Late-Onset Apparent Mineralocorticoid Excess Caused by Novel Compound Heterozygous Mutations in the HSD11B2 Gene


Abstract—Mutations in the gene encoding 11β-hydroxysteroid dehydrogenase type 2, 11β-HSD2 (HSD11B2), explain the molecular basis for the syndrome of apparent mineralocorticoid excess (AME), characterized by severe hypertension and hypokalemic alkalosis. Cortisol is the offending mineralocorticoid in AME, as the result of a lack of 11β-HSD2-mediated cortisol to cortisone inactivation. In this study, we describe mutations in the HSD11B2 gene in 3 additional AME kindreds in which probands presented in adult life, with milder phenotypes including the original seminal case reported by Stewart and Edwards. Genetic analysis of the HSD11B2 gene revealed that all probands were compound heterozygotes, for a total of 7 novel coding and noncoding mutations. Of the 7 mutations detected, 6 were investigated for their effects on gene expression and enzyme activity by the use of mutant cDNA and minigene constructs transfected into HEK 293 cells. Four missense mutations resulted in enzymes with varying degrees of activity, all <10% of wild type. A further 2 mutations generated incorrectly spliced mRNA and predicted severely truncated, inactive enzyme. The mothers of 2 probands heterozygous for missense mutations have presented with a phenotype indistinguishable from “essential” hypertension. These genetic and biochemical data emphasize the heterogeneous nature of AME and the effects that heterozygosity at the HSD11B2 locus can have on blood pressure in later life. (Hypertension. 2003;42:123-129.)

Key Words: hypertension, genetic ■ hypertension, essential ■ mutation ■ mineralocorticoids ■ genes

M utations in the HSD11B2 gene explain the syndrome of apparent mineralocorticoid excess (AME), an autosomal recessive inherited form of hypertension. This is characterized by hypertension and hypokalemia, suppression of plasma renin and aldosterone concentrations, because cortisol acts as the “apparent” mineralocorticoid.1,2 The type 2 “kidney” isozyme of 11β-hydroxysteroid dehydrogenase (11β-HSD2) normally inactivates cortisol to cortisone, ensuring the selective occupation of the mineralocorticoid receptor (MR) by aldosterone.3,4 The MR is nonselective in vitro and cannot distinguish between cortisol and its natural ligand, aldosterone.5,6 When 11β-HSD2 is defective, as in AME, or inhibited after liquorice ingestion, cortisol, which circulates at concentrations 100 to 1000 times higher than aldosterone, binds to the MR to act as a potent mineralocorticoid, causing intense sodium retention, hypokalemia, and hypertension.1 The human HSD11B2 gene is 6.2 kb long, comprising 5 exons, and is located on chromosome 16q22.7 More than 50 cases of AME have been reported, and more than 20 different mutations have been defined. Data from our own group and others have highlighted a close correlation between disease phenotype and genotype.8–10 Patients with mutations resulting in little or no 11β-HSD2 activity present in early life with a severe phenotype. In contrast, patients presenting in late adolescence or early adulthood with so-called “mild” forms of AME (also referred to as AME type II) have been found to harbor mutations that result in a partially functional 11β-HSD2 protein with attenuated activity.11,12 In this study, we describe the molecular basis for AME in 3 additional affected cases, including the seminal case reported by Stewart et al in 1988,13 and attempt to link genotype to phenotype through functional studies by using mutant cDNA and minigenes. We
provide evidence that the parents of the probands, heterozygous for mutations within the HSD11B2 gene, may present with a phenotype indistinguishable from “essential” hypertension in adult life, and we discuss the implications of this in the context of the wider population of patients with hypertension.

**Methods**

**Amplification and DNA Sequencing of the HSD11B2 Gene**

Genomic DNA was recovered from peripheral blood leukocytes from affected kindreds. Exons were amplified by means of polymerase chain reaction (PCR), as described elsewhere.8 The amplified products were sequenced directly with the use of an ABI prism 377 DNA sequencer (Perkin Elmer).

