**Candidate-Gene Analysis of White Matter Hyperintensities on Neuroimaging**

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**Background**

White matter hyperintensities (WMH) are a common radiographic finding in the elderly and may be a useful endophenotype for small vessel diseases. Given high heritability of WMH, we hypothesised that certain genotypes may predispose individuals to these lesions and consequently, to an increased risk of stroke, dementia and death. We performed a meta-analysis of studies investigating candidate genes and WMH to elucidate the genetic susceptibility to WMH and tested associated variants in a new independent WMH cohort. We assessed a causal relationship of WMH to methylene tetrahydrofolate reductase (MTHFR).

**Methods**

Database searches through March 2014were undertaken and studies investigating candidate genes in WMH were assessed. Pooled ORs and 95% CI were calculated for the association of each polymorphism with WMH. Associated variants were then tested in a new independent ischaemic cohort of 1202 WMH patients. Mendelian randomization was undertaken to assess a causal relationship between WMH and MTHFR.

**Results**

We identified 43 case-control studies interrogating eight polymorphisms in seven genes covering 6,314 WMH cases and 15,461 controls. Fixed-effects meta-analysis found that the C-allele containing genotypes of the aldosterone synthase CYP11B2 T(-344)C gene polymorphism were associated with a decreased risk of WMH (OR=0.61; 95% CI, 0.44 to 0.84; p=0.003). Using mendelian randomisation the association among MTHFR C677T, homocysteine levels and WMH, approached, but did not reach, significance (expected OR=1.75; 95% CI, 0.90-3.41; observed OR=1.68; 95% CI, 0.97-2.94). Neither CYP11B2 T(-344)C nor MTHFR C677T were significantly associated when tested in a new independent cohort of 1202 patients with WMH.

We found no statistically significant associations between WMH and the following gene polymorphisms: apolipoprotein E4 (OR=0.98; 95% CI, 0.87-1.11; p=0.78), apolipoprotein E2 (OR=1.42; 95% CI, 0.46-4.43; p=0.54), angiotensin-converting enzyme insertion/deletion (OR=1.46; 95% CI, 0.92-2.31; p=0.11), MTHFR C677T (OR=1.19; 95% CI, 0.95-1.51; p=0.14), angiotensinogen M235T (OR=1.12; 95% CI, 0.84-1.50; p=0.44), angiotensinogen II receptor 1 A1166C (OR=1.23; 95%CI, 0.59-2.54; p=0.58) and paraoxonase 1 L55M (OR=1.42; 95% CI, 0.61-3.28; p=0.41).

**Conclusions**

There is a genetic basis to WMH but anonymous genome wide and exome studies are more likely to provide novel loci of interest.

**Introduction**

White matter hyperintensities (WMH) are defined as diffuse white matter abnormalities detected on T2-weighted or FLAIR MRI and appearing as regions of low attenuation on brain CT scans 1. They are a common radiological finding, particularly in older individuals, with reported prevalence of up to 95% 2,3. These lesions, of presumed vascular origin, may represent an endophenotype for small cerebral vessel diseases, such as stroke and dementia; and thus, WMH could be used in early diagnosis and guided management of these conditions 4. WMH has consistently been associated with increasing age and hypertension, 5 as well as smoking 6, previous stroke 7 or TIA,8 and elevated homocysteine levels (Hcy) 9,10. Studies have reported high heritability estimates ranging between 55-71% 11-13 implying a significant genetic component to WMH development.

To date, a single WMH GWAS has been published by the CHARGE consortium 14that identified six single nucleotide polymorphisms (SNPs) in a novel locus on chromosome 17q25 associated with WMH burden in stroke-free subjects 14. The most significantly associated SNP on 17q25 was rs3744028 with a reported p value of 1.0x10-9 after adjustment for hypertension 14. This association between 17q25 locus and WMH has recently been tested in a cohort of ischaemic stroke patients, where it has replicated in association with WMH volume but not lacunar stroke status.15 The latter may suggest that these two diseases have distinct pathogeneses of cerebral microangiopathy. Rs3744028 was again found to be significantly associated with increased WMH burden (effect size=0.12; SE=0.04; p=0.003), although this SNP was not the most significantly associated in this study population (rs9894383; effect size=0.13; SE=0.04; p=0.0006).

