Association of a Mineralocorticoid Receptor Gene Polymorphism With Hypertension in a Spanish Population

Fernando Martinez¹², Maria L. Mansego³, Juan C. Escudero⁴, Josep Redon¹² and Felipe J. Chaves³

BACKGROUND
To assess the association of polymorphisms and haplotypes of the mineralocorticoid receptor (MR) (NR3C2) gene to the risk of essential hypertension (HTN) in a Spanish population.

METHODS
This is a population-based study which included 1,502 subjects (748 women) >18 years old. Twenty-four polymorphisms of NR3C2 gene were analyzed by using SNPlex (Genotyping System based on OLA/PCR technology).

RESULTS
Alleles of the single-nucleotide polymorphism (SNP) rs5522 were significantly associated with the risk of HTN, both in the recessive and codominant models adjusted by age, gender, and body mass index (BMI). Genotype GG of the rs5522 showed to be protective against HTN odds ratio (OR) 0.10 (0.02–0.56), P < 0.01. One haplotype, which included the G allele of the rs5522, was also associated with reduced risk of HTN and four haplotypes which included the A allele were associated with increased risk of HTN. When the 24-h urinary sodium excretion and the estimated glomerular filtration rate (eGFR) were added, they did not reduce the significance level. Interaction between genotypes of the rs5522 and quartiles of 24-h sodium excretion has been observed. In subjects with the A4 genotype, those with higher urinary sodium excretion had the lowest risk to be hypertensive.

CONCLUSION
A functional polymorphism of the NR3C2 gene was associated with risk of HTN. The data provided in this study seems to give credit to the hypothesis of the participation of MR gene in the development of HTN, although further studies are necessary to better assess its real impact.


Influence of genetic factors in the development of essential hypertension (HTN) has long been recognized.¹ Because it has a complex trait hereditary pattern, candidate gene strategies have been used to identify variations in genes, which can increase the susceptibility of being hypertensive. There are at least 150 candidate genes for essential HTN (http://cmbi.bjmu.edu.cn/genome/candidates/snps.html), and many of them play a major role in sodium handling. Likewise, the rare Mendelian forms of HTN involve key genes of sodium handling. Among them, a single mutation in the NR3C2 gene, S810L, causes early-onset HTN exacerbated during pregnancy.²

The NR3C2 (Entrez gene ID: 4306), located on chromosome 4q31.1, consists of nine exons with a coding region spanning from exons 2–9. It produces a protein of 984 amino acids,³⁴ which is a member of the nuclear receptor superfamily. It is expressed not only in the tubular cells of the kidney, but also in the heart and in both endothelial and vascular smooth muscle cells.³⁶ The NR3C2 has an amino terminal region including a DNA-binding domain and a C-terminal region with the ligand-binding domain.³ Aldosterone is the main ligand for the mineralocorticoid receptor (MR) in the kidney and in the cardiovascular system.⁶⁷

In vitro studies demonstrated that a missense mutation rs41511344 (p.S810L) of the NR3C2 gene produces a gain of activity in the MR which is activated not only by aldosterone but also by cortisone, 11-β-dihydrocorticosterone, and progesterone.⁸⁻¹¹ The receptor activation by these steroid hormones produces HTN in young women, which exacerbates during pregnancy.² This single mutation was not identified in large series of essential hypertensive subjects and seems to be that it does not play a role in essential HTN or in severe preeclampsia.¹²¹³ Other nonsense/missense or frameshift mutations in the NR3C2 gene as c.2839C>T (p.R947X), c.1308T>A (p.C436X), c.1132_1133insT, c.315del8bp, c.1935C>A (p.C645X), c.1897G>A (p.G633R), c.2327A>G (p.Q776R), c.2936T>C (p.L979P), and c.488C>G (p.S163X) have been associated with pseudohypoaldosteronism type 1 due to loss of MR activity.³⁴¹⁴⁻¹⁶ The mutation rs5522 (c.538A>G or p.I180V) have also been related with the response to mineralocorticoid treatment in patients with pseudohypoaldosteronism type 1¹⁷¹⁸ and with the response to stress.¹⁹
The potential impact of single-nucleotide polymorphism (SNP) of the NR3C2 gene on the risk of HTN, plasma-renin activity or serum aldosterone values, sodium urinary excretion, and on the response to thiazides has been tested with inconclusive results in a few number of studies. Wilk et al., by using genome-wide linkage analysis, showed that for early-onset HTN the maximum lod score was located in chromosome 4 overlaying the NR3C2 gene locus in African Americans.

