



Monoamine oxidase a gene polymorphisms common to blood pressure and depression scores in caucasian children

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Abstract

Background: Depression and cardiovascular disease risk factors develop in childhood. The objective of this study was to investigate cross sectional and longitudinal associations between blood pressure, mood scores and tagged SNPs within the Monoamine oxidase A (*MAOA*) gene in the Western Australian Pregnancy Cohort (Raine) Study.

Methods: Data from the five (n=1097), eight (n=1046), ten (n=1026) and fourteen (n=1124) year surveys were used. Blood pressure was measured at all surveys, anxious-depressed scores obtained from the Childhood Behavior Checklist at all surveys and depressive symptom scores from the Beck Depression Inventory for Youth at 14 years. Single nucleotide polymorphisms (SNPs) tagging the *MAOA* gene were identified from HapMap Phase II (CEU) data and genotyped. Cross sectional and longitudinal analyses were used to examine the association between blood pressure (outcome) and tagged SNPs within the *MAOA* gene and anxious/depressed scores (outcome) and tagged SNPs within the *MAOA* gene.

Results: At 14 years, boys with the risk allele of SNP rs5905859 and rs3027396 had higher systolic blood pressure ($\beta_{rs5905859} = 2.5$; 95% CI: 0.743, 4.337 and $\beta_{rs3027396} = 2.5$; 95% CI: 0.681, 4.383 respectively) and lower mood scores ($\beta_{rs5905859} = -0.1$; 95% CI: -0.100, -0.022 and $\beta_{rs3027396} = -0.2$; 95% CI: -0.313, -0.045 respectively). Longitudinally, boys with the risk allele of SNPs rs5905859 ($\beta = 0.3$; 95% CI: 0.026, 0.540) or rs6609257 ($\beta = 0.3$; 95% CI: 0.022, 0.521) had a higher mean systolic blood pressure trajectory compared to boys without.

Conclusions: Variation within or close to the *MAOA* gene may explain in part the association between lower depressive symptom scores and higher systolic blood pressure in Caucasian boys within the Raine cohort.

Keywords: *MAOA*, blood pressure, depression, children, gene

Background

Negative mood [1] and elevated blood pressure [2] emerge in adolescent and track throughout life. In childhood, higher negative affect scores, including depressive symptoms and anxiety, have been associated with lower systolic blood pressure [3,4]. This association persisted after adjusting for lifestyle factors

such as diet and exercise. Examining this relationship in childhood prior to the use of anti depressants and the development of common behavioural traits, such as smoking and alcohol use, may shed some light on mechanisms underlying this association.

Numerous complex interactions between genotype, phenotype and the environment are likely to be at play [5]. This study focused

on one facet, namely the hypothesis that a gene is associated with both blood pressure and anxious-depressed mood. The plausibility of this hypothesis is strengthened by heritability estimates of both blood pressure, depression and anxiety related disorders which range from 32%-60% [6,7], 25%-65% [8-11] and ~48% [12,13] respectively and a study [14] that estimated blood pressure and depression share 20% of their genetic variation.

Monoamine oxidase A (*MAOA*) gene is a potential genetic candidate that may underlie the association between negative affect and blood pressure in children. This gene was identified from a literature review using the search term "depression cardiovascular" and limited to genes implicated with both phenotypes. Each gene was individually entered into PubMed to verify that both phenotypes were in fact associated with the gene and further limited to studies published in English with 50 or more participants. Only 6 genes were identified from the initial search that were associated with depression and Cardiovascular disease risk factors, of which 1 gene *MAOA*, was associated separately with systolic blood pressure [15,16] and depression related phenotype [17].

The *MAOA* gene is located on the X chromosome. Functionally, *MAOA* gene codes for an enzyme expressed in the outer mitochondrial membrane that metabolises neurotransmitters such as serotonin and norepinephrine, both of which are known to be involved in mood and in blood pressure regulation [18].

Although a search of published genome wide association studies did not yield any results for blood pressure or depression or anxiety in childhood or adulthood (<http://www.genome.gov/>), one study suggests the *MAOA* gene or nearby genes may play a role in the development of blood pressure [15] and a functional variant in the promoter region of the *MAOA* gene has consistently been associated with mood disorders [17,19].

