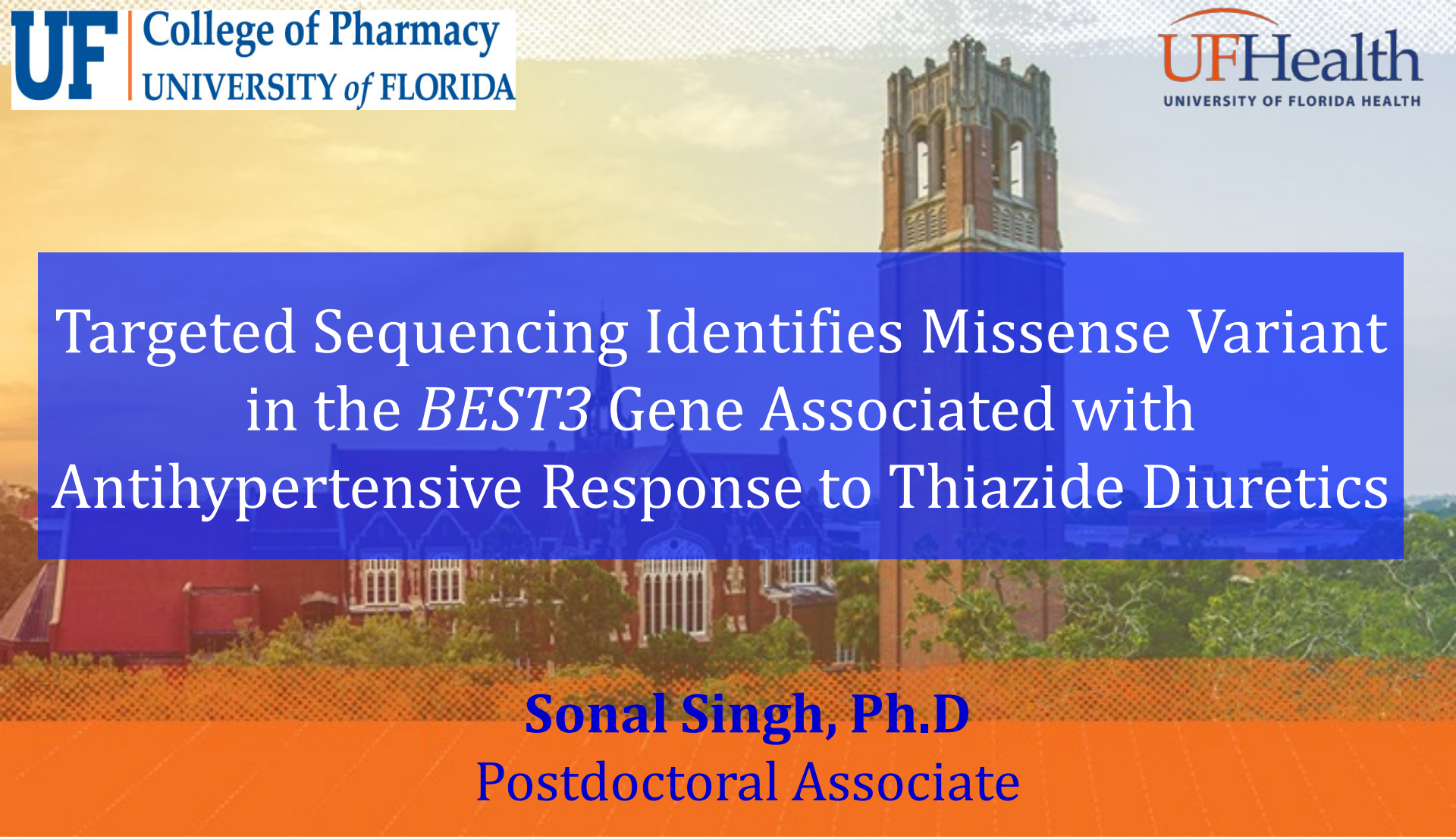
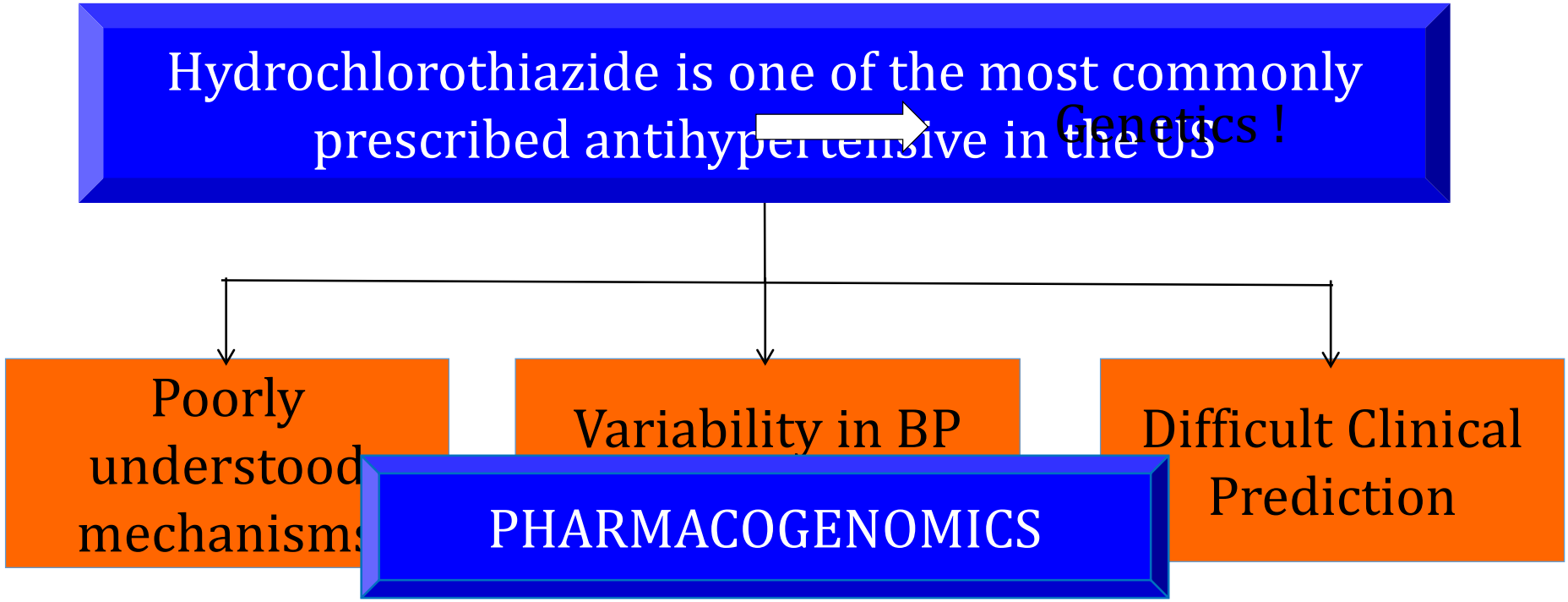


