

Hypertension /Blood Pressure Signature Genes and BP Response to Thiazide Diuretics: Results from PEAR and PEAR-2 Studies

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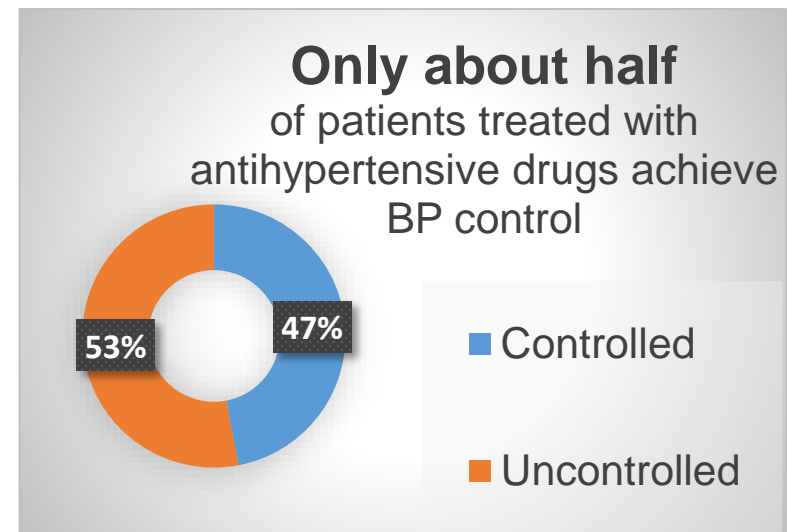
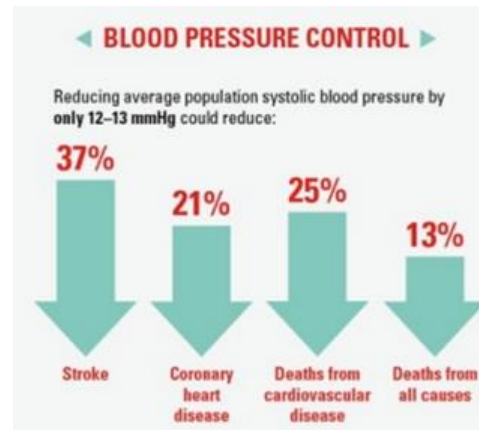
**PHARMACOGENETICS
RESEARCH NETWORK**

Hypertension (HTN) and Blood Pressure (BP) Control

Most common medical condition among American adults

1 in every 3 US adults

Contributes to ~1,000 deaths/day



34 BP signature genes explain ~ 9% of BP variability

Hypothesis

Genes associated with BP/HTN are also associated with BP response to **thiazide diuretics**

Study Objective

To identify **genes differentially expressed** in responders and non-responders to **thiazide diuretics**, based on the selected panel of BP signature genes

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Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)



Prospective, randomized, multicenter clinical trials

Examining the role of genetic variability on BP response to **thiazides** and/or β -blocker



Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)



- **RNA sequencing** (Illumina HiSeq) in whole blood samples from **150 HTN participants**
- **40 million RNA-Seq reads** aligned to the human reference genome (hg19) with TopHat2
- **Sample selection** - extreme of BP response to thiazides (HCTZ and chlorthalidone)
- **Comparisons** in gene expression abundances by Cufflinks / Cuffdiff
- **Meta-analysis** of differential expression: p-value combination

	PEAR1 whites HCTZ	PEAR2 whites Chlorthalidone	PEAR2 blacks Chlorthalidone
Response	Responders baseline n=25	Responders baseline n=25	Responders baseline n=25
	Non-responders baseline n=25	Non-responders baseline n=25	Non-responders baseline n=25

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Results

At 5 % false discover rate (FDR), we identified 12 genes that were differentially expressed in relation to thiazide diuretics BP response in one of the 3 groups

