Analysis of Aldosterone Synthase Gene Promoter (-344 C>T) Polymorphism in Indian Diabetic Nephropathy Patients

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Abstract

Aim: The aim of the present study is to evaluate the association between CYP11B2 gene and type 2 diabetic nephropathy patients in Indian population.

Result: There was a significant difference in age, cholesterol, triglycerides, HDL, creatinine, BUN, Uric acid, total protein, Albumin, SBP, DBP variables except LDL Cholesterol among the study groups. The frequencies of CYP11B2 gene CC, CT, TT genotypes among the T2DNH are 16.67 %, 51.19 %, 32.14 %; in T2DM patient 10.66 %, 52.46 %, 36.88 % and 16.95 %, 38.14 %, 44.91 % in controls respectively and we could not observe significant differences in both genotype (X²=7.289, p=0.121) and allele frequency (X²=1.82, p=0.403) of the CYP11B2 gene (-344 T>C) polymorphism between T2DNH, T2DM patients and Controls subjects.

Conclusion: Our findings do not support the hypothesis that CYP11B2 polymorphism is associated with prevalence of Type 2 diabetic nephropathy patients in Indian populations.

Introduction

Nephropathy is a chronic micro vascular complication of diabetes. Uncontrolled blood sugar level and high blood pressure are risk factor for the development of nephropathy or End Stage Renal Disease (ESRD) [1-4]. The Renin-Angiotensin-Aldosterone System (RAAS) is a regulator of both blood pressure and kidney functions and is suggested to play an important role in the development of nephropathy in Type 2 Diabetes Mellitus and genes encoding components of the RAAS can be candidate genes for evaluating predisposition for the development of hypertension, cardiovascular disease, ESRD or progression of renal disease in type 2 diabetes [5-12]. Aldosterone is an important component of RAAS, and plays an important role in controlling blood pressure, water and electrolyte homeostasis in the body [13]. Aldosterone is synthesized from deoxycorticosterone by a mitochondrial cytochrome P450 enzyme, aldosterone synthase (CYP11B2) [14] catalyze the final steps of the glucocorticoid and aldosterone biosynthesis pathways [15]. The CYP11B2 gene encodes a steroid 11/18-beta-hydroxylase that functions in mitochondria in the zonaglomerulosa of the adrenal cortex to synthesize the mineralocorticoid aldosterone and its expression is regulated by angiotensin II and potassium [16]. The CYP11B2 gene located on chromosome 8q22 [17-19] and contains 9 exons and 8 introns [20].

The -344 (C>T; rs1799998) variant is a commonly reported polymorphism of the CYP11B2 gene, which is located at a putative binding site for the steroidogenic transcription factor (SF-1) of the promoter region and involves a cytosine to thymidine substitution [21]. The -344 (C>T) polymorphism is associated with serum aldosterone level and production [22-24], blood pressure [19,25-27], left ventricular size and mass [18,28], Ischaemic Stroke [7]. Its association was reported with progression of renal function [29-31] and ESRD [6]. However, there were few studies from India have been found on the association of CYP11B2 -344C/T polymorphism and CRI [5], T2DM [9] healthy volunteers [32]; hypertension [33,34], high-altitude adaptation [35].

Therefore, the aim of this study is to evaluate the relation between CYP11B2 polymorphism and Type 2 Diabetic Nephropathy on Hemodialysis patients in Indian population and the genotype and allele frequency of CYP11B2 gene (-344 C>T) promoter polymorphism.

Materials and Methods

This is a cross-sectional case control study. Ethical committee clearance was obtained from the respective medical institutions prior to the recruitment of subjects in this study. An informed consent was obtained from all the participants prior to their recruitment for the study.

Subjects

The study participant were 84 type 2 diabetic nephropathy on hemodialysis (T2DNH), 122 type 2 diabetes patients without nephropathy (T2DM) and 118 healthy controls (H.CON). The detection of Type 2 diabetic and nephropathy patients was based on physician’s recommendation, registered patient for dialysis and a detailed medical history of each patient was recorded accordingly. The healthy unrelated controls were randomly selected and recruited from local community centers. Subjects for the study were recruited at the participating medical institutions namely Calcutta Medical College (Kolkata), B.P. Poddar Hospital and research Centre (Kolkata).