Targeted Sequencing Identifies Missense Variant in the *BEST3* Gene Associated with Antihypertensive Response to Thiazide Diuretics

Sonal Singh, Ph.D
Postdoctoral Associate



- Elucidation of genetic determinants of HCTZ blood pressure response

PEAR
(Pharmacogenomic Evaluations of Antihypertensive Response)

GERA
(Genetic Epidemiology of Responses to Antihypertensives)

STUDY DESIGN

PEAR/GERA

Baseline

PEAR -> 9 weeks
GERA -> 4 weeks
Hydrochlorothiazide
Treatment

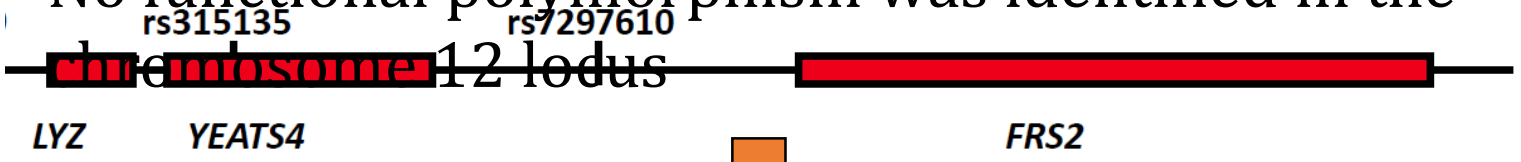
Post
Treatment

Genetic variability in this region is determinant of antihypertensive response to HCTZ