**cDNA Constructs and Mutagenesis**

Point mutations were introduced into the 11β-HSD2 cDNA cloned into the pCR3 expression vector (Invitrogen), using the Quick Change Mutagenesis kit from Stratagene. Table 1 provides oligonucleotide sequences for mutagenesis primers. Oligonucleotides 1 to 8 were used to carry out cDNA site-directed mutagenesis of cDNA. Oligonucleotides 9 and 10 were used to amplify the minigene. Oligonucleotides 11 to 14 were used to carry out minigene site-directed mutagenesis. Oligonucleotides 15 to 17 were used in RT-PCR for the detection of minigene transcripts in the transfected HEK 293 cells.

**Minigene Constructs and Mutagenesis**

An Xba I fragment containing the entire HSD11B2 gene (a gift from A.K. Agarwal) was used to create an HSD11B2 minigene construct in the pCR3.1 expression vector (Invitrogen). Primers 9 and 10 (Table 1) were used to PCR-amplify the 3' portion of intron 1 through exon 5 of the HSD11B2 gene, according to the protocol specified by the manufacturer of the polymerase used (Proofstart DNA Polymerase, Qiagen). The PCR product was ligated into the pCR3.1 vector. Mutations were introduced into the minigene as described above. Oligonucleotides 11 and 12 were used to generate IVS3+1G>A, and oligonucleotides 13 and 14 were used to generate 771C>G. All constructs were sequenced to verify that no extraneous mutations had been incorporated.

**Cell Culture, Transient Transfection, and Enzyme Assays**

HEK-293 cells were maintained in DMEM supplemented with 10% FCS and 1% nonessential amino acids (Life Technologies). HEK-293 cells do not express 11β-HSD2.14 Transfections were carried out with the Transfast reagent (Promega), according to the manufacturer's instructions. Cells were grown to 80% confluence in 6-well cell culture plates and transfected with 2 μg of the relevant construct per well. Cells were maintained in serum containing media for 48 hours for gene expression to occur. Resultant 11β-HSD2 activity (conversion of cortisol [F] to cortisone [E]) was measured with the use of tritiated tracer steroids, as previously reported.14 Activity of wild-type (WT) and mutant enzymes are expressed as picomoles of cortisone produced per milligram of protein per hour. Each transfection was carried 4 times in triplicate and is expressed as mean±SD.

**Reverse Transcription–PCR**

Total RNA was isolated from cells transfected with either cDNA or minigene constructs by using Tri reagent (Sigma); 1 μg of total RNA was reverse-transcribed with the use of 10 U of AMV reverse transcriptase (Promega) in a 10-μL reaction volume containing 10 μmol/L random hexamers, 1 mmol/L of each dNTP, 40 U of RNase inhibitor and 1× buffer. Reactions were carried out for 1 hour at 37°C, with a 5-minute, 95°C inactivation step at the end. PCR was performed to detect processed WT and mutant minigene mRNA transcripts by using primers 15 and 16 for the 771C>G minigene and 15 and 17 for the IVS3+1G>A minigene, with the PCR conditions used as described above.

**Results**

**Patients and Clinical Characteristics**

The clinical and genetic characteristics of 3 patients with AME are presented in Table 2.

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**TABLE 1. Oligonucleotides Used for Mutagenesis and RT-PCR**