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Biochemical analysis

10 ml venous blood was collected from each individual included in the study for biochemical (5 ml) and genetic analysis (5 ml). Biochemical analyses to determine Total Cholesterol (mg/dl), Triglyceride (mg/dl), HDL Cholesterol (mg/dl), LDL Cholesterol (mg/dl), Creatinine (mg/dl), BUN (mg/dl), Uric Acid (mg/dl), Total Protein (g/dl), Albumin (g/dl), Chloride by using automated analyzer (EM 360, TRANSASIA).

Molecular analysis of the aldosterone synthase (CYP11B2) gene

Approximately 5 ml of venous blood was drawn from each of the subjects in EDTA vials and genomic DNA was extracted from whole fresh blood using standard salting out method using phenol-chloroform [36]. The CYP11B2 (-344 C>T) polymorphism was identified by PCR-RFLP method. Subjects were genotyped for the (-344 C>T) polymorphism using primers CAGGAGGACCCCCATGTGGA (sense) and CCTCCACCCGTGTACGCCC (antisense). Standard PCR amplification was performed in a final volume of 10 μL reaction mixture containing 50 ng of genomic DNA, 20 pmol of each primer, 10X Taq PCR buffer, 25 mM MgCl₂, 100 mM of each dNTPs and 0.5 U/μL of Red Taq polymerase. PCR amplification was performed in a DNA thermal cycler (Gene Amp PCR 9700 - Applied Biosystems, USA). PCR was carried out with a Gradient standardize PCR condition with an initial denaturing time at 95°C for 5 min. Then the DNA was amplified for 35 cycles with denaturation at 94°C for 1 min, annealing at 69°C for 1:30 min and extension at 72°C for 1:30 min and final extension 72°C for 10 min. The PCR products were checked by 1% agarose gel electrophoresis with ethidium bromide staining and directly visualized in UV light.

Restriction fragment length polymorphism analysis (RFLP) was performed by adding 5 U of restriction endonuclease HaeIII (Fermentas) in the appropriate buffer to 4.5 μl of amplified 541 bp PCR product and by incubating at 37°C for 3 h and 30 min. Electrophoresis of the digested samples were done in 2.5% agarose gel with ethidium bromide stained, and analyzed under UV light. The C alleles are of the digested samples were done in 2.5% agarose gel with ethidium bromide stained, and analyzed under UV light. The C alleles are detected as fragments of 202 bp and the T alleles as fragments of 273 bp plus smaller fragments (138 bp, 125 bp, and 71 bp) in each case (Figure 1).

Statistical analysis

Data were analyzed using statistical package for Social Sciences statistical software (SPSS Version 16, Chicago, Illinois, USA). Data were expressed as mean and SD (continuous variables) or percentage. Statistical differences between groups were assessed by analysis of variance (ANOVA) or t test. Genotypes and allele frequencies of CYP11B2 gene polymorphism were compared between type 2 diabetic patients (T2DM), type 2 diabetic nephropathy on hemodialysis patients (T2DNH) and healthy match controls using χ²-test (MINITAB 11). Allele frequencies were calculated for the SNP and tested for Hardy-Weinberg equilibrium and allelic association with disease (exact tests, model tests) using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/). For comparing the allelic distributions between study groups the odds ratio (OR) with 95% confidence interval (CI) were also calculated. A level of p<0.05 was assumed statistical significance.

Results and Discussion

In this cross sectional case control study, 84 T2DNH subjects were compared with 122 T2DM subjects and 118 healthy control subjects. For the control subjects consisted of 61.9% male and 38.1% female and the T2DNH and T2DM cases 53.6%, 52.5% male subject and 46.4%, 47.5% female respectively. Mean age for the case samples was higher than control samples.