The fact that functional modifications in the sequence of NR3C2 gene can produce rare forms of monogenic HTN or hypotension makes to hypothesize whether or not common polymorphisms of the gene can result in susceptibility to essential HTN. The aim of this study was to evaluate the association of alleles and genotypes in 24 SNPs of the MR gene and its haplotypes with the blood pressure (BP) levels and therefore with the presence of essential HTN in a Spanish population. The possible interaction with sodium excretion was also analyzed. Furthermore, the presence of the rs41511344 (p.S810L) variant was investigated in the subset of young hypertensives.

**METHODS**

**Study design.** This is a population-based study from general population of Spain. Subjects >18 years old were randomly selected from the public register of the Western medical area of Valladolid (Spanish National Statistic Institute; http://ine.es). Subjects were invited to participate in the study by phone. Individuals with serious concomitant disease or psychiatric disorder were excluded. A second list of subjects was selected to replace those who rejected to take part in the study. The percentage of replacement was 32%. The calculated minimal sample size to be representative of the population was 1,400, from 1,504 individuals recruited. A more detailed description of the selection process has been previously described, which included a random sampling polystratified by all the relevant variables.

The study has been approved by the Ethical Committee and all the participants gave written agreement to participate.

**Procedures.** After inclusion, age and gender of each participant were registered along with a clinical record and a physical exam, which included height, weight, body mass index (BMI), and abdominal circumference. Information about individual and familiar cardiovascular risk factors as well as cardiovascular disease was collected. Spot urinary samples were collected for analytical procedures and into tubes containing K3-EDTA to obtain genomic DNA. The estimated glomerular filtration rate (eGFR) was calculated by using the Cockcroft–Gault formula.

**Sodium excretion.** Twenty-four hour sodium excretion in mEq/day was calculated from a spot sample of urine by the method developed by Tanaka and colleagues. Sodium and creatinine in urine were assessed by indirect potentiometry with selective electrode and Jaffé test, respectively. Both measures were performed in a Hitachi autoanalyzer (Roche diagnostics, Barcelona, Spain).

**Blood pressure measurement.** Omron model M6 automated device (Omron Healthcare, Hoofddorp, Netherlands) with appropriate cuff size according to the circumference of the arm was used to measure the systolic and the diastolic BP. Patients were not allowed to smoke or to drink coffee from 30 min before the measure. After 2 min of relaxation with the patient seated, three BP measurements were performed and the average of the last two measures was considered as BP value. According to the current blood pressure and the prior diagnosis of HTN, individuals were classified in three groups: (i) normotensive patients in the absence of a diagnosis of HTN and the current blood pressure’s values <140/90 mm Hg; (ii) hypertensive subjects previously diagnosed of HTN, independently of the current blood pressure’s values; (iii) new hypertensive subjects in the absence of previous diagnosis of HTN, current blood pressure’s values ≥140 mm Hg and/or ≥90 mm Hg and confirmed by 24-h ambulatory BP monitoring.

**SNPs selection and genotyping.** SNPs of the NR3C2 gene have been chosen based on frequency (≥0.1), location, distribution, and possible effect in MR function. Reference names, position along the gene, linkage disequilibrium (LD), and haploblocks of the 24 single SNPs selected are shown in Figure 1.