Previously, we found an association between low scores for depression and higher blood pressure in the 'Raine Study' West Australian children's cohort [4], the aim of the present study was therefore to see whether SNPs within *MAOA* were associated with both blood pressure and mood scores in this population.

Methods

Sample and study design

This study used data from the Raine Study, a prospective birth cohort of children whose mothers attended antenatal clinic at King Edward Memorial Hospital or nearby private practices in Western Australia.

Between 1989 and 1991, 2900 pregnant women were recruited at approximately 18 weeks of gestation and have previously been shown to be representative of the population presenting at King Edward Memorial Hospital [22]. Specific details of recruitment have been published elsewhere [20,21].

In this study, children were selected for analysis based on the following criteria: Singleton birth and no siblings in study, Caucasian ethnicity (both parents self-reported (82%)), DNA

sample and no congenital abnormalities.

Mood scores and certain CVD risk factors were assessed at 5, 8, 10 and 14 years. The characteristics of these children have been reported elsewhere [4]. The parents of participants, as well as the participants gave informed written consent at age 14. The study was approved by Human Ethics Committees at King Edward Memorial Hospital and Princess Margaret Hospital in Perth.

DNA extraction and genotyping

A total of 10 tagged single nucleotide polymorphisms (SNPs) for *MAOA* gene were identified from HapMap Phase II (CEU) data using a pairwise approach in Haploview (minor allele frequency (MAF) >5% and $r^2 > 0.8$) [23] (see online **Supplement Table S1**). Regions analysed include the entire gene, plus additional sequences 10 kb upstream and downstream of the gene.

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood and purified according to standard protocols. *MAOA* SNPs were genotyped using the GoldenGate[®] Genotyping Assay (Illumina Inc. San Diego, California, USA) as per the manufactures protocol (Fan et al., PMID: 16847463) at the Centre for Applied Genomics (Toronto, Ontario, Canada). Briefly, SNPs were uploaded to Illumina's Assay Design Tool (ADT) (<http://www.illumina.com/>) for probe design as part of a custom panel (GS0010538-OPA) of 1536 SNPs. A total of 5 µl of 50 ng/µl in 10 mM Tris-HCL pH 8.0, 1 mM EDTA of genomic DNA underwent an allele specific oligonucleotide hybridization followed by extension and ligation. A universal PCR step for all 1536 loci followed with primers labelled with either Cy3 (primer 1) or Cy2 (primer 2). The amplified products were then hybridized to a sentrix array matrix (SAM) and scanned using the Illumina BeadArray Reader (BAR) (Illumina, San Diego, CA). Data were analysed with Beadstudio v.3.0 using the default parameters. Only SNPs with GenCall scores >0.25 were called and samples were discarded if call rates were below 85%. Of the 10 tagged SNPs, all were of good quality for further analysis.

Outcome measures

Anxious-Depressed scores were available from the Child Behavior Checklist (CBCL/4-18) at all surveys [24]. The CBCL/4-18 was completed by the child's parent (usually their mother (85%)). The anxious-depressed subscale consisted of 13 items relating to anxious and/or depressive mood including whether the child cries a lot, is nervous, too fearful or anxious. Scores could range from zero to 26.

Depressive symptoms were measured using the Beck Depression Inventory for Youth (BDI-Y) in the 14 year survey [25]. The BDI-Y contains 20 items relating solely to depressed symptoms that an adolescent may have felt in the last 2 weeks. Scores could range from zero to 60. The BDI-Y was completed by the child.

Both the BDI-Y and CBCL/4-18 have excellent test-retest

reliability (BDI-Y: girls: $r=0.87$; boys: $r=0.89$) [25] and high sensitivity (CBCL/4-18: 66% anxious-depressed) and specificity (CBCL/4-18: 80% anxious-depressed) [26].

Consistent with previous studies [27,28], at each survey less than 5% of the cohort was anxious-depressed as defined by Achenbach [24]. Therefore our focus was on how *MAOA* genotypes affected the rate of change (longitudinal) or mean measures (cross sectional) of anxious-depressed scores within the cohort [29]. For consistency we analysed the BDI-Y similarly (8.4% were mildly, moderately or severely depressed according to the clinical thresholds defined by Beck et al., [25]).