GERA

Chromosome 12q15 locus associated with BP response to HCTZ

No functional polymorphism was identified in the chromosome 12 locus



No clear understanding of the underlying mechanism could be determined

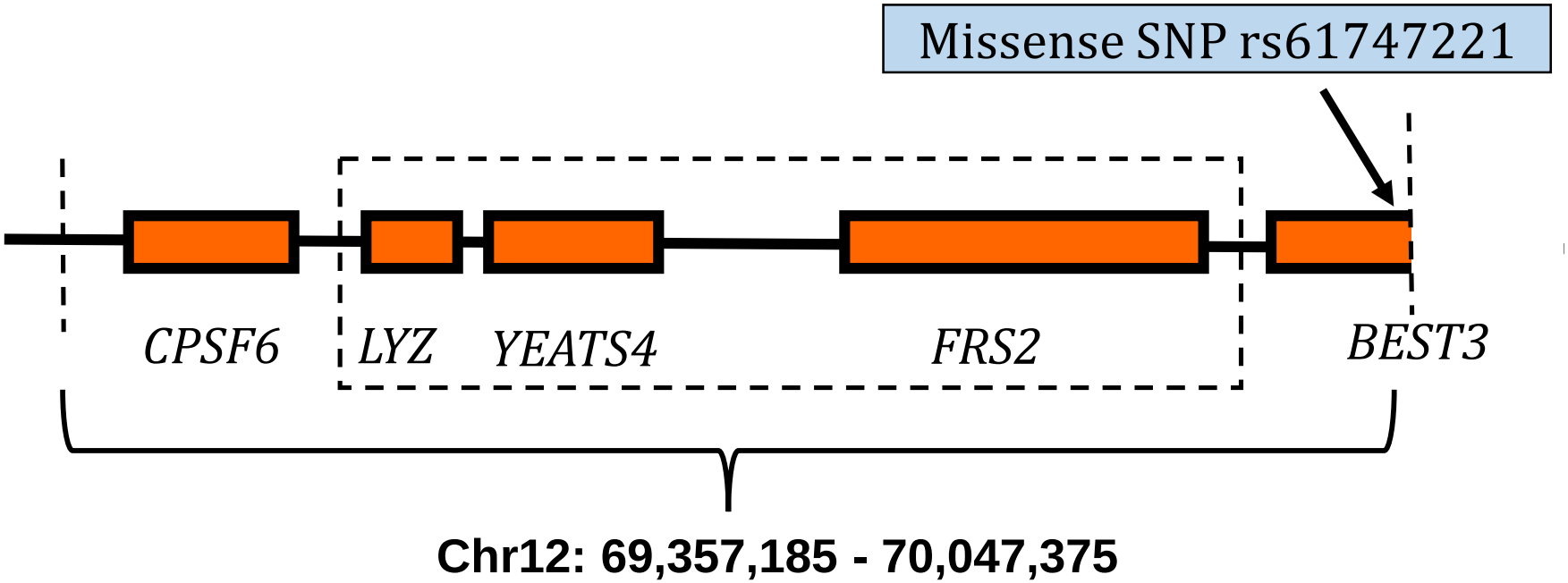
Successfully replicated in PEAR

PHASE I -> Participant Demographics

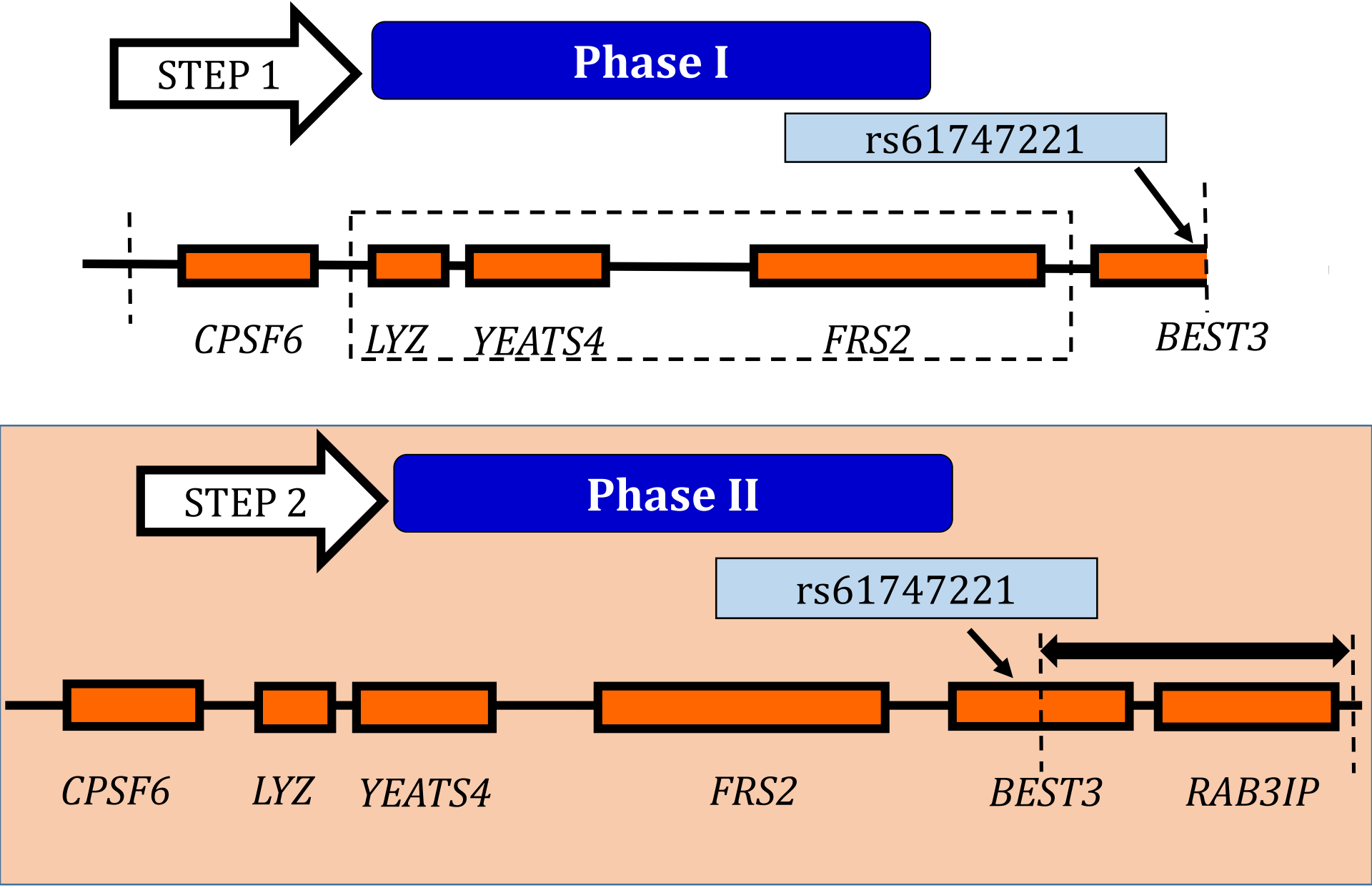
Characteristics	PHASE I (361)	
	Responder (%)	**Non-Responder (%)**
N	181(50.01)	180(49.86)
PEAR participants	97(27.14)	99(27.70)
GERA participants	84(23.26)	81(22.43)
African Americans	122(33.79)	120(33.24)
Baseline SBP (mmHg)	146.66±12.19	150.05±12.94
Baseline DBP (mmHg)	95.76±5.81	95.64±6.19
Post treatment SBP (mmHg)	125.06±10.54	145.67±13.53
Post treatment DBP (mmHg)	80.62±6.52	96.87±7.66
Δ SBP (mmHg)	-21.78±9.72	-3.75±10.24
Δ DBP (mmHg)	-15.04±6.04	1.14±5.59

