Abstract—Familial hyperaldosteronism type I is caused by an unequal crossover of 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) genes, giving rise to a chimeric CYP11B1/CYP11B2 gene (CG). We describe a family carrying a CG with high levels of free 18-hydroxycortisol but low prevalence of primary aldosteronism (PA) and an atypical CG inheritance pattern in a family of 4 generations with 16 adults and 13 children, we measured the arterial blood pressure, serum aldosterone, and plasma renin activity and then calculated the serum aldosterone:plasma renin activity ratio and urinary free 18-hydroxycortisol. We identified the CG by long-extension PCR and predicted its inheritance pattern. The CG was found in 24 of 29 subjects (10 children and 14 adults). In CG/H11001 patients, hypertension and high 18-hydroxycortisol were prevalent (83% and 100%, respectively). High serum aldosterone:plasma renin activity ratio was more frequent in pediatric than adult patients (80% versus 36%; P<0.001). An inverse association between serum aldosterone:plasma renin activity ratio and age was observed (r=−0.48; P=0.018). Sequence analysis identified the CYP11B1/CYP11B2 crossover in a 50-bp region spanning intron 3 of CYP11B1 and exon 4 of CYP11B2. The CG segregation differs from an autosomal disease, showing 100% of CG penetrance in generations II and III. Statistical analysis suggests that inheritance pattern was not attributed to random segregation (P<0.001). In conclusion, we describe a family with an atypical CYP11B1/CYP11B2 gene inheritance pattern and variable phenotypic expression, where the majority of pediatric patients have primary aldosteronism. Most adults have normal aldosterone and renin levels, which could mask them as essential hypertensives. (Hypertension. 2012;59:85-91.)

Key Words: familial hyperaldosteronism type I ▪ glucocorticoid-remediable aldosteronism ▪ chimeric CYP11B1/CYP11B2 gene

Familial hyperaldosteronism type I (FH-I; Online Mendelian Inheritance in Man No. 103900), is an autosomal dominant disorder, which is also known as glucocorticoid-remediable aldosteronism. Considered the most common monogenic cause of hypertension, it is characterized by severe hypertension, variable hyperaldosteronism, low plasma renin activity (PRA), normal or decreased serum potassium, and abnormal adrenal steroid production, including 18-oxocortisol and 18-hydroxycortisol (18OHF).1

FH-I occurs by an unequal crossing over of the genes encoding steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (AS; CYP11B2), resulting in a chimeric CYP11B1/CYP11B2 gene (CG) with AS activity that is regulated by plasmatic adrenocorticotrophic hormone levels instead of angiotensin II, which results in an ectopic expression of AS in the zona fasciculata.2-4 Different pedigrees exhibiting different crossover patterns of the hybrid gene have been described, which suggests that the mutations arose independently in each pedigree.5

In the hypertensive adult population, this monogenic form of aldosteronism is thought to account for only 0.5 to 1.0% of primary aldosteronism (PA) cases6; our group reported recently a higher prevalence of FH-I in a pediatric hypertensive population than in adults.7 An early diagnosis is clinically relevant, because FH-I may cause severe hypertension,5,8-10 heart hypertrophy,11-13 and cerebrovascular damage,14 and these patients could be specifically treated by suppressing adrenocorticotropic hormone production with cortisol or synthetic glucocorticoids, such as dexamethasone. In this report, we describe a family carrying a CG with high levels of 18OHF but with low PA expression and an atypical inheritance pattern.
Patients and Methods

We studied 29 subjects from a family of 4 generations with Hispanic-American ethnicity. The index case was a 15-year-old teenager (III-12), who exhibited systodiasstolic arterial hypertension (SAH) by hypertensive disease associated with hyperaldosteronism. He was diagnosed in a previously published study that focused on determining the prevalence of FH-I in a pediatric population. His family members consist of his mother, 1 twin brother, 1 additional brother, 1 sister, and 1 half-sister (Figure 1). His father died from cardiovascular disease in 2001, and there is no evidence of parental consanguinity or hypertensive disease associated with hyperaldosteronism. The maternal grandfather (patient I-1) also died because of cardiovascular disease and heart attack at the age of 55 years, and we suspect that he was affected with the chimeric gene (Figure 1).

