Prevalence and Characteristics of Familial Hyperaldosteronism

The PATOGEN Study (Primary Aldosteronism in TOrino-GENetic forms)

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Abstract—Primary aldosteronism (PA) is the most frequent cause of secondary hypertension, and patients display an increased prevalence of cardiovascular events compared with essential hypertensives. To date, 3 familial forms of PA have been described and termed familial hyperaldosteronism types I, II, and III (FH-I to -III). The aim of this study was to investigate the prevalence and clinical characteristics of the 3 forms of FH in a large population of PA patients. Three-hundred consecutive PA patients diagnosed in our unit were tested by long-PCR of the \textit{CYP11B1/CYP11B2} hybrid gene that causes FH-I, and all of the available relatives of PA patients were screened to confirm or exclude PA and, thus, FH-II. Urinary 18-hydroxycortisol and 18-oxocortisol were measured in all of the familial PA patients. Two patients were diagnosed with FH-I (prevalence: 0.66%), as well as 21 of their relatives, and clinical phenotypes of the 2 affected families varied markedly. After exclusion of families who refused testing and those who were not informative, 199 families were investigated, of which 12 were diagnosed with FH-II (6%) and an additional 15 individuals had confirmed PA; clinical and biochemical phenotypes of FH-II families were not significantly different from sporadic PA patients. None of the families displayed a phenotype compatible with FH-III diagnosis. Our study demonstrates that familial forms of hyperaldosteronism are more frequent than previously expected and reinforces the recommendation of the Endocrine Society Guidelines to screen all first-degree hypertensive relatives of PA patients. (\textit{Hypertension}. 2011; 58:00-00.)

Key Words: familial hyperaldosteronism ■ endocrine hypertension ■ primary aldosteronism ■ aldosterone

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension; it accounts for 5% to 15% of hypertensives, depending on the severity of the disease.\textsuperscript{1,2} These patients display an increased prevalence of cardiovascular events compared with essential hypertensives with similar blood pressure levels.\textsuperscript{3,4} PA can be either sporadic or familial and, to date, 3 familial forms have been described. Glucocorticoid-remediable aldosteronism (GRA; familial hyperaldosteronism type I [FH-I]) was first described in 1966 by Sutherland et al\textsuperscript{5} but was only characterized in 1992 by Lifton et al.\textsuperscript{6} FH-I/GRA is an autosomal-dominant form of hypertension that features elevated adrenocorticotropic hormone–dependent aldosterone secretion, renin suppression, and high levels of 18 hydroxycortisol (18OHF) and 18oxocortisol (18oxoF).\textsuperscript{7} The genetic defect leading to FH-I/GRA is an unequal genetic recombination between \textit{CYP11B1} (11-\beta-hydroxylase) and \textit{CYP11B2} (aldosterone synthase) that generates a chimeric \textit{CYP11B} gene containing \textit{CYP11B1} sequences (including the promoter) at its 5’ end and \textit{CYP11B2} sequences at its 3’ end. Most affected individuals develop severe hypertension in early life, but patients with a milder phenotype have also been described.\textsuperscript{8} FH-I/GRA patients display higher morbidity and mortality from cerebrovascular events and have an increased risk of preeclampsia.\textsuperscript{9,10} Diagnosis of FH-I/GRA is currently performed by long-PCR amplification of the hybrid gene.\textsuperscript{11} Familial hyperaldosteronism type II (FH-II), a non–glucocorticoid-remediable familial form of PA, was first described by Gordon et al in 1991.\textsuperscript{12} FH-II patients display higher morbidity and mortality from cerebrovascular events and an increased risk of preeclampsia.\textsuperscript{9,10} Diagnosis of FH-I/GRA is currently performed by long-PCR amplification of the hybrid gene.\textsuperscript{11} Familial hyperaldosteronism type II (FH-II), a non–glucocorticoid-remediable familial form of PA, was first described by Gordon et al in 1991.\textsuperscript{12} FH-II patients display a family history of PA caused by either an adrenal adenoma or hyperplasia and have been reported to be clinically and biochemically indistinguishable from sporadic forms of PA.\textsuperscript{13} In most families, vertical transmission suggests an autosomal-dominant inheritance. Diagnosis of FH-II is made when ≥2