<table>
<thead>
<tr>
<th>Oligonucleotide</th>
<th>Sequence 5’-3’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GAGCCGACGGGGGACATGCCAAATCGTGCTTGGGGGCTTA</td>
</tr>
<tr>
<td>2</td>
<td>CATAGGCCCCCAACGCAGATTTGGCATGCCCGGTGCCC</td>
</tr>
<tr>
<td>3</td>
<td>GTGCTTGGGGGCTGTGAACTCCAAGAG</td>
</tr>
<tr>
<td>4</td>
<td>CTTGAGGTTCCACAGCCCGCCAAGCAC</td>
</tr>
<tr>
<td>5</td>
<td>GGGGGGACATGCCAAATCGTTGCCCCC</td>
</tr>
<tr>
<td>6</td>
<td>CCGCCGGCGCCAGTGGCACCTTGACCAC</td>
</tr>
<tr>
<td>7</td>
<td>GGGGTCAGGTTGACATCATCCAG</td>
</tr>
<tr>
<td>8</td>
<td>CTTGATGATGCTCACCCTTGACCC</td>
</tr>
<tr>
<td>9</td>
<td>TAAAGCCTTGCTCACGTAGGGACACA</td>
</tr>
<tr>
<td>10</td>
<td>TACGGCGGGCGCCAGTTGGCACCTTGACAC</td>
</tr>
<tr>
<td>11</td>
<td>CGCTCTGAAACCGCTGTGCGGCGCTTCTG</td>
</tr>
<tr>
<td>12</td>
<td>CAGGAAGCGGCGGCCAACGCTTCAAGG</td>
</tr>
<tr>
<td>13</td>
<td>CCTCGAGACAGCGACCTGCGGCAC</td>
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<tr>
<td>14</td>
<td>GCTGAGCCAGCTCGGTTGCTCGAGG</td>
</tr>
<tr>
<td>15</td>
<td>CTGACAAACCGAGGAC</td>
</tr>
<tr>
<td>16</td>
<td>AGGCTGGATGATGCTGAC</td>
</tr>
<tr>
<td>17</td>
<td>AGACAGTGTAGTGAGAAG</td>
</tr>
</tbody>
</table>

Oligonucleotides 1 to 8 were used to carry out cDNA site-directed mutagenesis of cDNA. Oligonucleotides 9 and 10 were used to amplify the minigene. Oligonucleotides 11 to 14 were used to carry out minigene site-directed mutagenesis. Oligonucleotides 15 to 17 were used in RT-PCR for the detection of minigene transcripts in the transfected HEK 293 cells.
Patient 1 is a white male and has been described in detail. Briefly, he presented at 21 years of age with cardiac arrest secondary to hypokalemia while being investigated for low renin hypertension. Urinary steroid tetrahydrocortisols/tetrahydrocortisone ratio (THF + allo-THF/THE) was 13.5 (reference range, 0.7 to 1.3), and a diagnosis of AME was confirmed. At diagnosis, it was noted that the mother and father of patient 1 had developed hypertension at 45 years of age. When investigated, both had low but not suppressed plasma renin activity, and the mother additionally had mild hypokalemic alkalosis. The urinary THF + allo-THF/THE ratio was not elevated in either parent (Table 2).

Patient 2 is an Italian girl and has previously been described. Briefly, she presented at 16 years of age with hypertension, suppressed plasma renin, and undetectable plasma aldosterone. The urinary THF + allo-THF/THE ratio was 1.93. A diagnosis of mild AME was substantiated by an increased urinary free cortisol/cortisone (UFF/UFE) ratio of 5.0 (reference range, 0.5 to 0.8). Her mother is 58 years of age and has an 8-year history of hypertension. She has low but not suppressed PRA concentration (0.5 ng/mL per hour; reference range, 0.5 to 1.5). Urinary THF + alloTHF/THE and UFF/UFE ratios were slightly elevated at 1.74 and 0.92, respectively. The father is normotensive and has a low PRA of 0.3. Both THF + alloTHF/THE and UFF/UFE ratios were within the normal range.

Patient 3 is a white man who presented at 18 years of age with hypertension, a THF + allo-THF/THE ratio of 7.2, hypokalemia, suppressed plasma renin and aldosterone, and moderate renal impairment (creatinine, 169 mmol/L; reference range, 75 to 125). One year later, he had type 1 diabetes mellitus. His blood pressure was 136/98 mm Hg while on treatment with amiloride 30 mg/d, frusemide 80 mg/d, and bisoprolol 10 mg/d. A renal biopsy carried out within the first year of presentation indicated hypertensive renal damage.