All of the recruited subjects underwent a clinical-biochemical examination and a clinical survey. The subject’s height was measured using a wall-mounted Harpenden stadiometer (Holtain), and his or her weight and total fat mass percentage was assessed by bioelectrical impedance (Tanita, Corporation of America, Arlington Heights, IL). Pubertal development was assessed according to the Marshall and Tanner method. In pediatric and adult subjects, 3 measurements of BP were obtained consecutively from the right arm at 5-minute intervals using an oscillometric method (Dinamap CARESCAPE V100, GE Healthcare) in a seated position according to the published recommendations. In pediatric patients, we considered a patient as hypertensive according to the seventh report of the Task Force, as we reported previously. In adults, hypertension was diagnosed by the fourth report of the Task Force, as we reported previously.7,18 and in adults, hypertension was diagnosed by the seventh report of the Joint National Committee guidelines.16,17 We measured the serum creatinine, calcium, urea, glucose, and the hepatic profile (alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, and albumin) in all of the subjects after a 12-hour fasting period. We used these screenings to exclude subjects with renal disease, diabetes mellitus, hepatic failure, and hypercalcemia. After an overnight fast, basal blood samples were obtained between 8:00 and 10:00 AM. Subjects assumed a sitting position for at least a 15-minute rest period. The blood samples to measure potassium, sodium, creatinine, cortisol, serum aldosterone (SA), and plasma renin activity (PRA), as well as to calculate the SA:PRA ratio (ARR), were obtained using a indwelling catheter that was positioned in an antecubital vein. Serum cortisol was measured by immunoassay using automated equipment (IMMULITE 2000, Siemens Healthcare Diagnostics Inc). SA was measured by the Coat-A-Count kit (Siemens). PRA was determined as described previously.19

### Table 1. Clinical Profile of Patients With Chimeric Gene CYP11B1/B2

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<th>DBP, mm Hg</th>
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<th>BMI</th>
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<td>63</td>
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<td>112</td>
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</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SAH, systolic arterial hypertension; DAH, diastolic arterial hypertension; SDAH, systodiasstolic arterial hypertension; PH, prehypertension; S1, S2, S3, hypertensive stage (according to the seventh report of the Joint National Committee or Task Force 4); M, male; F, female; ND, not determined.

*Data show weight to height.
†Data show the use of angiotensin-converting enzyme inhibitors.
‡Data show the use of β-blockers.
§Data show the use of calcium channel blockers.
In accordance with our recently reported reference values for the pediatric population, we consider SA level values >17.7 ng/dL (491.7 pmol/L) to be high, PRA <0.5 ng/mL per hour to be suppressed (equal to the third percentile in Chilean normotensive healthy pediatric population), and ARR levels values >10 to be high. In our Chilean hypertensive adult population, the ARR level is considered high when it exceeds 2.5, and SA is considered high when it exceeds 16 ng/dL. A dexamethasone suppression test was not performed because it has a high frequency of false-positives when compared with long-extension PCR of the chimeric gene CYP11B1/CYP11B2.

Twenty-four-hour (adults) or 12-hour nocturnal (between 7:00 PM and 7:00 AM) (pediatrics) urine samples were collected. Total urine volumes were measured, and aliquots were stored to measure the urinary free cortisol, urinary free 18OHF, creatinine, sodium, and potassium. Urinary free 18OHF was measured by liquid chromatography-tandem mass spectrometry at Quest Diagnostic Laboratory. The normal value was set with urine samples of Chilean normal subjects with an age range of 4.9 to 49 years (18OHF: 34.4–29.9 μmol/mol of creatinine). The upper cutoff point (95%) was set at 54.2 μmol/mol of creatinine.

**Genetic Study**

A genetic study was performed to detect and characterize the chimeric gene CYP11B1/CYP11B2. Genomic DNA was isolated from peripheral blood leukocytes using the method described previously by Lahiri and Schnabl. Genetic analysis for FH-1 was conducted using long-extension PCR of the CYP11B1 (NG_007954), CYP11B2 (NG_008374), and CYP11B1/CYP11B2 genes, using a protocol that was described previously by our group. This technique uses 2 parallel long-extension PCR amplification reactions using the GeneAmp long-extension PCR kit (Applied Biosystems). Sequence analyses of the CYP11B1 and chimeric genes were performed in a ABIprism-377 DNA Sequencer (Applied Biosystems) in Macrogen using primers designed by our group (available on request), and then sequences were aligned with ClustalW.

