TREATMENT RESISTANT HYPERTENSION

UAB Genomic Medicine Retreat
9/25/2012

Ryan Irvin
Assistant Professor
UAB Epidemiology
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 pseudo-resistent 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
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
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.
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
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 4 drugs 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