Table 2. Clinical and Biochemical Characteristics of AME Kindreds

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at Diagnosis, y</th>
<th>BP, mm Hg</th>
<th>Complications</th>
<th>THF + alloTHF/THE</th>
<th>K+, mmol/L</th>
<th>Na+, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mother)</td>
<td>M</td>
<td>21</td>
<td>235/125</td>
<td>Cardiac arrest</td>
<td>13.57</td>
<td>1.7</td>
<td>148</td>
</tr>
<tr>
<td>1 (Father)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>16</td>
<td>220/120</td>
<td>Cerebral aneurysm</td>
<td>1.93</td>
<td>2.5</td>
<td>140</td>
</tr>
<tr>
<td>2 (Mother)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2 (Father)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>16</td>
<td>136/98</td>
<td>Type 1 diabetes</td>
<td>7.2</td>
<td>1.8</td>
<td>...</td>
</tr>
<tr>
<td>3 (Mother)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.6</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Data refer to original diagnostic data. Normal range: THF + allo-THF/THE=0.7–1.3; K+, potassium mmol/L=3.5–5.5; Na+, sodium mmol/L=137–144. THF + alloTHF/THE indicates tetrahydrocortisol + allo-tetrahydrocortisol/tetrahydrocortisone.

Mutations in the HSD11B2 Gene

Sequence data from 3 patients with AME identified 7 mutations in the HSD11B2 gene (Figure 1). Patient 1 was found to be a compound heterozygote carrying 3 novel mutations (Figure 2). A maternally inherited mutation occurred in exon 4, consisting of a base transition followed by a base transversion to give 675A>G; 676A>T (number is relative to the first base of the ATG start codon). The 675A>G mutation is silent (remaining proline, P225P, CCA to CCG), whereas the 676A>T creates a missense at codon 226 of tyrosine to asparagine (Y226N, ATA to TTA). A paternally transmitted base transition was detected, 1393C>T, in the 3’ untranslated region (3’UTR). Sibling II2 of patient 1 inherited the Y226N and 1393C>T mutations but does not have AME (Figure 2). However, a de novo base transition, 771C>G, was detected in exon 4 of the paternal allele (PCR cloning revealed 771C>G in the same allele as 1393C>T, data not shown). The 771C>G mutation is silent (V254V; TGC to TGG), but sequence analysis revealed that it created a canonical donor splice site and therefore could cause aberrant splicing. To assess the polymorphic nature of the novel 1393C>T mutation, 146 multiethnic control subjects were genotyped, and no “T” allele frequency was observed.

Patient 2 was found to be a compound heterozygote carrying 2 novel mutations. A maternally inherited base transition mutation, 1075C>T, was detected in exon 5, changing arginine to tryptophan (R359W, CGG to TGG). A
Simultaneous transfection of all mutants and RT-PCR for mutant enzymes because of their low activities in this level (data not shown). Enzyme kinetics were not calculated empty pCR3.1 vector metabolized cortisol to an appreciable extent, whereas mutant 11\(^{-}\)HSD2 cDNA resulted in enzyme activities of 2%, 1.5%, 5%, and 9%, respectively, of WT (Figure 3).

Expression of Mutant cDNA and Minigenes
Expression of the Y226N, Y232C, R359W, and L376P mutant 11\(\beta\)-HSD2 cDNA resulted in enzyme activities of 2%, 1.5%, 5%, and 9%, respectively, of WT (Figure 3). Neither sham-transfected cells nor cells transfected with empty pCR3.1 vector metabolized cortisol to an appreciable level (data not shown). Enzyme kinetics were not calculated for mutant enzymes because of their low activities in this study. Simultaneous transfection of all mutants and RT-PCR within the exponential phase of the reaction was used to ensure equal transfection efficiencies (data not shown).

To determine the consequences of the 2 putative splicing mutations, RT-PCR was carried out to assess pre-mRNA splicing from mutant HSD11B2 minigene constructs. Cells transfected with the WT minigene produced the predicted 702-bp PCR product that was sequence-verified. Analysis of RNA produced from the 771C>G mutant minigene (kindred 1) revealed a truncated product of 668 bp; no WT product was produced (Figure 4). Sequencing the truncated product showed that the final 34 bp of exon 4 had been lost from the mRNA as the result of the activation of a consensus donor splice site, AG/GU/AGU\(^{-}\). This would create a frame shift, introducing an in-frame TGA stop codon 6 bp into exon 5. Translation of the mutant mRNA product would result in the incorporation of 3 missense amino acids and the loss of 129 amino acids from the C-terminus. Previously, a premature stop codon revealed in exon 5 (R374X) yields an 11\(\beta\)-HSD2 enzyme with no activity.