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first-degree members of the same family have confirmed PA. The genetic background of FH-II remains unknown, but a linkage between FH-II and a locus at chromosome 7p22 has been shown in families from 3 different continents; however, this linkage has not been observed in other families. Finally, familial hyperaldosteronism type III (FH-III) has only been described in a single American family to date and is characterized by severe hypertension in early childhood associated with marked hyperaldosteronism, hypokalemia, and resistance to aggressive antihypertensive therapy, thus requiring bilateral adrenalectomy. Another distinctive feature of FH-III is the enormous production of 18OHF and 18oxoF that is even higher than in FH-I/GRA patients. The genetic cause of this disease has been elucidated recently and is composed of a mutation in the gene encoding the potassium channel KCNJ5 (Kir 3.4, potassium inwardly rectifying channel, subfamily I, member 5); interestingly, somatic mutations in the same gene have been shown in a subgroup of aldosterone-producing adrenocortical tumors (APAs) from patients with sporadic PA. The prevalence of familial hyperaldosteronism and its forms has not been studied systematically. In an Australian PA population, FH-II has been reported to be 5 times more frequent than FH-I/GRA. The aim of the present study was to investigate the prevalence of different forms of familial hyperaldosteronism in a large population of PA patients and their relatives and to characterize their specific phenotypes.

Methods

Patient Selection

We selected 300 consecutive patients with the diagnosis of PA performed in our hypertension center between 1996 and 2010; 68 of these patients had confirmed APA (23%). Patients referred to our unit for specific reasons, such as suspect GRA because of a positive dexamethasone suppression test, suspect familial hyperaldosteronism, confirmatory tests, or adrenal vein sampling (AVS) requests, were excluded from the study, because full clinical data were unavailable to our unit. The protocol was approved by our local ethics committee, and all of the participants gave their written informed consent.

Diagnosis of PA

Diagnosis of PA was performed as described in detail elsewhere. Briefly, patients were screened using the serum aldosterone:plasma renin activity (PRA) ratio (ARR), and PA was confirmed using the intravenous saline load test. All of the patients with confirmed PA underwent computed tomography scanning and AVS. AVS was considered successful if the adrenal vein/inferior vena cava cortisol gradient was ≥3 or ≥2 before 2008; lateralization was considered when the aldosterone:cortisol ratio from one adrenal was ≥4 times that of the other adrenal gland (lateralization ratio). A definitive diagnosis of APA was made as described elsewhere.

Diagnosis of FH-I/GRA

Diagnosis of FH-I/GRA was performed by long-PCR amplification of the hybrid gene, as described previously. When the diagnosis was positive, all of the family members of the index case were studied by long-PCR and/or Southern blot, dexamethasone suppression test, and 18OHF and 18oxoF measurement, as described before.

Diagnosis of FH-II

Diagnosis of FH-II was made when ≥2 members of the same family had confirmed PA. Of note, we used an ARR cutoff of 30 (aldosterone in nanograms per deciliter and PRA in nanograms per milliliter per hour instead of 40 (normally in use in our unit) without a predefined minimal aldosterone level to increase the sensitivity of the screening test. To define a patient and a family as affected/uncertain/nonaffected, we used predefined specific criteria (Table 1). A family was defined as “not informative” if there were no first-degree relatives alive or not living in our geographical area and, thus, unavailable for screening or if the only available relatives were normotensives of <25 years of age.

Eighteen subjects under the age of 18 years were tested; ARR cutoff for the screening was considered lower than in adults (13.5 instead of 40.0), as published recently. Two subjects (aged 2 and 16 years) resulted positive at the screening test: a 2-year-old hypertensive and hypokalemic girl displayed such high aldosterone levels in multiple determinations (all >100 ng/dL) and low PRA (all <0.2 ng/mL per hour) that we considered a confirmatory test unnecessary. A 14-year-old normotensive girl with a positive screening test (ARR=101.3) did not undergo the confirmatory test because of lack of parental consent.

Diagnosis of FH-III

Diagnosis of FH-III was considered in cases of familial hyperaldosteronism with severe hypertension at a young age and with 18OHF and 18oxoF levels elevated at least as high as those in FH-I/GRA patients but without hybrid gene amplification at long-PCR.

Hormone Assay

PRA, serum aldosterone, urinary 18OHF, and urinary 18oxoF were measured as described previously.
Statistical Analysis
Data were analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests to determine their distributions. Statistical significance between groups was calculated in normally distributed data by a Student t test for independent samples and in nonnormally distributed data by the Kruskal-Wallis and Mann-Whitney U tests using Bonferroni corrections for multiple comparisons. Data were expressed as mean ± SD or median (25th to 75th percentile).