Several statistically underpowered small candidate gene studies on WMH have been published, but the results remain invalid due to low power. By consolidating data from these smaller studies, a literature-based meta-analysis is considered to be the next best way to increase power and find a true genetic risk association. We conducted a comprehensive meta-analysis of all case-control studies investigating candidate genes in WMH, tested our findings in a new independent WMH cohort and sought to identify a causal relationship with MTHFR.

**Methods**

A comprehensive search strategy in electronic databases (PubMed, Google Scholar, Embase) was undertaken using a range of search terms for WMH (*leukoaraiosis, white matter hyperintensities, white matter lesions, white matter disease, age-related white matter changes, homocysteine, hyperhomocysteinemia*) in combination with the Boolean operator AND/OR (*genetics, genotype, genes or polymorphism)*. Further searches were conducted for each gene identified, using specific gene names combined with the WMH search terms. Additional studies were found by hand searching reference lists of relevant papers. For duplicate papers the largest cohort was selected.A variety of different methods were utilised to quantify WMH levels or volumes but in general, visual rating scales were more commonly used than automated programs. Most papers reported genotype frequencies within the Hardy-Weinberg equilibrium. Our study complied with PRISMA guidelines.

**Study selection**

Inclusion criteria were: (1) case-control studies wherein WMH was reported as a grade on a standardised scale or as a volume, (2) WMH was objectively confirmed by MRI or CT brain scans, (3) genotype frequency was reported for both WMH cases and controls. Studies were excluded if they did not explicitly distinguish WMH from other brain lesions such as lacunes and microinfarcts. For the mendelian randomization part of this study, additional selection was based on plasma homocysteine levels for cases and controls in the studies of subjects of European descent reporting standard deviations associated with mean homocysteine levels.

**Data extraction**

Some studies quantified WMH grade on a standardized scale and presented this as dichotomous data, so for each genotype the number of subjects in the highest and lowest WMH grade groups were extracted. Where studies subdivided WMH into two categories: deep (or subcortical) WMH and periventricular WMH, without providing data for WMH as a whole, data for the deep WMH was analysed. In cases where the scale cut-off could be chosen, the upper grade group included Fazekas scale 2 or 3 or equivalent 16. For continuous WMH grade data, the mean grade and SD for each genotype was taken and for studies presenting WMH data as a volume, we extracted the mean volume and SD for each genotype.

**Data Analysis for meta-analysis**

Data were analyzed using Review Manager v5.2. Using a Mantel-Haenszel statistical method, a pooled odds ratio (OR) and 95% confidence interval was calculated for each SNP-WMH association*.* Statistical significance was set at p<0.05. Where significant heterogeneity was detected, a random-effects analysis model was utilised in order to account for this interstudy heterogeneity. In all other cases, a fixed effects model was used. Heterogeneity was assessed with an I2 test for each meta-analysis (significance set at P<0.10) and an iterative analysis was performed where significant heterogeneity was found. Publication bias was assessed with Funnel plots and performing Egger’s regression analysis (two-tailed tests) using Comprehensive Meta-Analysis version 2.0 (CMA).

**Data analysis for mendelian randomisation**

Mendelian randomisation allows the testing of a causal effect of observed data in the presence of confounding factors. Review Manager was used to calculate an odds ratio (OR) and 95% confidence interval for MTHFR-WMH grade association using the TT vs. CC model so as to be in keeping with the model used by Casas et al 17 who report a weighted mean difference in Hcy level between TT and CC-genotype to be 1.93 μmol/L in their meta-analysis. A pooled mean difference in homocysteine levels between cases with WMH and controls was calculated and then converted into a corresponding odds ratio of WMH for that specific increase in homocysteine level using CMA software. The expected OR was then calculated using the following formula: 17

**Expected OR = X y/z**

Where **X** = the OR of risk of WMH for a **Z** μmol/L increase in plasma Hcy levels

And **Y** = the mean difference in Hcy level (μmol/L) between TT and CC-genotype subjects.

In order to calculate the 95% confidence interval for the expected OR, we took the natural log of this number to determine the logged OR. The 95% CI for this logged OR is calculated by taking 1.96 x standard error (SE) on either side of this logged OR 18. The SE is taken as the square root of the sum of the reciprocals of the number of cases and controls. The exponential function in Excel was used to convert the upper and lower confidence interval limits into the 95% confidence interval limits for the original OR.