**Data Analysis**

Statistical analyses were performed using Prism 5.0 (GraphPad Software Inc, La Jolla, CA). The results were expressed as median values (interquartile range, [minimum to maximum]). Additionally, a statistical analysis by exact binomial method was performed to predict the inheritance pattern of this CG. We tested the null hypothesis using the exact method of binomial distribution. For an autosomal dominant gene, inheritance is expected to occur with a probability of 0.5. We identified the DNA crossover breakpoint region using ClustalW. Sequence analysis detected the unequal crossover of CYP11B1/CYP11B2 in a region of 50 bp spanning intron 3 of CYP11B1 (c.2937–40) and exon 4 of CYP11B2 (c.2937+10; Figure 4A). The sequences obtained from CG patients showed perfect alignment with normal and GenBank CYP11B1 and CYP11B2 portions, except by a single nucleotide base difference in 7895 of (T>c) and 8279 of (c>T) (Figure 4B). We did not find common polymorphisms in the CYP11B2 gene in this family, but we detected 2 already known polymorphisms at positions 8499 (rs45356) and 8279 (rs28531895). The sequencing of the CYP11B1 gene detected 3 polymorphisms described previously (and present in all of

**Results**

**Clinical and Laboratory Studies**

The pedigree for the proband’s large family was traced through 4 generations. A total of 29 members were studied, including 13 pediatric subjects (with an age range between 7 months to 16 years old) and 16 adults (with an age range between 18 and 56 years old). Ten pediatric subjects were CG+. The group included 4 females, and 8 of 10 pediatric subjects had AH (Table 1). Fourteen of 16 adults patients were CG+. The group included 9 females, and 11 of 14 adult patients had AH. The 2 adult patients without the CG corresponded with patient I-2, the wife of the suspected founder, and patient II-6, who is a son from another father (Figure 1). The clinical features of all of the CG+ patients are shown in Table 1, which summarizes the clinical measurements.

In CG+ patients, the SA concentration was significantly higher in children (18.25 ng/dL [11.0–49.7 ng/dL]) than in adults (9.6 ng/dL [2.5–27.5 ng/dL]; P=0.0013; Figure 2A). PRA tended to be lower in children (0.35 ng/mL*h [0.20–13.6 ng/mL*h]) than in adults (0.85 ng/mL*h [0.20–3.40 ng/mL*h]; P=0.205; Figure 2B), and ARR was higher in the pediatric group (54.4 [1.6–248.5]) than adults (13.40 [0.96–40.50]; P=0.0242; Figure 2C). We also compared SA, PRA, and ARR in CG+ children without the 2 infants (n=8) versus CG+ adults. We found that in children CG+ without infants, their median SA (16.8 [11.0–24.5] P=0.0051) and ARR (54.4 [1.6–85.5] P=0.0154) were higher than adults CG+. The PRA was similar in both groups (P=0.1327). Both analyses shown that high ARR was more prevalent in children than adults, being consistent with an inverse correlation between ARR and age (r=-0.48; P=0.0176; Figure 3). Furthermore, we found an inverse correlation of aldosterone and age when we considered all children and adults CG+ (n=24; r=-0.5037 Pearson; P=0.0128). With regard to PRA, we found a trend with age (n=24; r=0.3894 Spearman; P=0.060), which is very close to achieve significance.

Free urinary 18OHF excretion was similar in both CG+ children and adults. The median free urinary 18OH-cortisol excretion was 364 μmol/mol of creatinine (85 to 1040 μmol/mol of creatinine; Figure 2D) for children and 348 μmol/mol of creatinine (236 to 667 μmol/mol of creatinine) for adults. The correlation between ARR and 18OHF in CG+ patients was not significant (data not shown). The median serum cortisol concentration was similar between children and adults (298.9 nmol/L [151.5–429.8 nmol/L] and 263 nmol/L [126.7–686.0 nmol/L], respectively). The sodium and potassium excretions between children and adults were similar for both group of patients. Sodium excretion was 170 mEq/L (58–216 mEq/L; n=7) versus 153 mEq/L (78–218 mEq/L; n=13), respectively, and potassium excretion was 39.0 mEq/L (9.3–98.0 mEq/L) versus 31.8 mEq/L (11.8–53.3 mEq/L), respectively. The biochemical characteristics of each patient are shown in Table 2.

**Genetic Analyses**

We identified the DNA crossover breakpoint region using sequencing and then conducted further analyses with ClustalW. Sequence analysis detected the unequal crossover of CYP11B1/CYP11B2 in a region of 50 bp spanning intron 3 of CYP11B1 (c.2937–40) and exon 4 of CYP11B2 (c.2937+10; Figure 4A). The sequences obtained from CG+ patients showed perfect alignment with normal and GenBank CYP11B1 and CYP11B2 portions, except by a single nucleotide base difference in 7895 of (T>c) between exons 3 and 4 (2 nucleotides upstream the crossover breakpoint; Figure 4B).
the patients studied) at positions 7326 (rs7814006), 7810 (rs6387), and 8258 (rs10956991), which are prevalent in the global population with a frequency close to 0.5 (http://www.ncbi.nlm.nih.gov/projects/SNP).