Results
Prevalence of Familial Hyperaldosteronism
From the 300 patients studied (Figure), we identified 2 cases of FH-I/GRA (0.66%); we subsequently tested 51 relatives of these patients and determined 21 new cases of FH-I/GRA, therefore reaching a total of 23 FH-I/GRA patients. For the screening of FH-II, 298 families were contacted (Figure). Ninety-nine were excluded (65 because they were not informative and 34 because they refused or were unavailable); therefore, 199 families underwent the screening test for PA. The excluded PA patients did not display significant differences in terms of blood pressure levels (systolic blood pressure/diastolic blood pressure = 155 ± 26/97 ± 12 mm Hg) or prevalence of hypokalemia and APA (24% and 29%, respectively), PRA (0.2 [0.1–0.3]), and aldosterone (30 [23–40]) compared with patients with FH-II, whereas similar potassium and hormonal levels but lower blood pressure levels were displayed compared with the group of sporadic PA included in the study. Therefore, the exclusion of these patients should not have affected the results of the present study. Twelve families (6%) were diagnosed with FH-II, 54 were of an uncertain status, and 133 families were negatives (Table 2). For the 12 families with FH-II, we tested 65 relatives and found 15 new cases of PA, 23 patients of uncertain status, and 27 unaffected subjects, plus 1 individual with a history of hypertension and hypokalemia (thus possibly affected) but deceased before the study (Table 2). However, because of the high prevalence of PA within the hypertensive population, we cannot exclude that, in a family with only 2 relatives having PA, the possibility exists that the cases occurred independently, as sporadic PA; in contrast, or 4 sporadic cases in 1 family (families 2 and 8) occurring by chance are highly unlikely, thereby making the diagnosis of FH-II more solid (Table 3). In 1 of the families (family 10) with 2 affected members, PA was diagnosed at the ages of 27 and 2 years, highly indicative of a genetic basis for the disease. Therefore, a very conservative estimate of the prevalence of FH-II composed of just these 3 families is 1.5% (Table 3).

None of the families displayed a phenotype similar to the family described by Geller et al16 and termed “FH-III,”17 that is, a particular severity of hypertension and hyperaldosteronism and high levels of hybrid steroids. Therefore, FH-III was apparently absent in our population.

Phenotypes of FH-I/GRA Families
Clinical and biochemical characteristics of FH-I/GRA patients are summarized in Table 4. One of the 2 families, displaying a particularly mild phenotype, has been described in detail previously.9 Briefly, hypertension was present in less than half of the affected members in 1 family and in all of the affected members in the second, with an overall prevalence of 44%. Prevalence of hypertension and systolic blood pressure levels were significantly lower than in FH-II and sporadic PA patients (P<0.01). Hypokalemia was absent in all of the affected members of the first family but was present in both affected patients of the second family (overall prevalence 13%). Potassium levels, but not prevalence of hypokalemia, were significantly higher than in FH-II and sporadic PA patients (P<0.01). Of note, all of the affected members of the 2 families displayed high levels of 18O HF and 18oxo F; and

Table 2. Patients and Families Status After Testing for FH-II

<table>
<thead>
<tr>
<th>Families Tested (n=199)</th>
<th>Affected</th>
<th>Unaffected</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>12</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Unaffected</td>
<td>133</td>
<td>0</td>
<td>246</td>
</tr>
<tr>
<td>Uncertain</td>
<td>54</td>
<td>0</td>
<td>73</td>
</tr>
</tbody>
</table>

FH indicates familial hyperaldosteronism.
Table 3. PA-Affected Members, Generations, and Subtypes in FH Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Affected/Tested (%)</th>
<th>Generations Affected/Generations Tested</th>
<th>Subtype (APA/BAH/und)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>2/8 (25)</td>
<td>1/2</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Family 2</td>
<td>4/10 (40)</td>
<td>2/3</td>
<td>0/2/2</td>
</tr>
<tr>
<td>Family 3</td>
<td>2/5 (40)</td>
<td>1/2</td>
<td>0/2/0</td>
</tr>
<tr>
<td>Family 4</td>
<td>2/5 (40)</td>
<td>1/2</td>
<td>0/2/0</td>
</tr>
<tr>
<td>Family 5</td>
<td>2/6 (33.3)</td>
<td>1/2</td>
<td>0/2/0</td>
</tr>
<tr>
<td>Family 6</td>
<td>2/8 (25)</td>
<td>2/3</td>
<td>0/0/1</td>
</tr>
<tr>
<td>Family 7</td>
<td>2/2 (100)</td>
<td>1/1</td>
<td>1/0/1</td>
</tr>
<tr>
<td>Family 8</td>
<td>3/8 (37.5)</td>
<td>2/3</td>
<td>0/2/1</td>
</tr>
<tr>
<td>Family 9</td>
<td>2/5 (40)</td>
<td>1/2</td>
<td>0/0/1</td>
</tr>
<tr>
<td>Family 10</td>
<td>2/9 (22.2)</td>
<td>2/3</td>
<td>0/0/2</td>
</tr>
<tr>
<td>Family 11</td>
<td>2/6 (33.3)</td>
<td>1/2</td>
<td>0/2/0</td>
</tr>
<tr>
<td>Family 12</td>
<td>2/5 (40)</td>
<td>2/3</td>
<td>0/2/1</td>
</tr>
</tbody>
</table>