**Replication of the associated genetic variants**

Any associated genetic variants were tested in a cohort of 1,202 ischemic stroke cases of European ancestry with genome-wide genotyping available (“MGH,” “ISGS,” “ASGS,” “SWISS” cohorts) that was previously used to replicate chromosome 17q25 locus association with WMH**15**. In this cohort, WMH volume (WMHv)was measured using a previously validated, semi-automated volumetric method (facilitated by *MRIcro*, University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com) 19. For this analysis, MRI scans obtained from a 1.5T scanner were converted from DICOM into Analyze format, and the contiguous, supratentorial axial T2 fluid attenuated inversion recovery (FLAIR) sequences were cross-referenced with diffusion-weighted images (DWI) and examined to exclude hyperintesities that represent edema, acute ischemia, or chronic infarcts. WMHs were manually outlined as regions of interest (ROI), and their intersection with automatically derived intensity thresholds were manually examined and touched up by a trained reader. The total WMHv was calculated by doubling the measurement from the hemisphere unaffected by stroke, or by adding bilateral WMHv values in subjects with infratentorial DWI lesions. To control for variation in head size, the intracranial area (ICA) was calculated from two middle saggital T1 slices and used to normalize WMHv by multiplying it by the individual-to-the-mean ICA ratio 20,21. Specific study characteristics and genotyping information of this cohort are previously described **15.**

**Results**

Our initial search identified 1248 studies with 20 additional records from references of relevant articles. Removal of duplicates and matches to our predefined inclusion and exclusion criteria resulted in 43 studies which had available data for meta-analysis interrogating nine polymorphisms in ten different genes (Fig 1). The majority used MRI to assess WMH in (mostly Caucasian) subjects aged between 60 and 80 years. Most of the genes studied were involved in the renin-angiotensin-aldosterone system (ACE, angiotensinogen, angiotensin II receptor 1, aldosterone synthase). The other identified genes had roles in homocysteine levels (MTHFR), anti-atherosclerosis (paraoxonase 1) and cholesterol regulation (apolipoprotein E). Other gene polymorphisms studied were brain-derived neurotrophic factor/Val66Met 22 and nitric oxide synthase 3/G894T 23,24 but some studies had yet to be replicated 22 and others did not have data available for meta-analysis 24 (Table 2).

***Methylene tetrahydrofolate reductase 677 cytosine/thymine (TT vs. CT/CC)***

Six studiesinvestigated the association between methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism (TT vs. CT/CC) and WMH (n=4002). 25-30 Five studies (n=2988) assessed the genotype difference between the lower and upper WMH grade groups 25,26,28-30 (Fig 2A) and one study (n=1014) compared mean WMH volume between different genotypes27 (Fig 2B). Fixed-effects meta-analysis demonstrated a trend of increased risk burden of WMH with MTHFR TT compared to CT / CC genotype (OR=1.19; 95% CI, 0.95 to 1.51; p=0.14; I²=28%; p=0.24) when the totality of data was plotted (see Fig 2). Only one study measured WMH volume, thus, limiting further analysis (standardized mean difference=-0.09; 95% CI, -0.29 to 0.11; p=0.37).

***Aldosterone synthase CYP11B2 T(-344)C (CC/CT vs. TT )***

Two studies (n=1153) evaluated the association between aldosterone synthase CYP11B2 T(-344)C polymorphism and dichotomous graded WMH, and fixed-effects meta-analysis demonstrated that the C-allele containing genotypes were at a reduced risk of white matter lesions (OR=0.61; 95% CI, 0.44 to 0.84; p=0.003; I² = 0%; p=0.70) 31,32.

***Apolipoprotein E (ε4 allele-containing genotypes vs. others)***

There were 31 studies/sub-studies that investigated the association between apoE (ε4 allele-containing genotypes vs other genotypes) and WMH (n=11,270) 29,33-57. Twenty-two of these studies (n=7622) assessed the genotype difference between the lower and upper WMH grade groups 29,33-41,50-58 , 3 studies (n=187) compared mean WMH grade 42-44 and 6 studies (n=3461) compared mean WMH volume between different genotype groups 45-49.