DNA was isolated of peripheral blood cells using Realpure Genomic DNA extraction kit (Real Pure, Paterna, Spain) and samples were diluted to a final concentration of 100 ng/μl. Selected SNPs were genotyped using an oligo-igation assay (SNPlex; Applied Biosystems, Foster City, CA) following the manufacturer’s instructions.

The mutation S810L was genotyped in 147 hypertensive subjects <55 years old by amplification and sequenced in an ABI3730 system (Applied Biosystems). The direct PCR-products were sequenced under standard conditions. The oligonucleotides used were forward gctaaagttagtctttgcattaattgttttg and reverse tggagaagcatacagcaatacttg.

**Statistical analysis.** All values are expressed as mean ± s.d. The χ² goodness-of-fit test was used to compare the distribution of the study population with the theoretical distribution of the reference population, which was estimated from the dates of the National Statistic Institute. Analysis of variance test was used to compare quantitative variates between groups and χ²-test for categorical variables using the software SPSS 12.0 for Windows (SPSS, Chicago, IL).

Genotype and alleles frequencies were calculated for every SNP. The best inheritance model was selected by the use of likelihood ratio test and the Akaike information criterion. The codominant model was used as the reference one. The Hardy–Weinberg equilibrium was sought by a χ²-distribution with one degree of freedom. Those SNPs that were not in Hardy–Weinberg equilibrium in the controls were excluded from the subsequent analysis. The Hardy–Weinberg equilibrium for every SNP was similar between the two different statistical packages used. HelixTree version 5.0 (Golden Helix, Bozeman, MT) and SNPStats developed by Sole and colleagues. The association of HTN with each polymorphism was sought by...
logistic regression models adjusted by potential confounders. Age, BMI, and gender were used as covariates in all the models and the eGFR and the urinary sodium excretion were also included in subsequent models. A formal test for interaction between SNP and urinary sodium excretion was included by using SStats.

Haplotypes were designed using possible functional SNPs (3’-untranslated region (UTR) and 5’-UTR and nonsynonymous coding SNPs), tag-SNPs with an $r^2$ of $\geq$0.8 and according to the haploblocks. The D-statistic (defined as the LD measure, D, divided by the theoretical maximum for the observed allele frequencies) was used to measure the LD. Haplotypes frequencies were estimated by the expectation maximization algorithm. The association between haplotypes and HTN was analyzed by logistic regression and the expectation maximization algorithm. The association between haplotypes and HTN was included using SStats.

The study population was finally 1,502, 49.7% women, mean age 52 years, 42.7% hypertensives and 7.6% diabetics. The main characteristics of the study population are shown in Table 1. According to the BP criteria, 860 (57.2%) individuals were normotensives, 297 (19.7%) were hypertensive under treatment, and 345 (23.0%) were newly diagnosed of HTN. Hypertensive subjects, compared with nonhypertensive, were aged and had significantly higher values of weight, BMI, and waist diameter. They also had higher levels of fasting glucose, plasma creatinine, triglycerides, total cholesterol, and low-density lipoprotein. Hypertensive patients under treatment were older to detect an OR $>1.5$ under codominant and dominant model. Similar statistical power was obtained with the PAWE-3D (http://linkage.rockefeller.edu/pawe3d/) considering a 10% of errors due to genotype and phenotype misclassification under dominant or multiplicative models.\textsuperscript{34,35}

Finally, we used the False Positive Report Probability (FPRP)\textsuperscript{36} to consider a true association between polymorphisms and haplotypes with phenotype. This method takes into account the prior probability of every SNP the observed $P$ value and the desired statistical power. We have chosen to detect a statistical power of 0.8, inferior than the statistical power calculated and an OR of 1.5 (or its reciprocal, 0.67). A threshold of $\leq$0.5 for the FPRP was considered as a significant association.