AVS indicates adrenal vein sampling; APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; PA, primary aldosteronism; FH, familial hyperaldosteronism; und, undetermined. Eight patients had undetermined subtype because they did not undergo AVS because of age/high risk for surgery (n=3), normotension (n=2), very young age (n=1), personal choice (n=2), and 1 patient because of unsuccessful AVS.

Table 4. Clinical and Biochemical Parameters of the Studied Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sporadic PA (n=18/7)</th>
<th>FH-I/ GRA Total (n=23)</th>
<th>FH-II Total (n=27)</th>
<th>Index Cases (n=12)</th>
<th>Relatives (n=15)</th>
<th>Relatives of FH-II (n=50)</th>
<th>Relatives of Sporadic PA (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, range</td>
<td>30–70</td>
<td>68</td>
<td>6–81</td>
<td>2–85</td>
<td>27–61</td>
<td>2–85</td>
<td>9–81</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>112/65</td>
<td>7/16</td>
<td>15/12</td>
<td>9/3</td>
<td>6/9</td>
<td>15/28</td>
<td>187/271</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>165±19</td>
<td>133±33</td>
<td>156±19</td>
<td>165±15</td>
<td>149±20</td>
<td>124±19</td>
<td>131±21</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>100±10</td>
<td>87±21</td>
<td>97±13</td>
<td>104±11</td>
<td>91±11</td>
<td>77±11</td>
<td>82±13</td>
</tr>
<tr>
<td>Subjects with hypertension, %</td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>100</td>
<td>87</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td>PRA, ng/mL·h⁻¹</td>
<td>0.2 (0.1–0.4)</td>
<td>0.2 (0.1–0.3)</td>
<td>0.2 (0.1–0.5)</td>
<td>0.2 (0.1–0.5)</td>
<td>0.2 (0.2–0.4)</td>
<td>1.3 (0.9–2.4)</td>
<td>1.2 (0.5–2.7)</td>
</tr>
<tr>
<td>s-Aldosterone, ng·dL⁻¹</td>
<td>32 (23–43)</td>
<td>19 (18–22)</td>
<td>29 (23–42)</td>
<td>32 (27–41)</td>
<td>24 (20–44)</td>
<td>15 (10–24)</td>
<td>15 (10–23)</td>
</tr>
<tr>
<td>s-K⁺, mEq·L⁻¹</td>
<td>3.7±0.6</td>
<td>4.1±0.5</td>
<td>3.6±0.6</td>
<td>3.4±0.6</td>
<td>3.9±0.5</td>
<td>4.3±0.3</td>
<td>4.4±0.3</td>
</tr>
<tr>
<td>Subjects with hypokalemia, %</td>
<td>24</td>
<td>13</td>
<td>35</td>
<td>50</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with low renin, %</td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Subjects with high ARR, %</td>
<td>100</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Subjects with APA, %</td>
<td>23</td>
<td>...</td>
<td>7</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>u18OHE, µg·d⁻¹·1⁻¹</td>
<td>206 (119–338)</td>
<td>654 (602–818)</td>
<td>...</td>
<td>183 (98–287)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>u18OxOF, µg·d⁻¹·1⁻¹</td>
<td>4.5 (3.2–6.7)</td>
<td>23 (17–79)</td>
<td>...</td>
<td>3.8 (2.9–5.9)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PRA, plasma renin activity; s-aldosterone, serum aldosterone; s-K⁺, serum potassium; APA, aldosterone-producing adenoma; u18OHE, urinary 18-hydroxycortisol; u18OxOF, urinary 18-oxocortisol; FH, familial hyperaldosteronism; ARR, aldosterone:renin ratio; PA, primary aldosteronism; BP, blood pressure. To convert aldosterone to nmol/L multiply by 0.0277; to convert PRA to ng·L⁻¹·s⁻¹ multiply by 0.2778; to convert 18OHE to µM/d multiply by 0.00265; to convert 18OxOF to µM/d multiply by 0.00266.