Fixed-effects meta-analysis demonstrated no association between apoE ε4-allele carriage status and having severe WMH on neuroimaging (WMH grade, dichotomous data, OR=0.98; 95% CI, 0.87 to 1.11; p=0.78; I²=5%; p=0.39). Within subjects with WMH, there was no significant predominance of the ε4 allele-containing genotypes (WMH grade, continuous data, pooled standardized mean difference=0.29; 95% CI, -0.03 to 0.61; p=0.07; I²=0%; p=0.87; WMH volume, pooled standardized mean difference=0.06; 95% CI, -0.02 to 0.14; p=0.14; I²=47%; p=0.09).

***ApoE/ε2 allele-containing genotypes vs others***

Three studies (n=817) evaluated the risk of WMH in apolipoprotein E ε2-containg genotypes compared to other apolipoprotein E genotypes 38,41,52 and random-effects meta-analysis reported no significant association (OR=1.42; 95% CI, 0.46 to 4.43; p=0.54) but significant heterogeneity was detected (I2=84; p=0.002). Iterative analysis revealed the source of inter-study heterogeneity was attributable to Smith 2004 52, the exclusion of which resulted in pooled OR=2.59; 95% CI, 1.60 to 4.19; p=0.0001; I2=0%; p=0.92.

***ACE (DD vs ID/II)***

Nine studies/sub-studiesevaluated the association between ACE (DD vs. ID/II model) and WMH (n= 2615) 29,31,33,59-63. 8 studies (n=2121) assessed the genotype difference between the lower and upper WMH grade groups 29,31,33,60-63 and 1 study (n=494) compared mean WMH volume between different genotypes 59. Random-effects meta-analysis suggested no increased risk of WMH with ACE DD-genotype compared to those with ID or II genotype (OR=1.46; 95% CI, 0.92 to 2.31; p=0.11) but there was substantial heterogeneity detected between studies (I²=67%; p=0.004). No one study contributed to the heterogeneity as determined by iterative analysis. One study assessed WMH volume and also reported non-significance (standardised mean difference=-0.07; 95% CI, -0.27 to 0.13; p=0.48).

***Angiotensinogen Met235Thr (TT/MT vs. MM)***

Four studies (n=1134) evaluated the association between angiotensinogen (AGT) M235T (TT/MT vs. MM model) and dichotomous graded WMH and fixed-effects meta-analysis found no association between them (OR=1.12; 95% CI, 0.84 to 1.50; p=0.77; I² = 0%; p=0.44) 31,60,61,64.

***Angiotensin II receptor 1 A1166C (CC vs. AC/AA)***

Two studies (n=459) investigated whether angiotensin II receptor 1 (AGTR1) A1166C polymorphism was associated with dichotomous WMH grade. Using the dominant model (CC vs. AC/AA) and a fixed-effects analysis, our meta-analysis found no association (OR=1.23; 95% CI, 0.59 to 2.54; p=0.58; I2=23%; p=0.26) 31,60.

***Paraoxonase 1 L55M ( LL/LM vs. MM)***

Two studies (n=343) evaluated the association between paraoxonase 1 (PON1) gene and dichotomous graded WMH and fixed-effects meta-analysis found no association between them (OR=1.42; 95% CI, 0.61 to 3.28; p=0.41; I² = 0%; p=0.33) 65,66.

**Mendelian randomization**

Ninety-seven studies and five additional records were identified in the search for papers investigating the difference in plasma Hcy levels between WMH cases and controls. After 21 duplicate records were removed, the remaining 81 were screened and 77 were excluded according to the predefined inclusion and exclusion criteria.

Ethnic differences in plasma Hcy levels are well documented with East Asians consistently reported to have significantly lower Hcy levels compared to Caucasians 67-70 (Table 1). Given these ethnic disparities, we considered it appropriate to exclude studies of East Asian (i.e., Japanese, Korean) subjects from the mendelian randomisation, as the majority of studies were conducted in subjects of European descent.

The remaining four studies covering 745 Caucasian subjects were meta-analysed and comparison of WMH cases vs. controls found a pooled mean difference in plasma Hcy levels of 3.71 μmol/L (95% CI: 2.79 to 4.63; P<0.00001; I2 = 0%) (Fig 3). CMA v2.0 software was used to calculate the corresponding pooled OR of risk of WMH for this mean difference in Hcy levels using a fixed effects analysis model, OR = 2.93 (95% CI: 2.18 to 3.94).