**RESULTS**

**Characteristics of the study population**

The study population was finally 1,502, 49.7% women, mean age 52 years, 42.7% hypertensives and 7.6% diabetics. The main characteristics of the study population are shown in Table 1. According to the BP criteria, 860 (57.2%) individuals were normotensives, 297 (19.7%) were hypertensive under treatment, and 345 (23.0%) were newly diagnosed of HTN. Hypertensive subjects, compared with nonhypertensive, were aged and had significantly higher values of weight, BMI, and waist diameter. They also had higher levels of fasting glucose, plasma creatinine, triglycerides, total cholesterol, and low-density lipoprotein. Hypertensive patients under treatment were older.

**Figure 1** Distribution of the selected SNPs of the NR3C2 gene and LD according to the haploblocks.
and had significantly lower levels of systolic BP, diastolic BP, eGFR, and urinary sodium excretion than normotensive subjects and hypertensive individuals in the absence of treatment. Likewise, hypertensive patients under treatment had significantly lower levels of eGFR and urinary sodium excretion as compared to normotensive subjects.

**SNPs, blood pressure, and HTN risk**

The following SNPs were excluded from the analysis because they were not in Hardy–Weinberg equilibrium: rs10032250 (c.2800–15793C>T), rs2248038 (c.–6987A>G), rs6849903 (c.1757+57210T>G), and rs10434100 (c.1757+68449C>T). Among the remaining SNPs studied, only alleles of the SNP rs5522 were significantly associated with the risk of HTN, both in the recessive and codominant models after adjusting by age, gender, and BMI and also when urinary sodium excretion and eGFR were added to the models (see Tables 2, 3, and 4). The minor allele frequency for this polymorphism was 0.1 and the genotype frequencies in cases and controls were: genotype AA (wild type) was present in 686 controls (80.5%) and 523 cases (82.4%); AG in 155 controls (18.2%) and 110 cases (17.3%); and the variant GG in 11 controls (1.3%) and 2 cases (0.30%).

The GG genotype of the rs5522 resulted protective against HTN (recessive model OR 0.10 (0.02–0.56), P < 0.01; codominant OR 0.10 (0.02–0.56), P < 0.05). There were no significant differences for the risk of HTN in each genotype of the 24 SNPs studied (Supplementary Table S1 online).

**Haplotypes, blood pressure, and HTN risk**

In the first step, we selected six polymorphisms containing 3′-UTR and 5′-UTR SNPs, functional mutation rs5522, and tag-SNPs, being the final haplotype formed by alleles of the following SNPs: rs2871, rs1040288, rs10519952, rs1512337, rs5522, and rs2070951. Four of the haplotypes were associated with risk of HTN as compared to the most frequent haplotype, AGTAAG, adjusted by age, gender, and BMI (see Table 2).

In a second step, we reduced the number of polymorphisms to three SNPs: rs10519952, rs1512337, and rs5522. Haplotype 5 was protective against the development of HTN (P < 0.05). This haplotype included the allele G of rs5522 and alleles T and G of the tag-SNPs, which were in LD with rs10519952 and rs1512337 (r² > 0.8).

The results of FPRP for the association between polymorphism rs5522 and haplotypes with the risk of HTN are shown in Table 2. The FPRP excluded that significant association between the rs5522 and the haplotypes and the risk for HTN were by chance.

**Relationship with sodium excretion**

The mean of urinary sodium excretion was 131 ± 62 mEq/day. The sodium excretion in each genotype of the rs5522 was no different (AA 130 mEq/day, AG 131 mEq/day, GG 129 mEq/day, P = 0.97). When the estimated 24-h sodium excretion was included in the logistic regression model, the degree of association for the rs5522 polymorphism and for the haplotypes did not change (Table 3). A significant interaction between genotypes of the rs5522 and quartiles of 24-h sodium excretion was observed (P < 0.05). In subjects with the AA genotype, those with higher urinary sodium excretion had the lowest risk to be hypertensive (Supplementary Table S2 online). Likewise, the addition of the eGFR to the logistic regression model did not change the degree of association either in the absence (data not shown) or in the presence of urinary sodium excretion (Table 4). The data corresponding to the full logistic regression model are shown in Supplementary Table S3 online.