As reported elsewhere blood pressure was measured by trained assessors [30]. Briefly, seated blood pressure was measured using a Dinamap electronic blood pressure recorder (Dinamap XL or Dinamap ProCare 100), at 2 minute intervals with the appropriate sized cuff placed on the right arm. With the exception of blood pressure measured at year 8 when only two readings were obtained, the second and third readings recorded at 2 minute intervals were averaged for each child [31].

Statistical analysis

To identify whether *MAOA* SNPs were associated with mood scores and blood pressure throughout childhood two set of analysis were conducted to determine if:

1. Tagged SNPs within the *MAOA* gene were associated with blood pressure (outcome)
2. Tagged SNPs within the *MAOA* gene were associated with mood scores (outcome)

If a SNP was associated with both outcomes, blood pressure and mood measurements were included in the models above to determine that SNP was independently associated with anxious-depressed scores and systolic blood pressure respectively.

Cross sectional analyses

Cross sectional analyses were conducted using data from the 14 year survey. A multivariate linear regression model previously described [4] was used to test for associations between genotype and blood pressure in adolescents. A \log_e transformation was used as the continuous measure of systolic blood pressure that was not normally distributed in boys.

A mixture of generalized linear models (GLMs) (personal SAS code calling the function PROC NLMIXED) was used to account for the extra zero counts and exponential shaped distribution of BDI-Y scores and CBCL anxious-depressed scores [32]. Briefly, the model consisted of a mixture of two components, a logistic model and a negative binomial model, each of them belonging to the GLM family. The logistic model was used to estimate the probability of not reporting any mood symptoms (i.e., BDI-Y or CBCL score of zero) versus reporting at least one mood symptom (i.e., CBCL or BDI-Y scores of 1 or greater). The second part of the model assumes that the BDI-Y or CBCL scores greater than 1 followed a negative binomial distribution.

Longitudinal analyses

Longitudinal analyses were used to examine associations between *MAOA* genotype and anxious-depressive scores (derived from the CBCL/4-18), systolic and diastolic blood pressure. Diastolic and systolic blood pressure trajectories were constructed using linear mixed effect (LME) models [33] from 5 to 14 years. Anxious-depressed mood trajectories were constructed using a generalised linear mixed effect (GLME) model with a Poisson distribution.

All trajectories included random effects for intercept (average systolic blood pressure, diastolic blood pressure or mood score) and slope (change in systolic blood pressure, diastolic blood pressure or mood score over time). Adjustments were made for potential confounders (low income and BMI).

Analyses were carried out separately in boys and girls due to sex specific associations between depressive symptom scores and blood pressure in this cohort [4]. Adjustments were made for the following potential confounders: age, age of first menstruation as an indicator of puberty (available for females only at 14 years), gross family income as an indicator of socio economic status, BMI and whether the adolescent smoked in the last 12 months (at 14 years only). All continuous confounders were mean centered (to the nearest whole number) to remove potential collinearity between the beta coefficients.

Significance was initially defined at the conventional 5% level and statistical analyses were performed in the statistical package R version 2.6.1 [34] and SAS version 9.1 [35].

The False Discovery Rate (FDR) approach [36] using the R package "qvalue" was performed to correct for multiple testing The q value in this study corresponded to a p value of ≤ 0.030 . An additive model was used unless otherwise specified. As males only have one allele (the *MAOA* gene is located on the X chromosome) Hardy-Weinberg Equilibrium was calculated for girls only.

Post-hoc power calculations were performed using Quanto [37]. This study had >80% power to detect genotype associations with systolic blood pressure or mood score when a SNP contributed at least 1.8% of the variation and had an allele frequency greater than 3% in girls and boys.

Results

Participant characteristics and allele frequencies

At the 5, 8, 10 to 14 year surveys 1097, 1046, 1026 and 1124 children, respectively, met this studies inclusion criteria. Participants that were genotyped differed only in respect to BMI when compared to those of who were not genotyped (Table 1). Minor allele frequencies were greater than 3% for the study population and most were consistent with HapMap CEU frequencies (see online Supplement Table S2). All SNPs were in Hardy-Weinberg Equilibrium.

Cross sectional analysis

Genotype common to both blood pressure and mood scores

After correcting for multiple testing, SNP rs5905859 within the *MAOA* gene was associated with systolic blood pressure

Table 1. Characteristics children at the 14 year survey within the Western Australian Pregnancy Cohort (Raine) Study with complete phenotype data who were genotyped compared to those who were not.