*18OHE and 18OxOF were measured in 54 subjects of the sporadic PA group, in all of the index cases of FH-II and in all FH-I/GRA patients. Data are expressed as mean±SD for variables with normal distribution and as median (25th to 75th percentile) for variable without normal distribution, unless otherwise specified.

4 Hypertension November 2011

Phenotypes of FH-II Families

Clinical and biochemical characteristics of FH-II patients are summarized in Table 4. Three FH-II patients experienced a stroke (2 ischemic and 1 hemorrhagic), and 1 displayed severe kidney damage (severe proteinuria and kidney failure); hypokalemia was present in 50% of the index cases and in 18% of the relatives with PA (35% overall in FH-II patients). Potassium levels were not significantly different in FH-II patients compared with sporadic PA but were significantly lower than in FH-I/GRA patients. Hypertension was present in 92% of the affected members, and blood pressure levels were not significantly different compared with patients with sporadic PA; it should be highlighted that 9 subjects displayed low-renin and high ARR, but aldosterone levels were still suppressible with saline load. It is conceivable that a number of these subjects may have the genetic alterations (P<0.01). PRA and ARR were not significantly different from the other group of patients, whereas aldosterone levels were lower than in both sporadic PA and FH-II patients (P<0.05). Very low doses of dexamethasone and/or mineralocorticoid receptor antagonists were able to control blood pressure levels satisfactorily. In the first family, 1 subject died of stroke at a young age before being studied (and, thus, with an unknown genotype), whereas the second family displayed a history of aortic dissection and myocardial infarction at a young age (4 subjects died before 50 years of age). Dexamethasone suppression test was positive in all of the affected members of both families.
responsible for FH-II and will develop florid PA in the future. APA was present in 17% of index cases and in none of the relatives with PA; however, 2 index cases and 6 PA relatives with a normal appearance of the adrenal gland did not undergo AVS for different reasons (high risk for surgery, personal choice, normotension, or very young age), and 1 index case with a nodule in the right adrenal had a nonsucces-
sful AVS; thus, some microAPAs may have been missed, and the proportion of APA could have been higher in the 2 subgroups of patients. Urinary 18OHF and 18oxoF levels of FH-II patients were similar to those measured in sporadic PA patients and significantly lower than FH-I/GRA patients (P<0.01).

Of note, 1 girl was diagnosed with PA at 2 years of age for polyuria, hypertension, and hypokalemia. 18OHF and 18oxoF levels were normal. The mother also displayed PA with a similar phenotype. So far, she is the youngest non–FH-I/GRA patient diagnosed as affected by familial hyperaldosteronism.

**Discussion**

The diagnosis of PA and the recognition of its subtypes are fundamental to address the correct therapy for these patients, thereby preventing consequent organ damage and cardiovascular events. In the present study, we investigated the prevalence of familial forms of hyperaldosteronism in a large number of consecutive patients diagnosed with PA in our hypertension center. To avoid a referral bias, all of the PA patients/families who were addressed to our unit with the suspicion of FH were excluded from the study.

The prevalence of FH has been reported previously only by the Brisbane group in an Australian population in which a prevalence of FH-I/GRA of 0.36% (5 families and 36 patients) and of FH-II of 2.8% (39 families and 98 patients) was described. In our study, the prevalence of FH was higher for both subtypes, 0.66% for FH-I/GRA and 6.00% for FH-II, whereas we did not find patients with a phenotype compatible with FH-III. It is possible that the prevalence of FH-II may be even higher than 6%, because 75% of families of uncertain status displayed patients with low-renin hypertension, which in some cases could evolve into florid PA over time. By contrast, it is possible that PA patients diagnosed in our center experience a more florid form of PA and that in these patients the prevalence of FH may be higher than that in the general PA population: a careful screening of hypertensive relatives of PA patients diagnosed in a primary care setting would resolve this issue.

Our study reinforces the recommendation of the Endocrine Society Guidelines to screen all first-degree hypertensive relatives of PA patients. To date, information is lacking on the necessity of screening normotensive relatives of PA patients who do not belong to FH-II families: follow-up of normotensive FH-II subjects will be of help in showing a potential effect of aldosterone on target organ damage independent of blood pressure, as shown for FH-I/GRA normotensive individuals.

