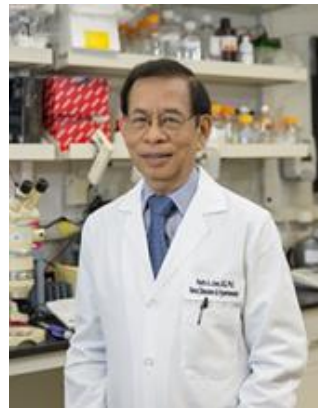


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Research Article

Contribution of Four Polymorphisms in Renin-Angiotensin-Aldosterone-Related Genes to Hypertension in a Thai Population

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Genetics of Hypertension

- Hypertension: 140/90 mmHg (systolic/diastolic BP)
- Genetic heritability
 - Blood pressure, hypertension 30-50%
- 280 genetic variants have been associated with hypertension.
- The renin-angiotensin-aldosterone system (RAAS) is commonly targeted for the treatment of hypertension.
- RAAS is a hormone system that regulates blood pressure (BP) and fluid and electrolyte balance.

Four polymorphisms in RAAS (EGAT)

Chr	gene	effect allele	non-effect allele	N of genotyped samples	Hypertension cases
rs699	AGT	A	G	3572	1112
rs5186	AGTR1	C	A	4108	1305
rs1799998	CYP11B2	G	A	4150	1331
rs1799752	ACE	D (deletion)	I (insertion)	3674	1171

ACTCTACGATTTACGGTACTTAGGAGCATATGCTACT
 ACTGTACGATTTACGGTACTTAGAGCATATGCTACT

SNP
 single nucleotide
 polymorphism

indel
 insertion /
 deletion

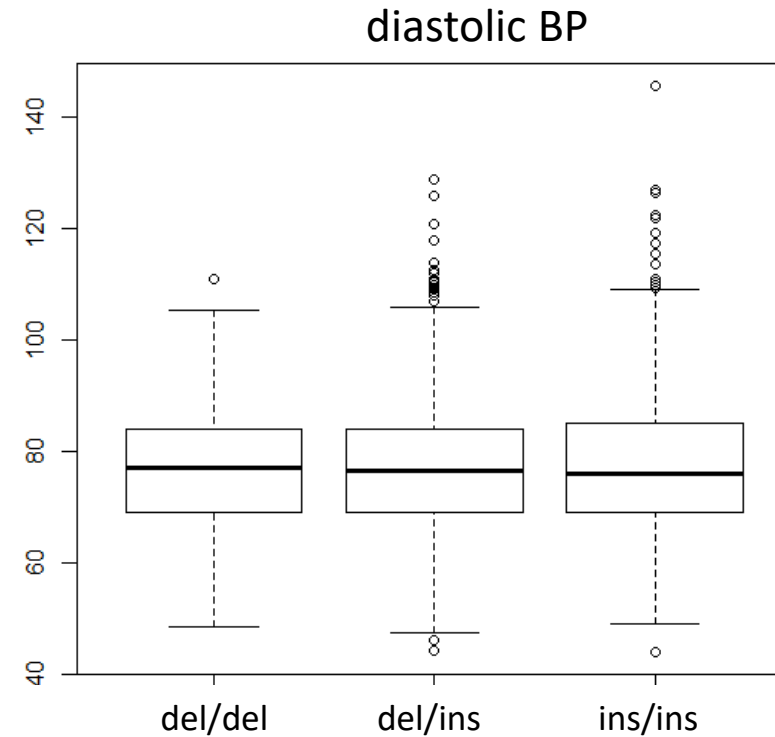
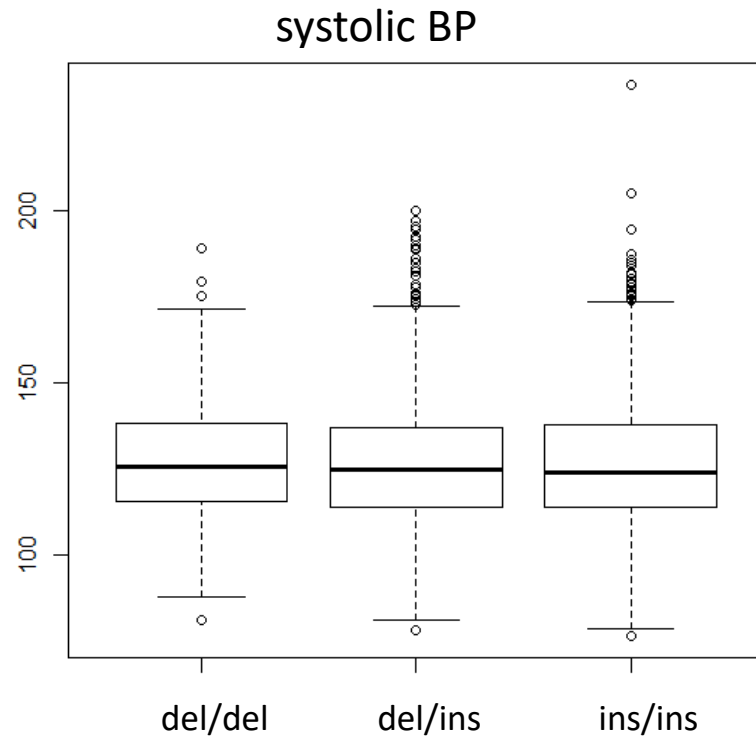
OR of developing hypertension