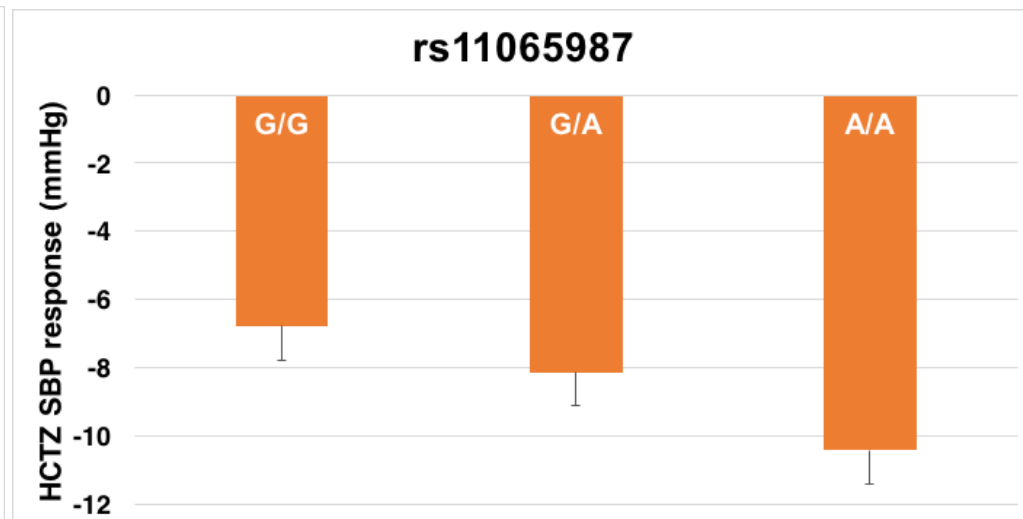
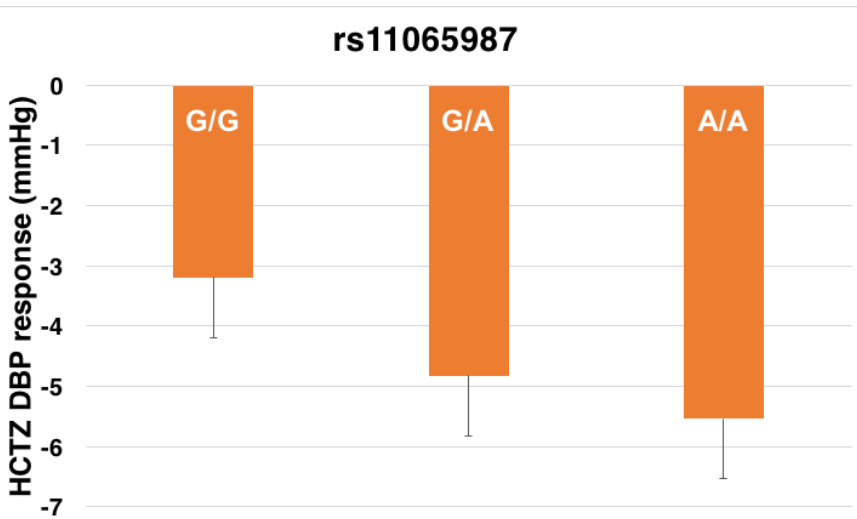
		HCTZ whites		Chlorthalidone Whites		Chlorthalidone Blacks		Meta-analysis
Gene	Chr.	Fold Change	P value	Fold Change	P value	Fold Change	P value	P value
FOS	14	1.3	2.90E-03	1.29	1.15E-03	1.46	5.00E-05	2.08E-12
DUSP1	5	1.4	1.50E-04	1.30	1.35E-03	1.29	3.55E-03	9.50E-12
PPP1R15A	19	1.3	1.15E-03	1.19	3.61E-02	1.29	1.75E-03	3.64E-08

All gene expression measurements (FPKM) > 24
 Fold change: responders (FPKM)/ non-responders FPKM

Chlorthalidone whites Chlorthalidone blacks

FOS and PPP1R15A trans eQTLs

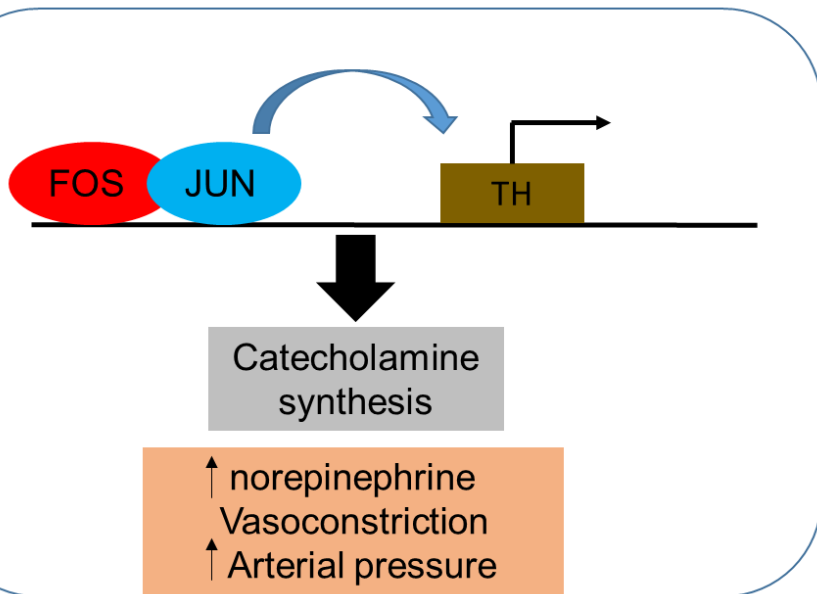
SNP	Blood eQTL database				PEAR whites participants								
	FOS		PPP1R15A		HCTZ DBP response			HCTZ SBP response					
	Z-score	P value	Z-score	P value	A1	A2	MAF	β	SE	P	β	SE	P
rs11065987	-5.43	5.60E-08	-4.68	2.81E-06	A	G	0.54	-1.4	0.5	0.002926	-2.1	0.7	0.001788



Discussion

- Expression of *FOS*: neuronal activation of vasomotor areas
- Blockade of *FOS* expression attenuates high BP in HTN induced and spontaneously HTN mice

TH: Tyrosine Hydroxylase



- PPP1R15A and DUSP1: no direct evidence of involvement in HTN or thiazides BP regulation
- DUSP1 inhibits ERK signaling *in vitro* potential effect on angiotensin II-mediated vasoconstriction
- PPP1R15A: regulatory subunit of PP1 may activate myosin light chain kinase (MLCK), leading to vasoconstriction
- Future studies with mouse models or Induced Pluripotent Stem Cells (iPSCs)

Conclusion & Future Directions

- This study reveals differences in **FOS**, **DUSP1** and **PPP1R15A** gene expression underlying thiazides BP response, and provides insights into new potential mechanisms involved in BP regulation
- Conduct functional studies to further investigate the potential role of these genes in the mechanisms for thiazides BP regulation

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