Characteristics	Not genotyped (n=325)	Genotyped (n=1061)	p value [‡]
Sex (Male) [†]	151(46.5)	555(52.3)	0.070
Body mass index (kg/m²)[†]	20.0(18.5-22.2)	20.5(18.6-23.4)	0.01
Puberty (years)	12.6(0.1)	12.8(0.1)	0.13
Becks depression inventory for youth (BDI-Y) [†]	4(1-9)	5(2-10)	0.12
Anxious-depressed score (CBCL/4-18) [†]	1(0-4)	1(0-4)	0.91
Family income* ≤\$25,000	45(13.9)	132(12.4)	0.63
≥\$25001 and ≤\$40,000	57(17.5)	172(16.2)	--
≥\$40,001	223(68.6)	757(71.4)	--
Systolic blood pressure (mm/Hg)	110.7(0.5)	111.7(0.3)	0.13
Diastolic blood pressure (mm/Hg)	58.9(0.4)	58.8(0.2)	0.84

Values represent means and standard errors of the mean unless indicated by †(representing medians (interquartile range) for skewed data) or *(representing n (%) for categorical data). Bold font represents significant associations. ‡Analyses used: Chi-squared test for categorical data, t test for continuous data and Mann-Whitney for skewed data.

and depressive symptom score in boys (Table 3) but not girls (Table 2). Boys with the C genotype had higher systolic blood pressure and lower depressive symptom scores than boys without the C genotype. These associations were independent of depressive symptom score ($\beta=2.5$; 95% CI: 0.743, 4.337; $p=0.004$) and systolic blood pressure ($\beta=-0.1$; 95% CI: -0.100, -0.022; $p=0.002$) respectively. SNP rs5905859 explained 1.6% and 0.7% of the variance of systolic blood pressure and depressive symptom score (respectively). The characteristics of the study participants did not differ by rs5905859 genotype (Table 4).

SNP rs3027396 was also associated with systolic blood pressure and anxious-depressed scores in boys but not girls. Boys with the A genotype had higher systolic blood pressure measurements and lower anxious-depressed scores when compared to boys without the A genotype. These associations were independent of anxious-depressed score ($\beta=2.5$; 95% CI: 0.681, 4.383; $p=0.006$) and systolic blood pressure ($\beta=-0.2$; 95% CI: -0.313, -0.045; $p=0.010$) respectively. SNP rs3027396 explained 1.2% and 0.7% of the variance of systolic blood pressure and anxious-depressed score (respectively). The characteristics of the study participants did not differ by rs3027396 genotype (Table 4).

Blood pressure and genotype

The risk alleles of the following SNPs rs6609257 or rs7052785 were associated with higher systolic blood pressure (Table 2) in boys. Boys with the risk alleles had 3.0mmHg and 6.4mmHg respectively higher mean systolic blood pressure compared to boys without the risk alleles.

No associations were found in girls or with diastolic blood

pressure in boys.

Mood scores and genotype

Boys with the A genotype of rs12843533 had a BDI-Y score 0.1 lower than boys without the A genotype (Table 3). Girls in contrast had a BDI-Y score 0.4 higher than girls without the AA genotype (Table 2).

Girls with the GG genotype of rs3027399 or GG genotype rs3027415 had a BDI-Y score 0.2 higher and 0.2 lower than girls who did not have GG genotype respectively. Boys with the A genotype of rs1181275 scored 0.2 lower on the BDI-Y than boys who did not have the A genotype.

Boys and girls with the risk allele of SNP rs3027396 and rs5906883 had anxious-depressed scores 0.1 lower than boys and girls without the risk allele.

Girls with the CC genotype of rs5905859 or GG genotype rs6609257 or rs7052785 had an anxious-depressed score 0.2, 0.1 and 0.4 lower than girls who did not have the CC, GG or GG genotype respectively. Boys with the G genotype of rs3027415 scored 0.1 higher on the CBCL anxious-depressed subscale than boys who did not have the A genotype.

Longitudinal analysis

Boys with the risk allele of rs5905859, had a greater rate of change for systolic blood pressure between 5 to 14 years (Figure 1). This persisted after adjusting for anxious-depressed score ($\beta=0.3$; 95% CI: 0.026, 0.540; $p=0.031$).