Inheritance Statistic Analysis

Chimeric gene segregation in this family differs from the typical pattern of an autosomal disease, where the risk of the descendants to be affected is 50%. Here, we found that the hybrid gene in 24 of 27 subjects (2 unrelated subjects I-2 and II-6) exhibited a preferential segregation of 100% in generations II and III and 62.5% in generation IV. To test whether this difference is explained by random inheritance, we performed a \( P \) test based on a binomial distribution, showing that a probability of occurrence of this genetic alteration (CG) in this family is 0.000025. The CI for the proportion of subjects with the condition was 0.708 to 0.976 when the probability of success is equal to 0.5 (\( P = 0.000025 \)). Thus, the probability of this atypical segregation pattern is only 3 occurrences in 100,000.

Discussion

We studied a Chilean family that exhibits a CYP11B1/B2 chimeric gene affecting 24 of 29 members that displays AH (19 of 29) and a high urinary 18O HF level (Table 2). However, in the CG+ subjects, the presence of a high ARR (suggesting PA) was demonstrated in only 50% of affected patients, and the inheritance of CG was close to 100% in the offspring. These findings suggest the existence of a CYP11B1/B2 chimeric gene with a different activity from that described previously for classic FH-I. In CG+ patients, a high ARR was demonstrated in only 13 (54%) of 24 patients, and most of them corresponded with subjects <16 years old (80% in children versus 36% in adults). In contrast, the adult population showed a high

![Figure 2. Comparison among serum aldosterone (SA; A), plasma renin activity (PRA; B), SA:PRA ratio (ARR; C), and urinary free 18-hydroxycortisol per creatinine (D) in 10 pediatric and 14 adult patients with the chimeric gene. The SA level upper cutoff (gray dotted line) is 17.7 ng/dL (pediatrics) and 16 ng/dL (adults). The PRA cutoff is 0.5 ng/mL per hour. ARR cutoff is 10 (pediatrics) and 25 (adults). The 18-hydroxycortisol (18O HF) upper cutoff was 54 \( \mu \)mol/mol of creatinine. Asterisks represent patients of 7 and 8 months of age. We were unable to obtain the urine sample from 1 pediatric and 1 adult (CG) patient.]

![Figure 3. The linear correlation was determined between serum aldosterone (SA):plasma renin activity (PRA) ratio (ARR) and age for CYP11B1/CYP11B2 gene (CG+) patients. We calculated their association, and then plotted the ARR vs age (\( r = -0.48; P = 0.0176 \)). This association highlights that older CG+ patients had lower ARRs.]

![Figure 4. The linear correlation was determined between serum aldosterone (SA):plasma renin activity (PRA) ratio (ARR) and age for CYP11B1/CYP11B2 gene (CG+) patients. We calculated their association, and then plotted the ARR vs age (\( r = -0.48; P = 0.0176 \)). This association highlights that older CG+ patients had lower ARRs.]

In CG+ patients, a high ARR was demonstrated in only 13 (54%) of 24 patients, and most of them corresponded with subjects <16 years old (80% in children versus 36% in adults).
number of CG+ hypertensives with normal aldosterone and PRA levels, as well as normal ARR, suggesting a partial impairment in the AS activity in older patients (Figure 2C). Furthermore, we observed an inverse correlation between age and ARR, suggesting a loss of activity in this hybrid enzyme to convert corticosterone to aldosterone. However, the presence of high levels of 18OHF in both populations suggests that 18-hydroxylation activity of the hybrid enzyme is maintained despite of the normalization of aldosterone levels. This phenotypic disparity also has been described by others, showing the presence of patients CG+ with normal aldosterone and PRA.

It has been suggested that CG could be influenced with either mutations in the coding region or in the promoter region of the gene. However, when we sequenced the chimeric gene, we did not find any mutations between subjects with PA or without PA, suggesting that genetic alterations in CG are neither necessary nor sufficient to explain the phenotypic differences of the disease in these subjects. The chimeric gene in this family had a full identity of sequence with both CYP11B1 and CYP11B2 portions, except by a single polymorphism, C>T at position 7895 (c.2937–42, intron 3 of B1), which could affect the expression of the CG, but this polymorphism was present in both patients with and without phenotypic expression of PA, making a genomic explanation unlikely. We found the CG breakpoint in the beginning of exon 4, which produces a hybrid enzyme with the capacity to synthesize both aldosterone and 18OHF, as shown previous studies by Pascoe et al in artificial chimeras from FH-I patients. The CG breakpoint determines the CYP11B1 and CYP11B2 gene portions that are shared, which has been described in several pedigrees occurring within a hotspot region spanning exon 1 to exon 5. Indeed, gene fusions after exon 5 display an AS activity undetectable, because exon 5 maintains the majority of the structural determinants for AS catalytic activity.