	Additive model	
	OR (95%CI)	P value
rs1799752 (ACE)	1.03 (0.92, 1.17)	0.60
rs699 (AGT)	0.91 (0.78,1.06)	0.24
rs5186 (AGTR1)	1.07 (0.87,1.32)	0.51
rs1799998 (CYP11B2)	0.98 (0.87, 1.09)	0.67

Heterozygote risk is assumed to be intermediate between the two homozygote risks

$$\text{hypertension} = \text{SNP} + \text{sex} + \text{bmi} + \text{age}$$

Systolic and Diastolic BP



rs1799752 (ACE)

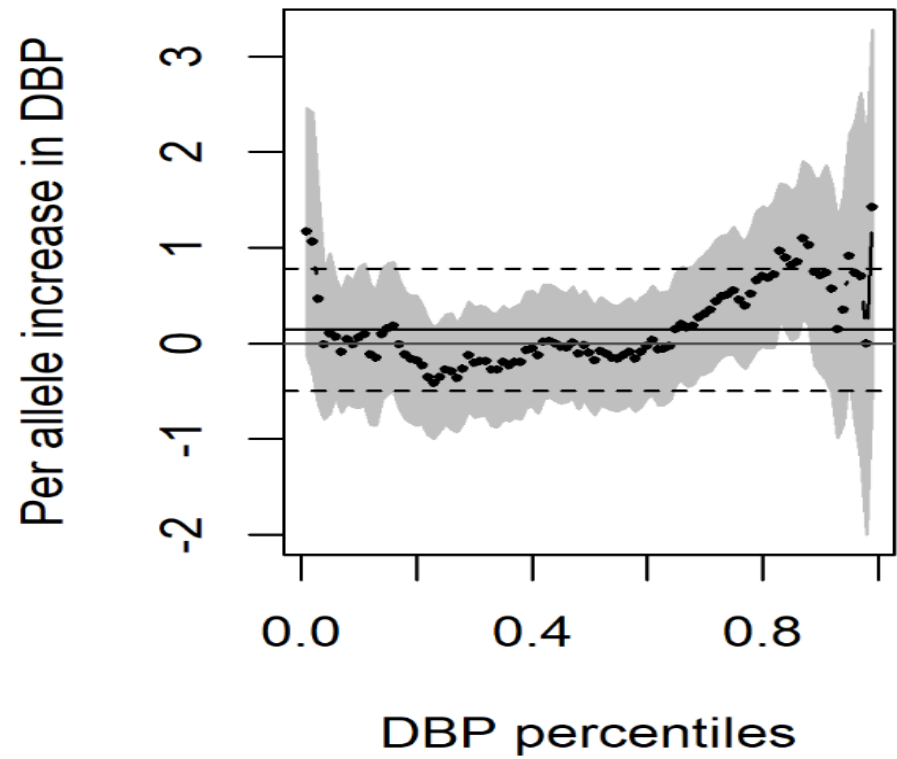
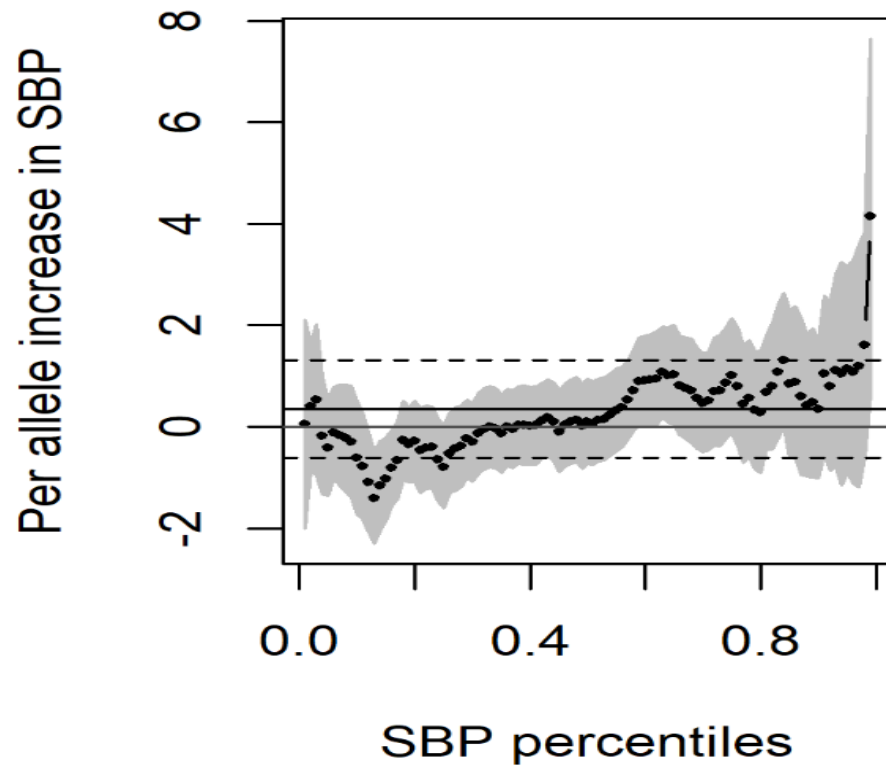
Samples under BP medication are removed to avoid BP levels that are artificially lowered regardless of the genetic background.