In a meta-analysis of 42 studies we had previously examined the effect of MTHFR on plasma Hcy levels in healthy subjects (n=15,635) and reported the weighted mean difference in Hcy level between TT and CC-genotype to be 1.93 μmol/L (95% CI, 1.38 to 2.47; p<0.0001) 17. Using these three pieces of data, the expected OR was calculated using the following formula:

Expected OR = 2.93 1.93/3.71 = 1.75

Where:

* 2.93 is the OR of risk of WMH for a 3.709 μmol/L increase in plasma Hcy levels,
* 1.93 is the mean difference in Hcy level (μmol/L) between TT and CC-genotype subjects,

In order to calculate the 95% confidence interval for the expected OR of 1.75, we took the natural log of 1.75 to get the logged odds ratio of 0.56. The 95% confidence interval for this logged OR was -0.108 to 1.227 and was calculated by taking 1.96 x standard error (SE) on either side of 0.56 18. The SE was 0.34 which was calculated as the square root of the sum of the reciprocals of the number of cases and controls. Using the exponential function in excel, these limits were converted into the 95% confidence interval limits for the original OR of 1.75 giving EXP (-0.108) = 0.897 to EXP (1.227) = 3.412. From our meta-analysis of 2 studies investigating the association between MTHFR (TT vs. CC) and WMH grade, the observed OR for WMH was 1.68 (95% CI: 0.97 – 2.94, p=0.07). Despite the results not reaching statistical significance, the similarity between the expected and observed ORs supports a likely causal relationship between MTHFR and WMH.

**Replication of associated genetic variants**

We examined the association between CYP11B2 T(-344)C and MTHFR C677T polymorphisms and WMH quantified on the MRI using a validated, semi-automated volumetric protocol in an independent cohort of 1,202 ischemic stroke cases with WMH. There was no association between either polymorphism and WMH volume in this cohort (CYP11B2 T(-344)C, P=0.5755; MTHFR C677T, P=0.68).

**Discussion**

**Figure** **5:** Table showing the corresponding odds ratios of risk for WMH for the mean difference in homocysteine levels and the pooled odds ratio of risk of WMH.

**Figure** **5:** Table showing the corresponding odds ratios of risk for WMH for the mean difference in homocysteine levels and the pooled odds ratio of risk of WMH.

In this largest to-date study of candidate genes in WMH burden, we interrogated 6,253 WMH cases and 15,239 controls for eight polymorphisms in seven genes (APO E/ε4 and ε2, ACE insertion/deletion, MTHFR C677T, AGT M235T, AGTR1 A1166C, CYP11B2 T344C, PON1 L55M). Our analysis demonstrated a likely genetic effect for ischemic white matter disease, with apparent inverse association between CYP11B2 and WMH. A trend for positive association between MTHFR and WMH severity could not be completely interrogated, given a relatively small sample size of the available studies as compared to other well-powered genetic studies on stroke.

The MTHFR gene is involved in plasma homocysteine levels and may contribute to endothelial dysfunction, which is one of the suggested mechanisms behind WMH 71. Whilst the association between MTHFR TT-genotype and WMH fell shy of statistical significance, the totality of the data suggested a trend for association. The mendelian randomisation approach allowed us to investigate any potential relationship between MTHFR and WMH in more depth and evaluate for potential causality. Particular strengths of this method are that confounding factors are equally distributed among genotypes, which facilitates testing causality in their presence, whereas measurement error bias, reverse causality and selection biases are largely overcome 72. Using this approach yielded similar values for the expected and observed OR, and there was considerable overlap of their 95% confidence intervals. Given that the two values are derived from meta-analyses of the different study types (genetic association vs. observational) - either of which being prone to a different source of bias – might be suggestive of a causal association between homocysteine and WMH burden. 73 However, this analysis was insufficiently powered, and future studies using adequate sample size may prove more conclusive.