Boys with the risk allele of rs6609257 had higher systolic and diastolic blood pressure trajectories between 5-14 years (Figure 2). Both associations persisted after adjusting for anxious-depressed score ($\beta=0.3$; 95% CI: 0.022, 0.521; $p=$

Table 2. Effect of MAOA SNPs on blood pressure and anxious/depressed mood for girls in the Western Australian Pregnancy Cohort (Raine). Study at 14 years.

SNP	Allele	N	DBP effect size in mm/Hg [§] (95% CI)	p	N	SBP effect size in mm/Hg [§] (95% CI)	p	N	BDI-Y score effect size [§] (95% CI)	p	N	CBCL/4-18 (SADRS) effect size [§] (95% CI)	p
rs1181275	<u>A</u> G	477	0.698 (-0.566,1.962)	0.28	477	1.000 (-0.736,2.822)	0.30	475	0.100 (-0.002,0.128)	0.060	469	0.029 (-0.090,0.148)	0.63
rs12843533	<u>A</u> G	475	0.880 (-0.437,2.196)	0.19	475	-0.102 (-1.920,1.747)	0.87	473	0.4 (0.236,0.603)[‡]	<0.001	467	0.126 (0.019,0.234) [‡]	0.020
rs3027396	<u>A</u> G	476	0.066 (-0.820,0.953)	0.88	476	-0.406 (-1.658,0.861)	0.47	474	0.000 (-0.042,0.052)	0.84	468	-0.142 (-0.227,-0.058)	0.001
rs3027399	<u>C</u> G	471	0.042 (-1.475,1.560)	0.96	471	-0.062 (-2.151,2.067)	0.90	469	0.200 (0.109,0.283)[†]	<0.001	464	0.030 (-0.113,0.174)	0.68
rs3027415	<u>A</u> G	474	0.167 (-0.816,1.151)	0.74	474	0.128 (-1.249,1.524)	0.68	472	-0.2 (-0.165,-0.055)	<0.001	466	0.059 (-0.027,0.144)	0.18
rs5905859	<u>A</u> C	476	0.496 (-0.386,1.378)	0.27	476	-0.231 (-1.491,1.044)	0.66	474	-0.1 (-0.074,0.022)	0.28	468	-0.204 (-0.292,-0.116)	<0.0001
rs5906883	<u>A</u> C	477	-0.034 (-0.939,0.871)	0.94	477	-0.256 (-1.536,1.038)	0.63	475	0.000 (-0.041,0.057)	0.75	469	-0.138 (-0.226,-0.050)	0.002
rs5906957	<u>A</u> G	476	-0.082 (-1.038,0.874)	0.87	476	-0.685 (-2.050,0.697)	0.31	474	0.000 (-0.036,0.069)	0.54	468	-0.113 (-0.207,-0.018)	0.020
rs6609257	<u>A</u> G	476	0.609 (-0.217,1.434)	0.15	476	-0.235 (-1.394,0.937)	0.68	474	0.000 (-0.048,0.041)	0.87	468	-0.097 (-0.174,-0.020)	0.010
rs7052785	<u>A</u> G	477	0.819 (-1.688,3.326)	0.52	477	-1.784 (-5.143,1.684)	0.29	475	0.000 (-0.104,0.167) [‡]	0.65	469	-0.355 (-0.621,-0.089)[†]	0.010

Girls SBP model adjusted for age, puberty and BMI; Beck's Depression Inventory for Youth (BDI-Y) model adjusted for Puberty and ever smoked; CBL-SADRS model adjusted for age and puberty Underlined allele represents risk allele. Bold font represents associations that remained significant after correcting for multiple testing (i.e. q value corresponding to a p value of ≤ 0.01). Additive mode of inheritance assumed unless indicated by [†](representing dominant mode of inheritance) or [‡](representing recessive mode of inheritance). N represents sample size; p represents p value. Analyses used: [§]Linear Regression; [§]Mixed distribution Linear Regression

0.033; $\beta=0.3$; 95% CI: 0.053, 0.449; $p=0.013$ (respectively)). No other longitudinal associations were detected (see online [Supplement Tables S3 and S4](#)).

Discussion

In a sample of Caucasian adolescents, the C genotype of SNP rs5905859 and the A genotype of SNP rs3027396 was independently associated with higher systolic blood pressure and lower mood scores in adolescent boys but not girls. Throughout childhood the risk alleles of SNPs rs6609257 and rs5905859 were associated with higher blood pressure trajectories in boys but not girls. This suggests that the MAOA gene or closely linked genes may be mutually exclusively associated with blood pressure and depression related phenotypes in Caucasian children and thus may have pleiotropic effects.