Quantile regression

- Quantile regression aims at estimating either the conditional median or other **quantiles of the response variable**, whereas the linear regression results in estimates of the conditional mean of the response variable.
- There is no theoretical reason to assume that the effect of the covariates is the same at different quantiles of the distribution. Quantile regression can also assess **how conditional quantiles of BP vary** with respect to measured covariates.
- age^2 is additionally adjusted in the BP model.

rs1799752 in ACE gene

rs1799752



EGAT data vs UK Biobank

	Hypertension				SBP				DBP			
	EGAT study		UK Biobank		EGAT study		UK Biobank		EGAT study		UK Biobank	
	β	Pval	β	Pval	β	Pval	β	Pval	β	Pval	β	P
rs699 (AGT) (0.15 vs 0.59)	0.11	0.16	-5.72x10 ⁻⁵	0.55	0.76	0.23	-0.02	7.28x10 ⁻¹¹	0.04	0.93	-0.02	4.15x10 ⁻¹⁰
rs5186 (AGTR1) (0.06 vs NA)	-0.23	0.05	5.31x10 ⁻⁵	0.60	-0.28	0.75	2.89x10 ⁻³	0.28	-0.71	0.20	1.25x10 ⁻³	0.64
rs1799998 (CYP11B2) (0.3 vs 0.49)	-0.08	0.18	3.79x10 ⁻⁵	0.69	-0.27	0.57	-9.61x10 ⁻³	1.03x10 ⁻⁴	-0.25	0.39	-0.01	1.30x10 ⁻⁶

Discussion

- Different SNP allele frequencies between Thais vs Caucasian
- Lower allele frequencies observed among Thais for SNPs previously shown association evidence in Caucasian.
- Sample size still restricted the statistical power.
- In our study design, 3500 cases and 3500 controls are required to obtain an 80% power to detect if there is a true association between rs1799752 in ACE and hypertension.
- Denser polymorphisms across these 4 genes are needed to provide a better coverage in the regions of interest.