Clinical characteristics of all subjects

The descriptive, ANOVA and Post Hoc tests had been done in order to find the means, SD, mean differences and significant differences between groups. Distribution of base line clinical characteristics of the CONTROL, T2DM, and T2DNH are shown in Table 1 and mean differences of multiple Comparisons are shown in Table 2. There was a significant difference in all (age, cholesterol, triglycerides, HDL, creatinine, BUN, Uric acid, total protein, Albumin, SBP, DBP) variables except LDL Cholesterol among the study groups. In the analysis of multiple comparisons for mean difference of different groups shows a different picture. Further, we compare between Control and T2DM, T2DNH and T2DM and T2DNH. Age, cholesterol, triglycerides, HDL, BUN, Uric acid, total protein, Albumin, SBP were significant while LDL, creatinine and DBP were not significant when compared between control and T2DM. Age, HDL, creatinine, BUN, Uric acid, total protein, Albumin, SBP, DBP were significant when compared between control and T2DNH. Creatinine, BUN, total protein, albumin, SBP was significant while age, cholesterol, triglycerides, HDL, LDL, Uric acid and DBP were not significant when compared between T2DM and T2DNH. Among the T2DNH case, the significant difference of SBP showed that increase in SBP was likely to develop T2DNH and supports the findings of [8,31,37] as they were all reported that the association of (-344 C>T) polymorphism and hypertensive renal failure population. Table 3 shows the comparison of baseline clinical and biochemical characteristics of T2DNH patients according to genotype of CYP11B2 gene promoter polymorphism. We could not observed significant different between three genotypes.

In this study, older age can be said to be more susceptible to get T2DM and T2DNH as the means and standard deviation of T2DM and T2DNH case samples showed higher value (54.90 ± 11.28 and 53.97 ± 8.91) than control (48.16 ± 7.28).

Genotypic and allele frequency

Our study was designed to test the hypothesis that the prevalence of type 2 diabetic nephropathy may be influenced by the aldosterone synthase (CYP11B2) gene polymorphism of the RAAS. Figure 1 shows the PCR-RFLP digestion product size in agarose gel electrophoresis stained with ethidium bromide of CYP11B2 gene (-344 T>C) polymorphism. Genotype and allele frequencies for the polymorphism of CYP11B2 in T2DNH, T2DM and Healthy controls are presented in Table 4. The frequencies of CYP11B2 gene CC, CT, TT genotypes among the T2DNH are 16.67 %, 51.19 %, 32.14%; in T2DM patient
10.66%, 52.46%, 36.88% and 16.95%, 38.14%, 44.91% in controls respectively. In our study, we could not observe significant differences in both genotype (x^2=7.289, p=0.121) and allele frequency (X^2=1.82, p=0.403) of the CYP11B2 gene (-344 T>C) polymorphism between T2DNH, T2DM patients and Controls subjects. The CT genotype was the highest percentage among T2DNH and T2DM subject (51.19%,

### Table 1: Distribution of Clinical and Biochemical characteristics of Healthy Control, T2DM and T2DNH patients.

| Variables                      | Control (n=118) | T2DM (n=122) | T2DNH (n=84) | F     | p     |
|--------------------------------|----------------|--------------|--------------|-------|-------|
| Age (years)                    |                |              |              |       |       |
| Mean ± SD                      | 48.16 ± 7.29   | 54.90 ± 11.29| 53.98 ± 8.91 | 17.516| 0.000*|
| Cholesterol (mg/dl)            | 159.71 ± 35.87 | 179.90 ± 42.10| 164.09 ± 50.58| 7.396 | 0.001*|
| Triglycerides (mg/dl)          | 151.38 ± 74.09 | 183.09 ± 88.64| 155.81 ± 68.27| 5.579 | 0.004*|
| HDL Cholesterol (mg/dl)        | 41.45 ± 15.00  | 50.75 ± 17.39| 50.45 ± 16.20| 11.99 | 0.000*|
| LDL Cholesterol (mg/dl)        | 96.10 ± 23.56  | 97.41 ± 30.28| 94.80 ± 31.15| 0.216 | 0.806 |
| Creatinine (mg/dl)             | 0.97 ± 0.14    | 1.25 ± 0.51  | 1.72 ± 1.81  | 14.623| 0.000*|
| Bun (mg/dl)                    | 7.74 ± 2.68    | 13.30 ± 6.65 | 27.45 ± 18.69| 89.365| 0.000*|
| Uric acid (mg/dl)              | 5.72 ± 1.39    | 8.00 ± 1.20  | 6.32 ± 1.62  | 5.579 | 0.004*|
| Total protein (g/dl)           | 6.99 ± 0.51    | 8.08 ± 1.07  | 7.61 ± 1.16  | 41.487| 0.000*|
| Albumin (g/dl)                 | 27.84 ± 19.12  | 32.60 ± 24.80| 35.40 ± 29.20| 22.765| 0.000*|
| Systolic blood pressure (mmHg) | 123.57 ± 21.00 | 137.19 ± 20.11| 151.49 ± 25.95| 39.557| 0.000*|
| Diastolic blood pressure (mmHg)| 82.89 ± 10.68  | 85.02 ± 10.11| 88.08 ± 13.76| 5.128 | 0.006*|