**Assessment of the S810L mutation**

We also investigated the presence of the functional mutation rs41511344 (p.S810L) in the hypertensive subjects <55 years old. No subjects carried the p.S810L among the 147 individuals tested.

**DISCUSSION**

In a general population of Caucasian subjects, the genotype GG of the rs5522 was significantly associated with lower risk of HTN after adjusted by potential confounders. The haplotypes containing the A allele of the rs5522 were also significantly related to an increased risk of HTN and one haplotype that included the G allele resulted protective. The associations remained when the sodium excretion and the eGFR were considered.
The rs5522 polymorphism, also named c.538A>G, produces a missense mutation changing isoleucine to valine at codon 180 (p.I180V), which has influence on the MR activity. The response to increasing aldosterone concentrations was lower for the homozygote genotype as compared to the wild type, although other authors found a mild loss of function when cortisol was the ligand instead of aldosterone. Although other authors found a mild loss of function when cortisol was the ligand instead of aldosterone.

Besides the experimental data supporting the functionality of the polymorphism, several clinical studies have tried to relate the rs5522 polymorphism with the responsiveness to stress and with sodium-handling abnormalities. In a German cohort of twins, allele G carriers had higher levels of salivary cortisol and plasma cortisol but not adrenocorticotropic hormone and higher heart rate response to the Trier Social Stress Tests. The authors suggested that taking into account the N-terminal position of the rs5522 in the exon 2, the amino acid valine instead of isoleucin at the position 180 of the MR protein could affect the binding of specific cofactors, rather than the ligand binding itself, and that this variant can be more important in the response to stress than for sodium handling.19

Previous studies did not find a relationship between the polymorphism rs5522 and HTN risk or aldosterone levels. In the offspring study of the Framingham cohort, which included 2,891 individuals, no relationship between genotypes of the rs5522 polymorphism and HTN risk or aldosterone levels. In the Framingham offspring study, no relationship between genotypes of the rs5522 polymorphism and HTN risk or aldosterone levels.

### Table 2 | Hypertension risk for genotypes of the SNP rs5522 and for haplotypes constructed with 6 and 3 polymorphisms adjusted by age, gender, and BMI with the false positive report probability results

<table>
<thead>
<tr>
<th>SNP</th>
<th>Model</th>
<th>Genotype</th>
<th>Frequency (total (controls/cases))</th>
<th>OR (95% CI)</th>
<th>Report P value</th>
<th>Prior probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5522</td>
<td>Codominant</td>
<td>GG</td>
<td>0.01 (0.012/0.003)</td>
<td>0.10 (0.02–0.56)</td>
<td>0.011</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>GG</td>
<td>0.01 (0.012/0.003)</td>
<td>0.10 (0.02–0.56)</td>
<td>0.0026</td>
<td>0.008</td>
</tr>
<tr>
<td>Haplotypes</td>
<td>Alleles</td>
<td>Frequency (total (controls/cases))</td>
<td>OR (95% CI)</td>
<td>Report P value</td>
<td>Prior probability</td>
<td></td>
</tr>
<tr>
<td>Ref&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AGTAAG</td>
<td>0.0992</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>ACTAAG</td>
<td>0.0912 (0.0899/0.0979)</td>
<td>2.45 (1.57–3.83)</td>
<td>0.0001</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>AGTGAC</td>
<td>0.0865 (0.0831/0.1026)</td>
<td>2.05 (1.32–3.19)</td>
<td>0.0015</td>
<td>0.006</td>
<td>0.017</td>
</tr>
<tr>
<td>3</td>
<td>AGTGAG</td>
<td>0.0488 (0.0367/0.0597)</td>
<td>2.06 (1.16–3.66)</td>
<td>0.014</td>
<td>0.050</td>
<td>0.136</td>
</tr>
<tr>
<td>4</td>
<td>GCTGAC</td>
<td>0.0476 (0.0349/0.053)</td>
<td>2.58 (1.33–5.03)</td>
<td>0.0054</td>
<td>0.020</td>
<td>0.057</td>
</tr>
<tr>
<td>Ref&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TAA0</td>
<td>0.4192</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TGG</td>
<td>0.0417 (0.0506/0.0271)</td>
<td>0.47 (0.26–0.87)</td>
<td>0.016</td>
<td>0.057</td>
<td>0.153</td>
</tr>
</tbody>
</table>