Phase I

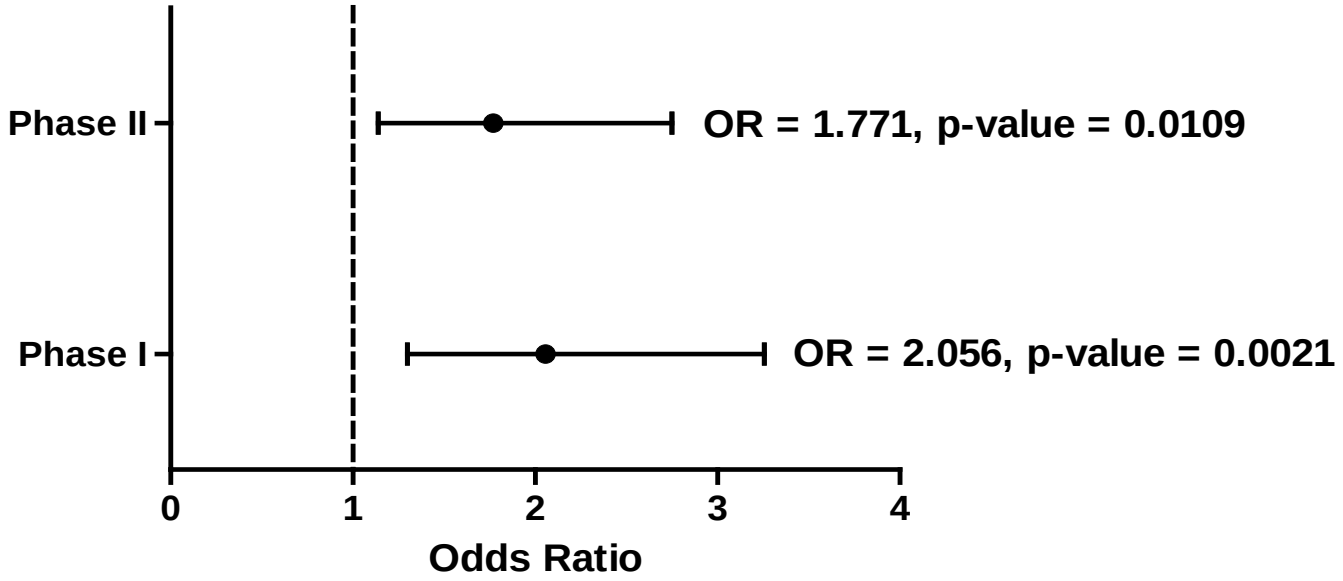
- Logistic regression was used for analysis and was adjusted for: Baseline BP, age, gender, race and principal components 1 and 2.



- **BEST3 was not annotated at the time of target selection**
- **Only a part of the BEST3 gene was captured in Phase I**



- All the participants of phase II were genotyped for rs61747221 and included in phase II data analysis analysis