To our knowledge this is the first study to examine the pleiotropic effects of SNPs within the MAOA gene as an explanation for the co-occurrence of depressive symptoms and

blood pressure in either adults or children. The tagged SNPs we have identified within the MAOA gene, including rs5905859 and rs3027396, are located within the intronic region of the gene, do not tag the functional variant in the promoter region of the MAOA gene and to date their functional significance remains undefined (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). The biological mechanism by which rs5905859 and rs3027396 may operate to independently affect both systolic blood pressure and mood is unknown. However these SNPs may be acting as marker for other SNPs in nearby genes that they may be in linkage disequilibrium with [38]. MAOA is part of the monoamine neurotransmitter pathway [18]. This pathway has been implicated in the degradation of neurotransmitters, such as serotonin and norepinephrine, that have been hypothesised to control mood [39,40] and are known to modulate the central and peripheral autonomic nervous system that control blood pressure [41]. It is therefore plausible that the MAOA gene or nearby genes may link mood and blood pressure via the monoamine neurotransmitter pathway.

Table 3. Effect of MAOA SNPs on blood pressure and anxious/depressed mood for boys in the Western Australian Pregnancy Cohort (Raine) Study at 14 years.

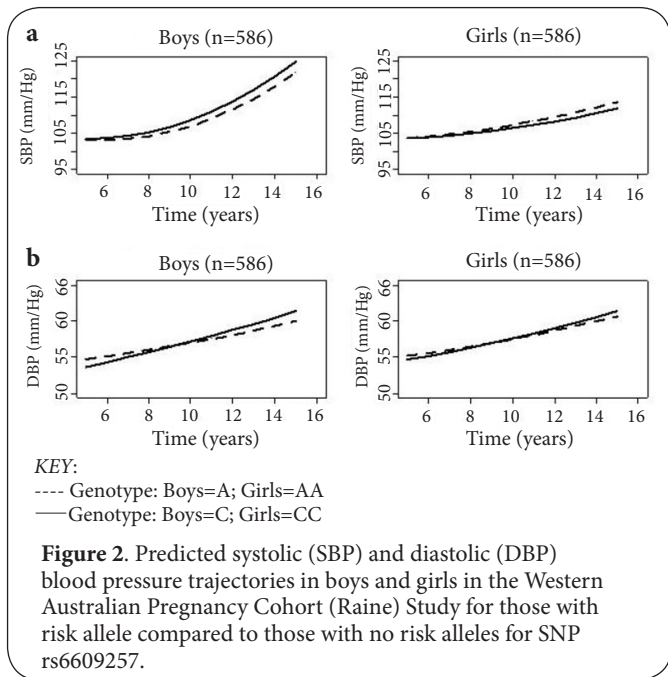
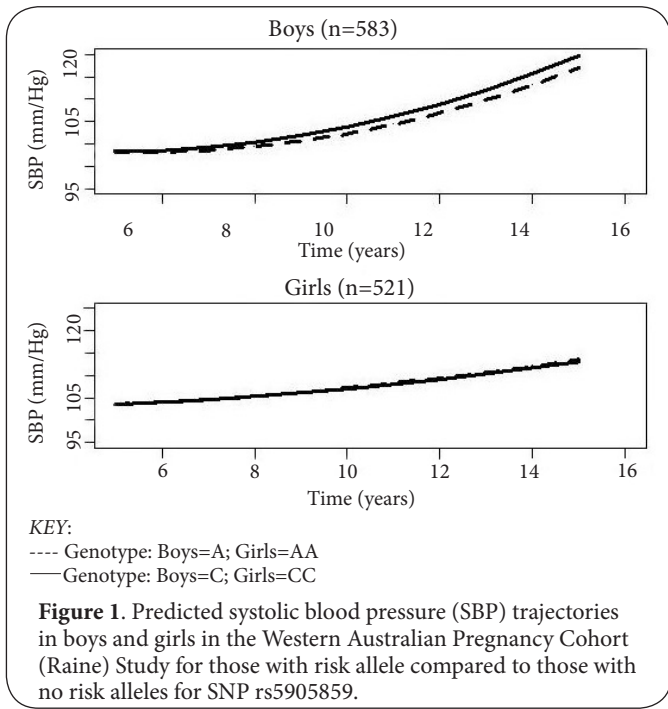
SNP	Allele	N	DBP effect size in mm/Hg [‡] (95% CI)	p	N	SBP effect size in mm/Hg [‡] (95% CI)	p	N	BDI-Y score effect size [§] (95% CI)	p	N	CBCL/4-18 (SADRS) effect size [§] (95% CI)	p
rs1181275 [†]	<u>AG</u>	568	1.534 (-0.146,1.680)	0.10	568	3.000 (0.152,5.872)	0.04	562	-0.215 (-0.289,-0.141)	<0.001	560	-0.134 (-0.256,-0.013)	0.03
rs12843533	<u>AG</u>	567	0.315 (-0.520,1.150)	0.46	567	0.1 (-1.192,1.368)	0.91	561	-0.106 (-0.167,-0.045)	0.001	560	-0.020 (-0.111,0.070)	0.66
rs3027396 [†]	<u>AG</u>	565	0.275 (-0.311,0.861)	0.36	565	2.300 (0.465,4.086)	0.01	559	-0.039 (-0.078,0.000)	0.050	559	-0.087 (-0.153,-0.021)	0.01
rs3027399	<u>CG</u>	541	-0.644 (-1.693,0.405)	0.23	541	-1.300 (-2.880,0.292)	0.15	535	0.056 (-0.015,0.126)	0.12	555	-0.047 (-0.160,0.066)	0.42