### Table 3 | Hypertension risk for genotypes of the SNP rs5522 and for haplotypes constructed with six and three polymorphisms adjusted by age, gender, BMI, and urinary sodium excretion

<table>
<thead>
<tr>
<th>SNP</th>
<th>Model</th>
<th>Genotype</th>
<th>Frequency (total (controls/cases))</th>
<th>OR (95% CI)</th>
<th>Report P value</th>
<th>Prior probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5522</td>
<td>Codominant</td>
<td>GG</td>
<td>0.01 (0.013/0.004)</td>
<td>0.11 (0.02–0.57)</td>
<td>0.012</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>GG</td>
<td>0.01 (0.013/0.004)</td>
<td>0.11 (0.02–0.57)</td>
<td>0.0028</td>
<td>0.010</td>
</tr>
<tr>
<td>Haplotypes</td>
<td>Alleles</td>
<td>Frequency (total (controls/cases))</td>
<td>OR (95% CI)</td>
<td>Report P value</td>
<td>Prior probability</td>
<td></td>
</tr>
<tr>
<td>Ref&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AGTAAG</td>
<td>0.0991</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>ACTAAG</td>
<td>0.0913 (0.0872/0.0985)</td>
<td>2.50 (1.39–3.29)</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>AGTGAC</td>
<td>0.0865 (0.0838/0.0995)</td>
<td>2.14 (1.39–3.29)</td>
<td>0.0006</td>
<td>0.007</td>
<td>0.021</td>
</tr>
<tr>
<td>3</td>
<td>AGTGAG</td>
<td>0.0484 (0.0372/0.0592)</td>
<td>2.13 (1.20–3.77)</td>
<td>0.0095</td>
<td>0.095</td>
<td>0.240</td>
</tr>
<tr>
<td>4</td>
<td>GCTGAC</td>
<td>0.0478 (0.0303/0.0545)</td>
<td>2.63 (1.37–5.06)</td>
<td>0.002</td>
<td>0.007</td>
<td>0.022</td>
</tr>
<tr>
<td>Ref&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TAA0</td>
<td>0.4192</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TGG</td>
<td>0.0418 (0.0501/0.0292)</td>
<td>0.47 (0.26–0.85)</td>
<td>0.013</td>
<td>0.046</td>
<td>0.128</td>
</tr>
</tbody>
</table>

The localization of different SNPs is in parentheses. It was calculated beginning in the first nucleotide of exon 1, GenBank accession no. NM_000901.2. Build 126, Ensembl release 41. FPRP, false positive report probability; OR, odds ratio; SNP, single-nucleotide polymorphism.
rs5522 and serum aldosterone was found and a low heritability rate (0.10) for serum aldosterone was reported. In hyper-tensive subjects, who underwent the Weinberger’s test to assess salt sensitive or salt resistant between carriers and noncarriers of the variant allele. Moreover, no relationship between the genotype those who excreted more sodium had a lowest risk to be hypertensive. This apparent contradiction to the main results of the study, in which the presence of the G allele resulted protective, can be explained by the fact that the AA subjects as a group had more risk to develop HTN but those able to excrete more sodium had the lowest risk as compared to those who excreted less sodium in the urine.

