Blood Pressure and Hypertension Genetics

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Outline

• Blood pressure and hypertension in China
• Update on genetics of blood pressure
• BP/HTN Genetics project update
Blood Pressure and Hypertension

• Complex traits with both environmental and genetic basis

• Well known risk factor of cardiovascular events including stroke, MI and cardiovascular death

• At least 200 million hypertensive patients in China

• 60% Chinese hypertensive patients are salt sensitive type
BP Genetics: Current state of knowledge

- 29 loci for SBP, DBP and HTN discovered in study of 70,000 European ancestry individuals
- For MAP and PP additional loci identified
- Discovery of common variants in a samples of 19,600 including diverse East Asian ancestry, ~6,000 Chinese from Beijing. 7 associations in European ancestry studies were validated; 4 new associations were found.
- Effects of environmental variables and anti-hypertensive medications are not well-assessed in other studies.
Genetics of BP and HTN in China: Opportunities

- Evaluate recent GWAS-identified loci for association in the Chinese population.
- Prospective enrollments can focus on collection of very precise phenotype data.
- BP has a strong environmental (i.e. diet) component, and defining gene-environment contributions would be unique.
- Exome sequencing (intermediate scale) and exome chip (large scale) projects are underway in non-Asian samples; PI’s are collaborating and leading projects with international consortia.
Study Questions

• Primary study question: What are the genetic determinants of BP and HTN in individuals of Chinese ancestry?

• How do these genetic determinants interact with environmental factors?

• How do genetic determinants of BP influence risk for cardiovascular events? (in collaboration with MI project)

• How do genetic determinants for BP interact with biochemical, metabolic and transcriptional regulators such as miRNA? What functional, mechanistic hypotheses can be generated and tested in the lab?
BP Project Objectives

**Hypothesis:** novel genetic loci may be identified through discovery association analyses, and determinants of BP and HTN identified in a Chinese population are likely to have a high impact on our understanding of blood pressure variation.

**Objectives:**

1. To investigate associations of previously identified variants with BP and HTN in Chinese individuals.
2. To conduct a discovery analysis for genetic factors influencing BP and HTN in Chinese individuals.
3. Collaborate with consortia investigating these traits to maximize impact
Three main choices of approach

• High-impact longer-term study
  – Likely based on sequencing as this approach will dominate genetics in a few years

• High-impact shorter-term study
  – Exome chip: variants distilled from ~12,000 samples, including 620 Asian samples (300,000 markers, ~0.5% MAF).
  – Sequencing extreme samples (strong effect alleles)

• Leverage Asian ancestry samples
  – Metabochip for fine-mapping known loci (200,000 markers)
Chip-based genotyping

- Cost-effective and high quality genotypes
- Limited to content on chip
- Platforms
  1. Genome-wide markers (~ $500/chip)
  2. Metabochip ($50/chip, 200,000 SNPs)
    - Follow-up known loci (~29 for BP); genetic variants selected from all HapMap populations, including Asian samples
    - Follow-up GWAS in Europeans
  3. Exome chip ($39/chip, early access)
    - Primarily nonsynonymous SNPs
    - Asians samples incorporated into design
Project Flowchart

Investigate the associations of variants (predominantly from studies of European ancestry individuals) with BP and HTN.

Exome Chip
Whole genome sequencing

1st +3rd Hospital cath lab (N=4000)

- Add >1000 per year

Baseline Data & Follow-up

Metabochip Testing in Chinese

- 29 BP hits from GWAS 186 loci for other traits

Association & interaction

Functional Study

Maximize the return on genotyping cost
BP/HTN Project Progress

- Application reviewed and funded by UMHS-PUHSC Joint Institute
- IRB process initiated
- Extraction of DNA from 3100 samples in cath-lab database as of August 31st
- Clinical data analysis
- Collaborations with Beijing Shijingshan Cohort, enrollment to start next month (n=5000)
- Exploring additional samples and other replication partners.
Samples

• Hospitals 1&3 cardiology database

• Beijing Shijingshan Cohort

• Additional cohorts and consortia
Cardiology Database in Hospitals 1

• Cardiac catheterization lab database
  – Enrolled from cath-lab with CAG result
  – Started from 2005
  – repeated noninvasive BP measurements
  – In-patient medical records

• Follow-up cohort
  – Enrolled from cardiovascular wards
  – Started from 2008
  – Follow-up every 3 months

• Prospective continued collection
DNA Database in Hospital 1

- N= 3100, by the end of Aug 31, 2011
- Age, 63.8±10.8
Disease Proportion of DNA Database