*Significant at the P<0.05 level

### Table 2: Multiple Comparisons for Mean difference of different groups.

| Variables                      | Group (I) | Group (J) | Mean Difference (I-J) | p     |
|--------------------------------|-----------|-----------|-----------------------|-------|
| Age (years)                    | Control   | T2DM      | 6.7406                | 0.000*|
|                               | T2DNH     |           | 5.8152                | 0.000*|
|                               | T2DM      | T2DNH     | 0.9254                | 0.785 |
| Cholesterol (mg/dl)            | Control   | T2DM      | 20.1903               | 0.001*|
|                               | T2DNH     |           | 4.3791                | 0.770 |
|                               | T2DM      | T2DNH     | 15.8112               | 0.033*|
| Triglycerides (mg/dl)          | Control   | T2DM      | 3.6709                | 0.008*|
|                               | T2DNH     |           | 4.4299                | 0.925 |
|                               | T2DM      | T2DNH     | 27.2800               | 0.051 |
| HDL Cholesterol (mg/dl)        | Control   | T2DM      | 9.3038                | 0.000*|
|                               | T2DNH     |           | 9.0020                | 0.001*|
|                               | T2DM      | T2DNH     | 0.3018                | 0.991 |
| LDL Cholesterol (mg/dl)        | Control   | T2DM      | 1.3159                | 0.937 |
|                               | T2DNH     |           | 1.2974                | 0.950 |
|                               | T2DM      | T2DNH     | 2.6133                | 0.809 |
| Creatinine (mg/dl)             | Control   | T2DM      | 0.2742                | 0.095 |
|                               | T2DNH     |           | 0.7507                | 0.000*|
|                               | T2DM      | T2DNH     | 0.4765                | 0.033*|
| Bun (mg/dl)                    | Control   | T2DM      | 5.5620                | 0.000*|
|                               | T2DNH     |           | 19.7090               | 0.000*|
|                               | T2DM      | T2DNH     | 14.1470               | 0.000*|
| Uric acid (mg/dl)              | Control   | T2DM      | 0.0883                | 0.886 |
|                               | T2DNH     |           | 0.6033                | 0.010*|
|                               | T2DM      | T2DNH     | 0.5150                | 0.034 |
| Total protein (g/dl)           | Control   | T2DM      | 1.0970                | 0.000*|
|                               | T2DNH     |           | 0.6177                | 0.000*|
|                               | T2DM      | T2DNH     | 0.4792                | 0.002*|
| Albumin (g/dl)                 | Control   | T2DM      | 0.5270                | 0.000*|
|                               | T2DNH     |           | 0.2471                | 0.018*|
|                               | T2DM      | T2DNH     | 0.2799                | 0.005*|
| Systolic blood pressure (mmHg) | Control   | T2DM      | 13.6207               | 0.000*|
|                               | T2DNH     |           | 27.9203               | 0.000*|
|                               | T2DM      | T2DNH     | 14.2996               | 0.000*|
| Diastolic blood pressure (mmHg)| Control   | T2DM      | 2.1348                | 0.348 |
|                               | T2DNH     |           | 5.1935                | 0.006*|
|                               | T2DM      | T2DNH     | 3.0587                | 0.166 |

*The mean difference is significant at the 0.05 level
52.46 % respectively) than the control subjects (38.14%). The CC genotype was almost same percentage among the T2DNH and Control subject (16.67%, 16.95% respectively) and the TT genotype was the highest among the control (44.91%). From the Table 5 it is evident that no significant association was observed for all the study groups and the minor T allele (44.91%) was not found to be significantly associated with the development of T2DNH. 