Validation – Entire Cohorts of PEAR and GERA

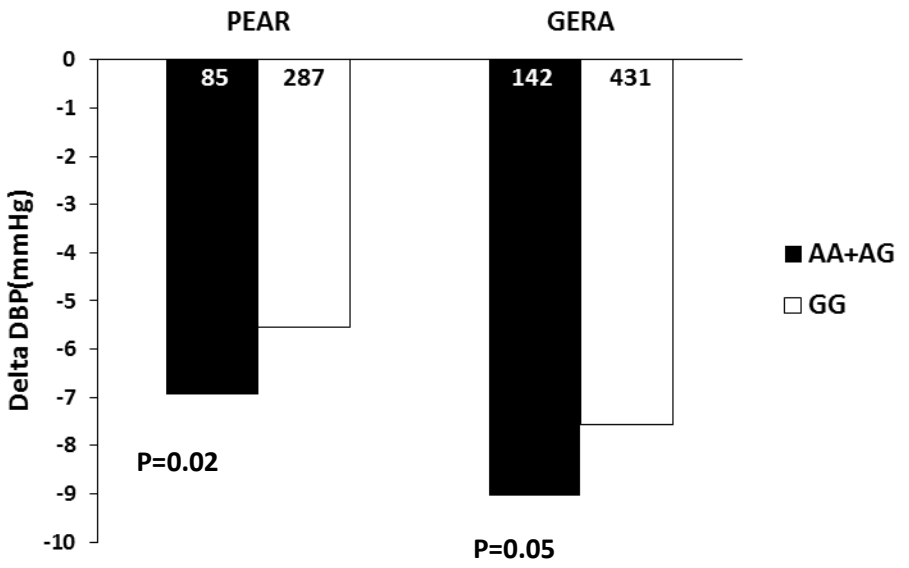
- Rs61747221 was tested for association with change in systolic (ΔSBP) and diastolic BP (ΔSBP) response post hydrochlorothiazide treatment

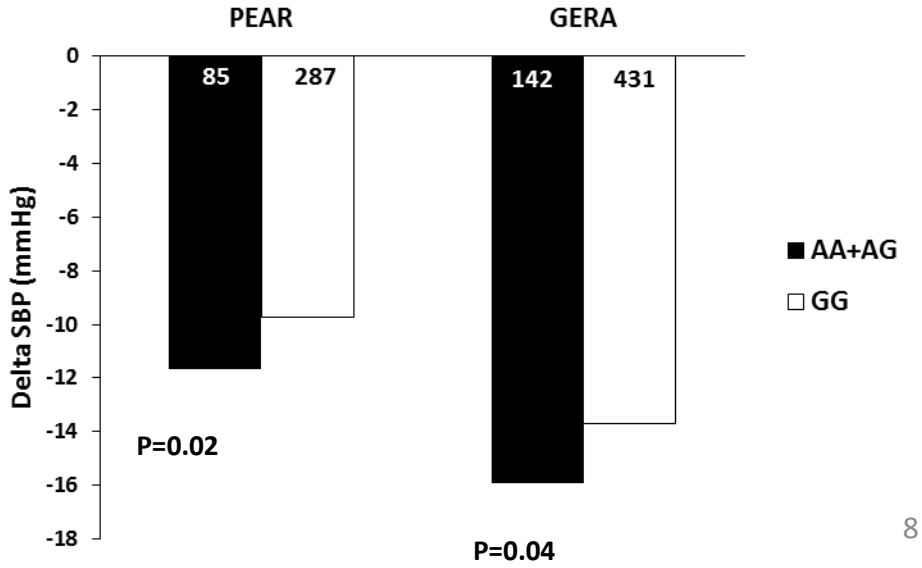
SNP	PEAR (N=370)				GERA (N=571)			
	DBP		SBP		DBP		SBP	
	P-Value	β	P-Value	β	P-Value	β	P-Value	β
rs61747221	0.023	-1.08	0.021	-1.60	0.032	-1.28	0.028	-1.95

BP Response by Genotype

Minor Allele Frequency = 0.13

- **The variant allele carriers were grouped together**
- **Association analyses using dominant model**





rs61747221

SNP	Function	Allele Change	Residue Change
rs61747221	missense	CCA → CTA	PRO → LEU

Pathogenicity Prediction using SIFT

SIFT predicted rs61747221 to have an "intolerant/damaging" effect on BEST3 protein

BEST3 gene - Biological Candidate for HCTZ BP response

- *BEST3* encodes for bestrophin3 and acts as a **calcium-activated chloride channel**
- **Essential** for the cyclic GMP-dependent **vascular smooth muscle relaxation and maintaining the vaso-motion of blood vessels**

CONCLUSION

- We identified and validated **a novel missense SNP in the *BEST3* gene** highly associated with blood pressure response to HCTZ treatment

- BEST3 is an **excellent biological candidate** for HCTZ mediated BP regulation

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PEAR
Pharmacogenomic Evaluation of Antihypertensive Responses

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