In kindred 2, the WT minigene produced the predicted 372-bp PCR product that was sequence-verified. The IVS 3+1G>A mutation produced a minor WT product and a major 278-bp product (Figure 5). Sequencing revealed the 279-bp product was missing the last 94 bp of exon 3 as the result of splicing from a cryptic splice donor site within exon 3, AG/GGTGAA\(^{-}\). This would create a frame shift, introducing the same in-frame TGA stop codon as the C771G mutant. Translation of the mutant product would result in the incorporation of 81 missense amino acids and the loss of 129 amino acids from the C-terminus.

Discussion
In this study, we report novel coding and noncoding mutations that explain the molecular basis for a further 3 cases of AME. Six mutations were identified that severely affect enzyme activity. A novel 3' UTR mutation was also identified. Although the 3'UTR mutation appeared not to be polymorphic, it may yet have a frequency in a population not yet analyzed. Zaehner et al\(^{17}\) studied the HSD11B2 gene in >500 individuals, and the 1393C>T mutation was not reported. The 1393C-T transition is at a CpG site and may be the result of deamination of 5-methyl cytosine to thymine and may represent a founder mutation arising in this family. This now brings the total number of mutations observed in the HSD11B2 gene to 29, causing AME in both homozygote and compound heterozygote individuals (Figure 1).

Activity of the mutant 11\(\beta\)-HSD2 enzymes in transfected HEK 293 cells was severely attenuated (<10% WT). The Tyr\(^{226}\), Tyr\(^{232}\), Arg\(^{259}\), and Leu\(^{276}\) residues are well conserved across species and are therefore likely to be structurally and catalytically important. The 11\(\beta\)-HSD2 enzyme exists as a dimer, and the Tyr\(^{226}\) residue is next to the dimer interface.\(^{18}\) It also lies within the sequence of residues thought to create the substrate-binding pocket, therefore the substitution of an aromatic tyrosine residue for an amide asparagine residue could be expected to alter this local structure. The Tyr\(^{232}\) is a critical amino acid for catalysis and therefore any change at this site would be expected to result in loss of function.\(^{18,19}\) The R359W and L376P missense substitutions would alter local hydrostatic interactions and disrupt protein folding, attenuating enzyme activity.
One splicing mutation has previously been shown in the \textit{HSD11B2} gene (occurring in 2 cases of AME). This C-T transition has been detected in the homozygous and compound heterozygous state (in addition to an R208H mutation), 14 bp 3' of the intron 3 donor splice site. This mutation was suggested to cause significant change in the secondary structure of the pre-mRNA affecting splicing, and, as a result, exon 4 was lost from the mRNA. Mutations in the \textit{HSD11B2} gene in patients 1 and 2 reported in this study are novel and also disrupt RNA splicing.

The 771C>G mutation in patient 1 is the first de novo mutation described in the \textit{HSD11B2} gene causing AME. The mutation generates a sequence within exon 4 that perfectly matches a consensus donor splice site sequence and acts as the preferred donor splice site; only mutant mRNA was produced. Since his original presentation in 1988, patient 1 has fathered 2 children who have not been studied to date. As they will have inherited mutant alleles, there may be implications for their blood pressure status in later life.

These studies suggest that patient 1 would express 2 severely attenuated enzymes. With the close correlation between genotype and phenotype, this genotype would be expected to present early with AME, yet he did not present until 21 years of age. It is possible that the minigene system that we used may not completely reflect the \textit{HSD11B2} pre-mRNA splicing that takes place in vivo. A small amount of normal RNA generated in vivo with residual activity from Y226N may be sufficient to escape early presentation.

The IVS3+1G>A mutation in patient 2 directly affects the splice donor site by disrupting the exon/intron consensus sequence. The IVS3+1G>A mutant in patient 2 showed that despite the mutation of the splice donor site, some normal splicing still occurred. Extrapolating this in vivo, some normal mRNA and residual activity from R359W may account for the milder phenotype and late presentation seen in this patient.

Patient 3 harbors 2 missense mutations, both attenuating enzyme activity. In this case, later presentation might be explained by residual activity of the L376P mutation (10\% of WT). Although his mother has the Y232C mutation, she has...
no apparent signs of hypertension or deranged steroid metabolism.