A number of study limitations need to be documented. Publication bias is always a concern in meta-analysis. However, funnel plots were produced for each gene-WMH association and Egger’s regression analysis (two-tailed test) was performed to assess publication bias. Given that the majority of included studies reported non-significant results, substantial publication bias is considered unlikely, although can never be completely excluded. Further, of the 78 studies investigating the association of candidate genes and WMH, just under half did not have usable data for meta-analysis. It may be that the authors of these papers did not consider the data to be interesting enough to report (selective outcome reporting). The vast majority of these studies found no association and their inclusion would have strengthened our finding of no relationship between WMH and any of the studied gene polymorphisms. Some studies reported data according to a genetic model they had chosen rather than reporting event rates for each genotype separately which limited our ability to incorporate their studies into other genetic models. There was considerable variation in WMH measurement methods used between studies, which introduces methodological heterogeneity. Assessing WMH using visual rating scales can be subjective and observer dependent, 3although most papers reported good inter-rater agreement. The inclusion of both CT and MRI studies adds another source of inter-study heterogeneity. CT has been shown to be less sensitive at detecting WMH and its use may result in an underestimation of the true WMH load within those studies. However, removal of these studies did not lead to a substantial change in the pooled OR; thus, we considered it appropriate to include them. Finally, results could be confounded by failure to adjust for age, intracranial volume and vascular risk factors in all studies. Additionally, consideration ought to be given in analyses to the known WMH risk factors since genes may be exerting their effect through these factors. The variable disease status of the study populations could have introduced heterogeneity into our analysis. For example six studies in our APO E4 analysis were conducted in subjects with probable or pathologically confirmed Alzheimer’s disease 74,75. Combining these studies with those of asymptomatic subjects could have confounded our results. Finally, a number of covariates which we are not able to assess because of lack of complete datasets may influence our final results.

Despite undertaking, to the best of our knowledge, the largest meta-analysis to date along with studying a new independent WMH cohort, the genetics of this condition remains unclear. Future genetics studies not using a priori hypothesis may shed further light on this field.

**Figures**



**Figure 1:** PRISMA flow chart demonstrating the search strategy.

**Figure** **2**: Meta-analysis, forest plot and pooled odds ratio of risk from studies investigating the association between WMH and methylene tetrahydrofolate reductase, MTHFR (TT vs. CT/CC, recessive model). (**A**) Graded WMH, dichotomous data (**B**) WMH volume



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| --- | --- | --- | --- | --- | --- |
| **Study** | **Sample** | **n** | **Mean tHcy ± SD (μmol/L)** | **P value** | **Association** |
| Anand et al. 68 | EuropeansChinese | 326317 | 10.0 ± 3.89.2 ± 3.8 | P=0.02 | Chinese had significantly lower Hcy levels. |
| Carmel et al. 69 | WhiteAsian-Americans | 23768 | 14.8\*12.8\* | P<0.05 | Whites had higher Hcy concentrations than Asian-Americans. |
| Senaratne et al. 70 | CaucasiansEast Asians (Chinese, Japanese) | 10617 | 10.8 ± 0.67.6 ± 0.5 | P<0.001 | East Asians had significantly lower plasma Hcy compared to Caucasians. |
| **Table 1: Ethnic differences in plasma homocysteine level between East Asian and Caucasian subjects.** \*Standard deviation not reported by study |

**Figure** **3:** Meta-analysis of studies investigating the mean difference in homocysteine levels (μmol/L) between WMH cases and controls.



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Polymorphism** | **Model used** | **Cases** | **Controls** | **OR** | **95% CI** | **P value** |
| **Apolipoprotein** | E4 | E4 carriers vs. non-carriers | 2614 | 5008 | 0.98 | 0.87 – 1.11 | 0.78 |
| **Apolipoprotein** | E2 | E2 carriers vs. non-carriers | 248 | 569 | 1.42 | 0.46 – 4.43 | 0.54 |
| **Angiotensin Converting Enzyme** | Insertion/deletion | DD vs. ID/II | 756 | 1365 | 1.46 | 0.92 – 2.31 | 0.11 |
| **MTHFR** | C677T | TT vs. CT/CC | 800 | 2188 | 1.19 | 0.95 – 1.51 | 0.14 |
| **Angiotensinogen** | M235T | TT/MT vs. MM | 328 | 806 | 1.12 | 0.84 – 1.50 | 0.44 |
| **Angiotensinogen II receptor 1** | A1166C | CC vs. AC/AA | 105 | 354 | 1.23 | 0.59 – 2.54 | 0.58 |
| **Aldosterone synthase CYP11B2** | T(-344)C | CC/CT vs. TT | 197 | 956 | 0.61 | 0.44 – 0.84 | 0.003 |
| **Paraoxonase 1** | L55M | LL/LM vs. MM | 77 | 266 | 1.42 | 0.61 – 3.28 | 0.41 |

**Table 2**: Summary table demonstrating each gene, polymorphism, model used, number of cases and controls and resulting odds ratio, confidence interval and p values.

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