statistical significance probably because of the small number of patients in each group. To reconcile these differences, multi-center studies including larger numbers of patients are currently being conducted.

The exact mechanism by which the presence of the DD genotype leads to renal disease operates at the cellular level. Caucasians with DD genotype have serum ACE levels and intra-cellular ACE activity twice those of II genotype. Higher ACE activity leads to increased Angiotensin II levels, which in turn promotes proliferation of mesangial cells and matrix and expression of growth factors leading to glomerulosclerosis. In experimental models of chronic renal disease and in human diabetic nephropathy, pharmacological blockade of ACE significantly slows down the rate of decline in renal function. The data regarding the relationship between response to ACE inhibition and DD genotype has been conflicting. A good correlation was found in IgA nephropathy and diabetic nephropathy, but others did not confirm this finding in primary glomerulonephritis and in patients with proteinuria. Studies in children have confirmed similar findings in different ethnic backgrounds. In our study the overall frequency of 38.6% for the I allele and 61.4% for the D allele among W/H controls is similar to that found among Caucasians. Therefore the significant difference in I and D allele frequency (61.5 and 38.5%, respectively, p < 0.05) between W/H with FSGS and W/H controls is noteworthy. There are two limitations to our study. First, it is a single center experience that reflects a certain referral population. Secondly, due to small numbers in each group a type II error in statistical evaluation cannot be fully excluded. To the best of our knowledge, this is the first study of its kind comparing DD genotype with rapidity of progression of FSGS resulting in ESRD, especially in an AA population.

In conclusion, our data reveals no association between the D allele of the ACE gene and the presence of or rapidity of progression of FSGS in AA and W/H patients. A multi-center study with a large number of patients is needed to further study the issue.

References

Higher ACE activity leads to increased Angiotensin II levels, which in turn promotes proliferation of mesangial cells and matrix and expression of growth factors leading to glomerulosclerosis.


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