In this study, which included 24 SNPs along the entire gene, only the rs5522 was associated with the risk of HTN, but haplotypes carrying both the protective and the risky alleles were significantly associated with HTN. The fact that some mutations in the gene NR3C2 can be related to the risk of HTN, and others with their protection, makes this gene a potential candidate gene for HTN. Considering the functional characteristics of the rs5522 of the MR gene, we hypothesize that the allele G of the rs5522, when it is in homozygosis, could modify the MR function and could produce salt waste and consequently protect from blood pressure elevation. Carriers of the wild type, however, would have greater susceptibility of HTN in combination with other alleles in different positions forming haplotypes of risk. Nowadays, it is thought that it would be the combination of variants of slight risk what would produce the genetic susceptibility in complex inheritance diseases altogether with environmental factors. It could be inferred that this functional SNP and the haplotypes described above might produce different responses to salt intake. Even though the inclusion of 24-h sodium excretion did not modify the associations observed, an interaction between genotype and sodium excretion was observed.

The interaction between urinary sodium excretion and the 4 to 46%, with a low prior association of 0.01 supported immigration rate.

Table 4: Hypertension risk for genotypes of the SNP rs5522 and for haplotypes constructed with six and three polymorphisms adjusted by age, gender, BMI, eGFR, and urinary sodium excretion

<table>
<thead>
<tr>
<th>SNP</th>
<th>Model</th>
<th>Genotype</th>
<th>Frequency (total controls/cases)</th>
<th>OR (95% CI)</th>
<th>Report P value</th>
<th>Prior probabilitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5522</td>
<td>Codominant</td>
<td>GG</td>
<td>0.01 (0.013/0.004)</td>
<td>0.11 (0.02–0.56)</td>
<td>0.011</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>GG</td>
<td>0.01 (0.013/0.004)</td>
<td>0.10 (0.02–0.56)</td>
<td>0.0027</td>
<td>0.010</td>
</tr>
<tr>
<td>Haplotypes</td>
<td>Alleles</td>
<td>Frequency (total controls/cases)</td>
<td>OR (95% CI)</td>
<td>Report P value</td>
<td>Prior probabilitya</td>
<td></td>
</tr>
<tr>
<td>Refa</td>
<td>AGTAAG</td>
<td>0.0992</td>
<td>2.48 (1.64–3.75)</td>
<td>&lt;0.0001</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>1</td>
<td>ACTAAG</td>
<td>0.0913 (0.0872/0.0985)</td>
<td>2.08 (1.38–3.12)</td>
<td>0.0004</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>2</td>
<td>AGTAAC</td>
<td>0.0865 (0.0838/0.0995)</td>
<td>2.10 (1.21–3.65)</td>
<td>0.0086</td>
<td>0.031</td>
<td>0.088</td>
</tr>
<tr>
<td>3</td>
<td>AGTGAG</td>
<td>0.0484 (0.0372/0.0592)</td>
<td>2.67 (1.58–4.50)</td>
<td>0.0002</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>4</td>
<td>GCTGAC</td>
<td>0.0478 (0.0303/0.0545)</td>
<td>2.48 (1.64–3.75)</td>
<td>&lt;0.0001</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Refb</td>
<td>TAA</td>
<td>0.4192</td>
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<td></td>
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</tr>
<tr>
<td>5</td>
<td>TGG</td>
<td>0.0418 (0.0501/0.0292)</td>
<td>0.46 (0.25–0.84)</td>
<td>0.012</td>
<td>0.043</td>
<td>0.119</td>
</tr>
</tbody>
</table>

The localization of different SNPs is in parentheses. It was calculated beginning with the first nucleotide of exon 1, GenBank accession no. NM_000901.2. Build 126, Ensembl release 41.
Mineralocorticoid Receptor Gene in Hypertension

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