rs3027415	<u>AG</u>	566	-0.015 (-0.666,0.637)	0.96	566	-0.020 (-1.015,0.978)	0.96	560	-0.041 (-0.086,0.003)	0.070	559	0.107 (0.044,0.170)	0.001
rs5905859 [†]	<u>AC</u>	562	0.410 (-0.165,0.984)	0.16	562	2.500 (0.766,4.333)	0.003	556	-0.070 (-0.110,-0.032)	<0.001	557	-0.034 (-0.097,0.028)	0.28
rs5906883	<u>AC</u>	567	0.302 (-0.298,0.902)	0.32	567	0.900 (-0.032,1.808)	0.050	561	-0.044 (-0.084,-0.004)	0.030	560	-0.099 (-0.167,-0.030)	0.005
rs5906957	<u>AG</u>	567	0.314 (-0.312,0.940)	0.33	567	2.000 (0.120,3.994)	0.030	561	-0.001 (-0.051,0.031)	0.64	560	-0.077 (-0.148,-0.007)	0.030
rs6609257 [†]	<u>AG</u>	567	0.506 (-0.052,1.065)	0.08	567	3.000 (1.282,4.730)	<0.001	561	-0.038 (-0.075,-0.001)	0.050	560	-0.070 (-0.130,-0.009)	0.020
rs7052785 [†]	<u>AG</u>	567	0.954 (-0.494,2.401)	0.20	567	6.400 (1.836,11.180)	0.005	562	0.072 (-0.014,0.157)	0.10	560	0.053 (-0.090,0.196)	0.47

Boys SBP model adjusted for BMI Systolic blood pressure (SBP): effect size and 95% confidence intervals (95% CI) back transformed; Underlined allele represents risk allele. Bold font represents associations that remained significant after correcting for multiple testing (i.e. q value corresponding to a p value of ≤0.01). Additive mode of inheritance assumed unless indicated by * (representing dominant mode of inheritance) or † (representing recessive mode of inheritance). N represents sample size; p represents p value. Analyses used: ‡Linear regression; §Mixed distribution linear regression.

Table 4. Characteristics of boys within the Western Australian Pregnancy Cohort (Raine) Study by SNP rs5905859 and rs3027396 genotype.

	rs5905859 (n=531)			rs3027396 (n=487)		
	A (n=345)	C (n=185)	p [†] value	G (n=362)	A (n=171)	p [†] value
Body mass index (m²/kg)	21.0(0.2)	21.4(0.3)	0.25	21.1(0.2)	21.3(0.3)	0.38
Income*						
≤\$25,000	44(12.8)	22(11.9)		47(13.0)	19(11.1)	--
≥\$25001 and ≤\$40,000	43(12.5)	26(14.1)	0.85	48(13.3)	22(12.9)	0.81
≥\$40,001	258(74.8)	137(74.1)		267(73.7)	130(76.0)	--
Never Smoked*	325(94.2)	171(92.4)	0.54	340(93.9)	159(93.0)	0.82
Age	14.1(0.01)	14.1(0.01)	0.33	14.1(0.01)	14.1(0.01)	0.55

Values represent means and standard errors of the mean unless indicated by *representing n (%) for categorical data. †Analyses used: Chi square test for categorical characteristics and one-way analysis of variance for continuous characteristics.