Recent evidence from the Framingham Offspring Study has emphasized the importance of aldosterone in the development of hypertension. This study found a significant relationship between ARR and both blood pressure progression and hypertension development among Framingham study participants and significant heritability of the ARR. Interestingly, in a linkage analysis that included 1225 genotyped individuals from 328 families, logARR was demonstrated to be in linkage with 7p21-22 with a LOD score of 2.78. It is, therefore, conceivable, that a higher percentage of patients with sporadic PA or low-renin essential hypertension may have genetic alterations similar to those responsible for FH-II.

We confirm the prevalence of FH-I/GRA to be relatively low; however, its diagnosis should be excluded in subjects with a higher risk of this form, such as patients with a family history of PA or of strokes at a young age or with an onset of hypertension at a young age; a recent study reported a relatively high prevalence (3.1%) of FH-I/GRA in hypertensive children in Chile, and, thus, it seems reasonable to test for FH-I/GRA in all hypertensive children with low renin levels. In our study we observed 2 FH-I/GRA families with different phenotypes, particularly mild in one (low prevalence of hypertension and cerebrovascular events, no hypokalemia, and relatively low aldosterone levels) and more severe in the other (all of the subjects were hypertensives, hypokalemic, and with high aldosterone levels and with relatives who died at young age for cardiovascular events). This is in agreement with a reported variability of FH-I/GRA between affected families and even within the same family.

In this context, our reported low prevalence of hypertension and hypokalemia in the present study may have been exaggerated by the disproportion between patients from the family with the mild phenotype (n=21) and the family with the more severe phenotype (n=2). Our study also confirms that low renin is the most sensitive clinical parameter for detecting affected patients; although 18OHF and 18oxoF are also very sensitive parameters, they are not available in most centers.

FH-II patients showed a higher prevalence of hypertension compared with FH-I/GRA; however, this should be interpreted with caution, because the genetic alteration responsible for FH-II is unknown, and its diagnosis is based on clinical parameters. Therefore, it is possible that other patients carrying the same genetic background had not yet developed a clinically detectable disease. In agreement with this hypothesis, a hypertensive woman with normal renin and aldosterone levels shared the same haplotype as her 2 affected brothers in a family for which a linkage with the region 7p22 has been shown. Interestingly, FH-II index cases had higher blood pressure levels than their relatives with PA, which can be accounted for by the fact that they were originally screened for secondary forms of hypertension. By contrast, it should be acknowledged that some of the families classified as FH-II may have in fact been composed of 2 relatives affected by sporadic PA, making the prevalence of FH-II between 1.5% and 6.0%.

Prevalence of APA was not significantly different in FH-II patients compared with sporadic PA, although these data must be interpreted with caution, because not all patients underwent AVS. In particular, 39 patients with sporadic PA (all with normal appearance of adrenal gland at computed tomography scanning) and 9 FH-II did not have a subtype

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**Mulatero et al Prevalence of Familial Hyperaldosteronism**

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diagnosis performed with AVS (7 with normal adrenals, 2 of which were normotensives, 1 because they were at risk for surgery and 1 with unsuccessful AVS). Therefore, the actual prevalence of APAs may be higher in these subgroups of patients. However, it should be noted that, in our experience, patients with bilaterally normal appearance of the adrenal glands on computed tomography scanning are often associated with a very high probability of bilateral adrenal hyperplasia (95%).

A limitation of the present study is that the prevalence of FH-III has been based on the clinical phenotype. When the present article was in preparation, Choi et al demonstrated the genetic cause determining FH-III as a mutation in the potassium channel KCNJ5. Further genetic studies addressing the prevalence of mutations in KCNJ5 in FH are required.

In conclusion, our study demonstrates that the prevalence of FH-I/GRA and FH-II is higher than reported previously and should be suspected and diagnosed or excluded in groups of patients with higher prevalence. FH-I/GRA exhibits a highly variable degree of severity, whereas FH-II displays a phenotype similar to sporadic PA.

Perspectives
PA is the most frequent cause of secondary hypertension, and FH-II accounts for ≤6% of PA cases. The recognition of FH-II in the relatives of PA patients will enable their treatment with the appropriate therapy (adrenalecctomy for patients with APA, and mineralocorticoid receptor antagonists for patients with bilateral adrenal hyperplasia). Genetic studies are ongoing to elucidate the gene(s) involved in this disease and will provide tests, like the long-PCR for the diagnosis of FH-I/GRA, that will allow the early diagnosis of this disease, thus preventing the detrimental effects of aldosterone on the cardiovascular system.

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References


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