Because precise enzyme kinetics were not determined for the missense mutants in each patient, the real properties of each enzyme in vivo may modify our assumptions about patient presentation. All 3 patients have AME but presented with a milder condition later in life. Previously, such cases have been termed the type II variant of AME, but because both variants are due to mutations in the same gene, AME should be regarded as a continuum of phenotype, dependent on the severity of the underlying genotype.

The prevalence of monogenic forms of hypertension such as AME remains uncertain. Deficient inactivation of cortisol by 11β-HSD2 has been documented in patients with essential hypertension.20,21 Mutations or polymorphisms within the HSD11B2 gene might predispose to low-renin, adult-onset hypertension. Indeed, studies suggest that a microsatellite in intron 1 of the HSD11B2 gene may be linked to a predisposition to salt-sensitive hypertension.22,23 It is still feasible that decreased 11β-HSD2 activity over time may result in an essential hypertension phenotype. In support of this, we have previously shown in a Brazilian kindred that a 38-year-old father heterozygous for the A328V mutation had “essential” hypertension (140 to 170/110 mm Hg), suppressed renin and aldosterone levels, and a raised THF+allo-THF/THF ratio of 2.79.24 Similarly, in a Sardinian kindred, heterozygous carriers of an R279C mutation were shown to have hypertension.56 pregnancies of an R279C mutation were shown to have hypertension. Indeed, studies suggest that a microsatellite in intron 1 of the HSD11B2 gene may be linked to a predisposition to salt-sensitive hypertension.22,23 It is still feasible that decreased 11β-HSD2 activity over time may result in an essential hypertension phenotype. In support of this, we have previously shown in a Brazilian kindred that a 38-year-old father heterozygous for the A328V mutation had “essential” hypertension (140 to 170/110 mm Hg), suppressed renin and aldosterone levels, and a raised THF+allo-THF/THF ratio of 2.79.24 Similarly, in a Sardinian kindred, heterozygous carriers of an R279C mutation were shown to have hypertension and subtle defects in cortisol metabolism.11 Again, biochemical and genetic evidence (Table 1 and Figure 1) from the mothers of patients 1 and 2 suggests a diagnosis of late-onset, mild AME caused by heterozygous mutations attenuating 11β-HSD2 enzyme activity. Haploinsufficiency or dominant negative effects may underlie the molecular basis for late-onset AME in heterozygotes. Similarly, inhibitors of 11β-HSD2 activity and modulating environmental factors such as dietary salt intake could all contribute to presentation. Based on the prevalence of “essential” hypertension in the general population, it remains possible that these parents do indeed have “essential” hypertension as the result of unrelated genetic and environmental interactions, but this seems less likely. We believe such individuals represent a model of low-renin hypertension caused by 11β-HSD2 enzyme deficiency, and the prevalence of this model in the wider population remains to be determined.

Perspectives

In general, there is a lack of reported parental phenotype in the majority of AME cases. Because severe AME presents in infancy, parents are invariably young when the phenotype is defined in their offspring. Prolonged follow-up of existing kindreds is warranted to define a parental phenotype and possible hypertension in siblings who may have inherited mutant alleles. The prevalence of HSD11B2 mutations, specifically heterozygosity at this locus, contributing to hypertension has not been fully defined. The continued identification of novel HSD11B2 gene mutations, especially compound heterozygotes, raises the possibility of a greater proportion of mutation carriers than previously thought. Wilson et al12 suggest that patients with low-renin, essential hypertension should undergo genetic analysis of the HSD11B2 gene. Until the true prevalence of AME is established in large hypertensive populations, our advice would be to recommend measuring plasma renin and aldosterone levels in all hypertensive persons <50 years of age with a family history of hypertension or hypokalemia or premature cerebrovascular disease. Patients with suppressed plasma renin and aldosterone values should be investigated with a urinary steroid profile (THF+allo-THF/THF or UFF/UFF ratio), and sequencing studies should be performed on the HSD11B2 gene in those with elevated urinary ratios. Ongoing molecular analysis of the whole HSD11B2 gene including the 5′ region seems likely to uncover additional polymorphisms or mutations modulating gene regulation.

Acknowledgments

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References


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