Epigenetic factors have been proposed to influence gene expression. We speculate on their possible role in the expression of the chimeric gene, which would affect the production of aldosterone but not the 18-hydroxylated products of cortisol in an age-dependent manner. It is known that the adrenal cortex changes histologically and biochemically throughout life. In the newborn period, the fetal adrenal gland is proportionally bigger and more active that adult adrenal gland, but it regresses from the sixth month after birth, which is consistent with a partial aldosterone resistance at this early stage of life. The transition zone occurs at the glomerular and fascicular layers that produce aldosterone and cortisol, respectively. These zones are fully developed at the age of 3 years. After the zones are completely developed, the reticular zone produces androgens and develops after the age of 4; its development is probably not complete until the age of 15 years. It is unlikely that antihypertensive therapy has a confounding effect, because the therapies described affect the aldosterone-renin system and not the glucocorticoid axis. Moreover, some patients (independent of antihypertensive treatment) display features of PA (Table 2).

The inheritance pattern in this family is different than the normal pattern of an autosomal dominant disease that affects 50% of the offspring. In this case, the inheritance of the CG alteration occurs close to 100%, except by the subject II-6, who only holds a maternal affiliation. We hypothesize a preferential segregation of chromosomes carrying the CG, resulting in an unequal representation of the CG in the offspring. Reports in medical genetics about this kind of segregation are scarce, but preferential segregation in some diseases has been reported. This phenomenon might be caused by mitotic errors in germ cells, biased meiotic segregation of chromosomes, and differential selection by viability or functionality of gametes, as well as a differential survival of cells during development.

Notably, most of the adult subjects in this family are hypertensive, although their values of aldosterone and PRA, as well as their ARR, have normalized. This might be because the hypertensive phenomenon generated in childhood and not detected in time could induce structural vascular alterations, which could cause the hypertension to become fixed, independent of the cause. This has been observed previously in obese children, who showed increases in the intima media thickness, impaired endothelial function, and elevated plasma markers of endothelial activation and injury, suggest-

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Na indicates serum sodium; K, serum potassium; PRA, plasma renin activity; ARR, aldosterone to PRA ratio; 18OHF, 18-hydroxycorticoid; ND, not determined.
ing the early onset of an alteration that leads to an increase in arteriole resistance in adulthood.

In summary, we describe a family with a chimeric CYP11B1/CYP11B2 gene that shows differences in clinical, biochemical, and genetic characteristics in relation to classic FH-I. In this family, the majority of pediatric patients present biochemical parameters of PA, but only a few adults are affected, suggesting a partial inactivation of this gene with age. This finding is highly relevant and points out the importance of detecting the disease in pediatric patients, because, in adults, normal aldosterone and renin levels may mask their essential hypertension.

**Perspectives**

FH-I is a familiar genetic condition that joins 3 key factors, AH, high ARR, and a chimeric gene. A nonclassic FH-I in a large pedigree represents an opportunity to find out the genetic and biochemical determinants involved in the phenotypic expression of the chimeric gene. In the family studied, most of the adult subjects continue being hypertensive, although the values of aldosterone and the PRA, as well as their ARR, have normalized. This could be explained by the hypertensive phenomenon generated in childhood undetected in time, which could lead to structural vascular alterations, may causing hypertension to become fixed, independent of the cause. This highlights the importance of detecting the disease in pediatric patients, because, in adults, normal aldosterone and renin levels may mask their essential hypertension.

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**Disclosures**

None.

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**Figure 4. A,** Sequence analysis showing CYP11B1, CYP11B2, and the CYP11B1/CYP11B2 chimeric gene in representative electrophoretograms of a CG+ patient. The formation of CG by unequal crossing over was identified in a region of 50 bp spanning intron 3 of CYP11B1 (c.2937→40) and exon 4 of CYP11B2 (c.2937+10). The chimeric gene has no mutation, except for a polymorphism located in c.2937→42 (see red arrow). **B,** Scheme of the CYP11B1/B2 chimeric gene, showing the full identity of the sequence with both B1 and B2 portions (100%), except for a unique polymorphism C>T located at position 7895 (c.2937→42, intron 3 of B1). Asterisks represent the nucleotides flanking the cross-over region.
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