TREATMENT RESISTANT HYPERTENSION

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TRH DEFINITION

- Treatment resistant hypertension (TRH) is an extreme form of hypertension (HTN) characterized by multi-drug resistance to antihypertensive treatments
- Definition:
  - Blood pressure (BP) above goal with the use of 3 antihypertensive agents from different classes or treatment with ≥ 4 classes regardless of BP control
  - Medications should be prescribed at optimal doses
  - Ideally 1 should be a diuretic

Calhoun *et. al., Circulation* 2008

DIAGNOSIS

- Requires the exclusion of pseudoresistant HTN characterized by
  - poor blood pressure measuring technique
  - non-adherence to medication
  - inadequate dosing
  - white-coat hypertension

Calhoun *et. al., Circulation* 2008

PREVALENCE AND INCIDENCE

- We and others have estimated the prevalence of TRH to be 10-16% among persons with HTN
- Using patient data collected over a 4-year period in the Kaiser Permanente Colorado and Northern California healthcare systems, Daugherty *et. al.* reported the incidence of TRH was 1 in 50 or ~2%

Irvin *et. al.*, *JOH* 2012; Egan *et. al.*, *Circulation* 2011; Daugherty *et al.*, *Circulation* 2012

PROGNOSIS

- Cross-sectional data indicate that among those with HTN persons with TRH have increased burden of cardiovascular complications (MI, stroke, CHF, CKD) and higher 10-yr Framingham Coronary Risk score
- Few data are available on outcomes in TRH
- The study by Daugherty *et. al.* was the first to demonstrate a 50% increase in cardiovascular events (largely attributable to development of chronic kidney disease) in patients with TRH compared with patients with controlled BP on 3 medication classes

Pimenta *et. al.*, *Circulation* 2012

RISK FACTORS

- Increasing age
- Diminished kidney function
- Higher body mass index (BMI)
- Diabetes mellitus (DM)
- African American (AA) ethnicity
  - ✓ AAs are ~2 times as likely to be affected

Calhoun *et. al., Circulation* 2008

GENETIC BACKGROUND OF TRH

- Incompletely understood and largely understudied
- A handful of small candidate gene studies suggest a genetic role for TRH
- No estimates of heritability of TRH or other severe forms of hypertension are available
  - Using data from the familial Hypertension Genetic Epidemiology Network study (HyperGEN) with proband ascertainment on HTN status, we estimated sibling relative risk of aTRH to be 3.46, suggesting this extreme form of hypertension is heritable within families

Calhoun *et. al., Circulation* 2008

ADVANTAGES OF EXTREME SAMPLES IN GENOMIC STUDIES OF HTN

- Recent research suggests extreme phenotype samples such as TRH may be enriched for high impact, low-frequency variants
- Advancements in next generation sequencing (NGS) technologies enable this type of variation to be captured within clinical populations

Majewski *et. al., J Med Genet* 2011

GENOMIC TRH PROJECTS AT UAB

- Genetics of Hypertension Associated Treatment Study (GENHAT) is the largest antihypertensive pharmacogenetic study ever conducted which leverages rich clinical data collected as part of the Antihypertensive and Lipid lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
- Includes data on 13,544 African Americans (~10% with TRH at follow-up year 3)

Arnett *et. al., Pharmacogenomics J 2002*

GENOMIC TRH PROJECTS AT UAB

- GenHAT was awarded a sequencing project through the NIH Exome Project at the Broad Institute (S. Gabriel, PI).
  - Exome sequencing targets the gene coding regions of the genome
- We selected 94 extreme TRH AA individuals in GenHAT for whole exome sequencing
- These individuals were ascertained with criteria more strict than the accepted definition of TRH: still hypertensive after taking 4drugs or taking 5 or more drugs
- They represent 0.7% of the AA individuals in GenHAT

GENOMIC TRH PROJECTS AT UAB

- Frequency of single nucleotide variants (SNVs) in GenHAT TRH whole exome data was compared to a publically available database (AA exomes from NHLBI's GO Exome Sequencing Project (ESP) /ESP5400)
- In GenHAT there were an excess number of SNVs that were low frequency (1-5%) in GenHAT but rare (0%-1%) in the reference AA samples
- Those particular SNVs were enriched for missense and nonsense ones suggesting that GenHAT individuals with extreme TRH have a higher burden of functional mutations
- R01 proposal was submitted to expand this work to 700 extreme AA TRH cases and 700 treatment responsive controls from GenHAT in June 2012

CONCLUSIONS

- Genomic studies of TRH have been limited
- Small genomic studies support expansion of research to larger cohorts
- NGS studies of extreme samples like TRH hold great potential to identify low frequency, functional alleles with high clinical impact