Several studies of the association between this polymorphism and hypertension [10,27,38,39] left ventricle size and mass [18,40] and myocardial infarction [28,37] in the general population and hypertensive individuals with normal renal function have been performed. Various studies had reported the CYP11B2 gene polymorphism associated with CRI [5]; renal insufficiency in the hypertensive population [10,31] and [30] reported that there was no association between the CYP11B2 genotype and progression of renal failure among the diabetic ESRD patients.

In ESRD patients, however, studies of association of CYP11B2 -344C>T polymorphism and left ventricular hypertrophy and cardiovascular morbidity are few. It is also possible that the type 2 diabetic patients with high risk genotype may be excluded from the present study because of premature mortality due to cardiovascular influences by CYP11B2 polymorphism. Thus, further prospective investigation is needed to explore the role of CYP11B2 polymorphism in the susceptibility of diabetes and cardiovascular effect in type 2 diabetic patients.

**Conclusion**

Our findings do not support the hypothesis that CYP11B2 polymorphism is associated with prevalence of Type 2 Diabetes and diabetic nephropathy patients in Indian populations. The minor T allele of CYP11B2 gene polymorphism is not associated with T2DNH in Indian subjects. Therefore, CYP11B2 gene (-344 C>T) polymorphism may not be a genetic marker and might not considered as a genetic risk factor for Indian Type 2 Diabetic nephropathy patients.
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References

1. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, et al. (1995) Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 25: 577-594.
2. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, et al. (1996) Blood pressure and end-stage renal disease in men. N Engl J Med 334: 13-18.
3. Shiush Li, Bercovicci S, Wasser WG, Yudkowsky G, Templeton A, et al. (2014) Admixture mapping of end stage kidney disease genetic susceptibility using estimated mutual information ancestry informative markers. BMC Med Genomics 3: 47.
4. Abbasi M, Chertow GM, Hall YN (2010) Clinical evidence, kidney disorder, end stage renal disease. Clinical Evidence.
5. Prasad P, Tiwari AK, Prasanna Kumar KM, Ammini AC, Gupta A, et al. (2006) Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. BMC Medical Genetics 7: 42.
6. Lee W, Liu C (2012) The -344C/T polymorphism in the CYP11B2 gene is associated with essential hypertension in the Chinese. J Renin Angiotensin Aldosterone Syst 11: 180-186.
7. Vasudevan R, Ali AB, Mansoor MS, Zulkifli NF, Ismail P (2011) Analysis of T344C Genetic Polymorphism of CYP11B2 Gene in Malaysian End Stage Renal Disease Subjects. Research Journal of Biological Sciences 6: 213-218.
8. Purkait P, Sarkar BN, Naidu JM, Sarkar BN, Naidu JM (2012) Null association of aldosterone synthase (cyp11b2) gene-344 c > t promoter polymorphism in type 2 diabetic patients among Indian population. (Abstract). J Diabetes Metab. 3: 8.
9. Li W, Liu C (2012) The -344C/T polymorphism in the CYP11B2 gene is associated with essential hypertension in the Chinese. J Renin Angiotensin Aldosterone Syst.
10. Pan XQ, Zhang YH, Liu YY, Tong WJ (2010) Interaction between the C(-344) T polymorphism of CYP11B2 and alcohol consumption on the risk of essential hypertension in a Chinese Mongolian population. Eur J Epidemiol 25: 813-821.
11. Vasudevan R, Ismail P, Stanislaus J, Shamsudin N, Ali AB (2008) Association of insertion/deletion polymorphism of alpha-adrenoceptor gene in essential hypertension in a south Indian Tamil population. Indian J Med Res 127: 372-376.
12. Lovati E, Richard A, Frey BM, Frey FJ, Ferrari P (2001) Genetic polymorphisms of the renin-angiotensin-aldosterone system in end-stage renal disease. Kidney Int 60: 46-54.
13. Fabris B, Bortolotto M, Candido R, Barbone F, Cattin MR, et al. (2005) Genetic polymorphisms of the renin-angiotensin-aldosterone system and renal insufficiency in essential hypertension. J Hypertens 23: 309-316.
14. Rajan S, Ramu P, Shewade DG, Adithan C (2009) Promoter region polymorphism of CYP11B2 (344 C>T) gene in healthy volunteers of South Indian Tamilian population. Indian Journal Biotech. 8: 358-362.
15. Rajput C, Makhijani K, Narboor A, Afrin F, Sharma M, et al. (2005) CYP11B2 gene polymorphisms and hypertension in highlanders accustomed to high salt intake. J Hypertens 23: 79-86.
16. Rajan S, Ramu P, Umamaheswaran G, Adithan C (2010) Association of aldosterone synthase (CYP11B2 C-344T) gene polymorphism & susceptibility to essential hypertension in a south Indian Tamil population. Indian J Med Res 132: 379-385.
17. Rajput C, Arif E, Vibhuti A, Stobdan T, Khan AP, et al. (2006) Predominance of interaction among wild-type alleles of CYP11B2 in Himalayan natives associates with high-altitude adaptation. Biochem Biophys Res Commun 348: 735-740.
18. Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16: 1215.
19. Hautanen A, Toivainen P, Manttari M, Tenkanen L, Kupari M, et al. (1999) Joint findings of the Olivetti Prospective Heart Study. J Hypertens 20: 1785-1792.
20. Cheng X, Xu G (2009) Association between aldosterone synthase CYP11B2 polymorphism and essential hypertension in Chinese: a meta-analysis. Kidney Blood Press Res 32: 128-140.
21. Olapade-Olomu IS, Asilami SO, Ipinle M (2011) The polymorphism of CYP11B2 gene in Nigerians with essential hypertension. J Hum Hypertens 25: 101-7.
22. Bassett MH, Zhang Y, Clyne C, White PC, Rainey WE (2002) Differential regulation of aldosterone synthase and 11beta-hydroxylase transcription by steriodogenic factor-1. J Mol Endocrinol 28: 125-135.
23. Russo P, Siani A, Venezia A, Iacone R, Russo O, et al. (2002) Interaction between the C(-344)T polymorphism of CYP11B2 and age in the regulation of blood pressure and plasma aldosterone levels: cross-sectional and longitudinal findings of the Olivetti Prospective Heart Study. J Hypertens 20: 1785-1792.
24. Keavney B, Mayosi B, Gaukrodger N, Imrie H, Baker M, et al. (2005) Genetic variation at the locus encompassing 11-beta hydroxylase and aldosterone synthase accounts for heritability in cortisol precursor (11-deoxycortisol) urinary metabolite excretion. J Clin Endocrinol Metab 90: 1072-1077.
25. Davies E, Holloway CD, Ingram GC, Inglis GC, Friel EC, et al. (1999) Aldosterone excretion rate and blood pressure in essential hypertension are related to polymorphic differences in the aldosterone synthase gene CYP11B2. Hypertension 33: 703-707.
26. Kumar NN, Benjafel AV, Lin RC, Wang WY, Stowasser M, et al. (2003) Haplotype analysis of aldosterone synthase (CYP11B2) polymorphisms shows association with essential hypertension. J Hypertens 21: 1331-1337.
27. Tomasi S, Iwai N, Tsujita Y, Kinosita M (1999) Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. Hypertension 33: 266-270.
28. White PC, Hautanen A, Kupari M (1998) Aldosterone synthase (CYP11B2) polymorphisms and cardiovascular function. Endocr Rev 24: 797-804.
29. Song J, Narita I, Goto S, Saito N, Omori K, et al. (2003) Gender specific association of aldosterone synthase gene polymorphism with renal survival in patients with IgA nephropathy. J Med Genet 40: 372-376.
30. Sovio U, Laurikainen E, Kuoppala J, et al. (2006) Genetic variation at the aldosterone synthase gene locus predicts blood pressure and hypertension in a south Finnish population. J Hypertens 24: 1949-1957.
31. Sovio U, Laurikainen E, Kuoppala J, et al. (2006) Genetic variation at the aldosterone synthase gene locus predicts blood pressure and hypertension in a south Finnish population. J Hypertens 24: 1949-1957.
32. Sovio U, Laurikainen E, Kuoppala J, et al. (2006) Genetic variation at the aldosterone synthase gene locus predicts blood pressure and hypertension in a south Finnish population. J Hypertens 24: 1949-1957.