![Pie charts showing disease proportions.](chart.png)
## HTN vs. non-HTN Groups

<table>
<thead>
<tr>
<th></th>
<th>Non-HTN (n=1355)</th>
<th>HTN (n=1745)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, blood withdraw</strong></td>
<td>63.3±11.0</td>
<td>64.1±10.7</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>944(70.9)</td>
<td>1053(60.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>388(29.1)</td>
<td>692(39.7)</td>
<td></td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no</td>
<td>842(62.1)</td>
<td>367(21.0)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>513(37.9)</td>
<td>1378(79.0)</td>
<td></td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no</td>
<td>1124(83.0)</td>
<td>1027(58.9)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>231(17.0)</td>
<td>718(41.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no</td>
<td>1155(85.2)</td>
<td>1183(67.8)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>200(14.8)</td>
<td>562(32.2)</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up Database in Hospital 1

- N= 5546, by the end of Aug 31, 2011
- Age, 66.1±12.8
DNA-Follow up Database in Hospital 1

Overlap (n=1857)

DNA
N=3100

Follow-up
N=5546

68.3%
31.7%

non-HTN
HTN
Beijing Shijingshan Cohort

- Population based cohort for ongoing vascular phenotyping studies with Hospital 1 investigators.
- 5,000 subjects aged over 40.
- Vascular measurements improve phenotype assessment of blood pressure and atherosclerosis: carotid IMT, ABI, pulse-wave velocity, central BP.
- Dietary sodium questionnaire specific for Chinese diet (pickled foods, etc.)
- Follow-up data available for cardiovascular events evaluation
Additional cohorts and consortia

• Purpose of collaborations
  – Replication partners to test associations in independent samples
  – Increase sample size through meta-analysis
  – In multi-ethnic samples, we can fine map associated loci.

• Cohorts and Consortia
  – **FEHGAS** - sequencing in European and African ancestry samples
  – **AGEN** (~6,000 people from Beijing)
  – **CHRI** - NHLBI funded study at George Institute- urine sodium, longitudinal BP before and after dietary interventions, N=5000+1400
BP/HTN Project Next Steps

- **Phase 1**: Clinical database QC and genotyping of exome chip in 5,000 samples in Beijing Shijingshan cohort.
  - (5000 samples x $59/chip) - (5000 samples x $39/chip) = $295,000 - $195,000 = $100,000 saved for genotyping
  - Finished in next July (Site for 5 month, genotyping 3 5 month)
- **Phase 2**: Additional genotyping of Asian samples (~25,000 additional possible) and *in silico* replication tests in non-Asian samples
- **Phase 3**: Meta-analysis across ethnicities and other multi-ethnic analyses for fine-mapping (team has experience and has developed methods for hematologic traits)

Perform quantitative trait association analysis for SBP, DBP, MAP and PP and dichotomous trait analysis for HTN.
  - Single marker tests
  - Multi-marker “burden tests”
Training Curriculum

• Training period 1:
  – ~3 months, at the inception of the project
  – Study design, clinical database, DNA collection and QC, project oversight

• Training period 2:
  – ~1 – 2 years, after data has been generated.
  – Genetic association analysis and next steps

• Skills
  – Study design for genetic association studies
  – Clinical database development and QC
  – DNA collection and QC
  – Genotype data calling, QC and statistical analyses
  – (Functional analysis: in vitro cell culture systems, in vivo for a select locus or few loci, integrative genomic analyses)
Training site: Ganesh Lab

• Hybrid wet + dry lab
• Human genetics of complex cardiovascular traits and disease
  – Genetic association discovery
    • Arterial remodeling in common vascular diseases: Hypertension, restenosis after PCI, atherosclerosis and pleiotropy with hematologic traits.
    • Affiliations: **CHARGE consortium** (N~30,000+ European ancestry samples for GWAS, exome and genome sequencing in Framingham, ARIC, CHS, Rotterdam, and others; leading for hematology traits and BP manuscripts); **Co-I on FEHGAS Study**; **NHLBI CARe Program** and **COGENT consortium** (N~16,000 African American samples); other multi-ethnic collaborations
  – Functional hypothesis testing (follow-up of genetic associations)
    • Integrative genomics:
    • Functional analysis of candidate genes and candidate variants in cell culture and animal models.
Trainees

• Lei Meng, M.D.

• Yang Yang, M.D.

• Postdoc for genetic analysis TBD
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