The relative small magnitude of effect and variance of SNPs rs5905859 and rs3027396 on mood scores in this study may be attributed the multifactorial nature of depression or alternatively to the low rate of “depression” within this cohort (8.4% children could be classified as mildly, moderately or severely depressed; >75% had a BDI-Y score less than 9 out of a possible score of 60).

The blood pressure effects are relatively large, for a population

of this age and blood pressure, ranging from 2.3mmHg to 6.4mmHg for SNPs rs3027396, rs6609257 and rs7052785. The effect of these SNPs on systolic blood pressure is of potential clinical importance as relatively small changes in systolic blood pressure in adults have been shown to have significant effects on population CVD mortality rates [42]. For example a 2mmHg increase in systolic blood pressure in adults has been estimated to lead to a 4% increase in coronary heart disease and 6% increase in stroke [43].

There may be several explanations for the specific gender effects found. Firstly it has been suggested that sex specific associations of the *MAOA* gene may be due to differing patterns of monoamine metabolism and signal transduction [44]. Thus SNPs within the *MAOA* gene in our study may be associated with systolic blood pressure in boys but not girls because of differing hormonal environments in boys and girls, particularly during adolescence. Secondly blood pressure was substantially lower in girls than in boys with a narrower range of values so there may have been less power to show associations. Hypertension is more prevalent in men than premenopausal women [45] so it is possible that gender related hormonal differences may influence genetic susceptibility to systolic blood pressure. This hypothesis has been supported by a study that found systolic blood pressure to be a sexually dimorphic trait, however that study only examined genes on autosomal chromosomes [46].

Limitations of our study include lack of replication and modest statistical power. Although we have corrected for multiple testing we cannot exclude the possibility that the associations may be specific to our study population and as such replication of our findings in an independent sample is necessary to determine the external validity of our findings. The statistical power of this study was adequate to show single SNP effects but we were inadequately powered to examine gene-environment and gene-gene interactions. Given the multifactorial nature of both depression and cardiovascular disease, the hypothesis of a pleiotropic gene is only one of many possible genetic mechanisms that may contribute to both diseases.

Conclusion

Our results suggest a common underlying genetic contribution to the co-occurrence of depressive symptoms and lower blood pressure in adolescents. We have shown for the first time that lower mood scores and higher systolic blood pressure were both independently associated with SNP rs5905859 and rs3027396 in boys but not girls. In addition we have shown relatively large effects of *MAOA* SNPs on systolic blood pressure in boys and that *MAOA* SNPs were associated with higher systolic blood pressure trajectories. Further studies are required to confirm our findings and examine the underlying biological mechanism as to how the *MAOA* gene or genes close to the *MAOA* gene may be contributing the co-occurrence of lower blood pressure and higher mood scores.

List of abbreviations

MAOA: Monoamine oxidase A
 SNPs: Single nucleotide polymorphisms
 CVD: Cardiovascular disease
 MAF: Minor allele frequency
 DNA: Deoxyribonucleic acid
 CBCL/4-18: Child Behavior Checklist
 BDI-Y: Depression Inventory for Youth
 GLMs: Generalized linear models
 GLME: Generalised linear mixed effect
 BMI: Body Mass Index
 FDR: False Discovery Rate

Additional files

[Supplement Table S1](#)
[Supplement Table S2](#)
[Supplement Table S3](#)
[Supplement Table S4](#)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SL	LB	TAM	EM	PAM	CEP	LJP	LJB
Research concept and design	✓	--	--	✓	✓	--	✓	✓
Collection and/or assembly of data	--	--	--	--	--	--	--	--
Data analysis and interpretation	✓	--	--	--	--	--	--	--
Writing the article	✓	--	--	--	--	--	--	--
Critical revision of the article	✓	✓	✓	✓	✓	✓	--	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	✓	✓	--	--	--	--	--	--

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