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


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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

Materson BJ. The Am J Med. 2007;120:S10-20
Materson BJ, et al. NEJM 1993;328:914-21
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
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

Hypertensive Patients

4 weeks washout

Baseline BP

Start Thiazide

8-9 weeks

PEAR: HCTZ
PEAR2: Chlorthalidone

After treatment
Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)

- **RNA sequencing** (Illumina HiSeq) in whole blood samples from 150 HTN participants
- **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 method
- **P-values** from independent studies were standardized into a distribution with mean of 0 and standard deviation of 1
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.

Results

All gene expression measurements (FPKM) > 24

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr.</th>
<th>Fold Change</th>
<th>P value</th>
<th>Fold Change</th>
<th>P value</th>
<th>Fold Change</th>
<th>P value</th>
<th>Meta-analysis</th>
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<tbody>
<tr>
<td>FOS</td>
<td>14</td>
<td>1.3</td>
<td>2.90E-03</td>
<td>1.29</td>
<td>1.15E-03</td>
<td>1.46</td>
<td>5.00E-05</td>
<td>2.08E-12</td>
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<tr>
<td>DUSP1</td>
<td>5</td>
<td>1.4</td>
<td>1.50E-04</td>
<td>1.30</td>
<td>1.35E-03</td>
<td>1.29</td>
<td>3.55E-03</td>
<td>9.50E-12</td>
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<tr>
<td>PPP1R15A</td>
<td>19</td>
<td>1.3</td>
<td>1.15E-03</td>
<td>1.19</td>
<td>3.61E-02</td>
<td>1.29</td>
<td>1.75E-03</td>
<td>3.64E-08</td>
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</tbody>
</table>

All gene expression measurements (FPKM) > 24
Fold change: responders (FPKM) / non-responders FPKM
**FOS and PPP1R15A trans eQTLs**

<table>
<thead>
<tr>
<th>SNP</th>
<th>FOS Z-score</th>
<th>P value</th>
<th>PPP1R15A Z-score</th>
<th>P value</th>
<th>A1</th>
<th>A2</th>
<th>MAF</th>
<th>HCTZ DBP response</th>
<th>SE</th>
<th>P</th>
<th>HCTZ SBP response</th>
<th>SE</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>rs11065987</td>
<td>-5.43</td>
<td>5.60E-08</td>
<td>-4.68</td>
<td>2.81E-06</td>
<td>A</td>
<td>G</td>
<td>0.54</td>
<td>-1.4</td>
<td>0.5</td>
<td>0.002926</td>
<td>-2.1</td>
<td>0.7</td>
<td>0.001788</td>
</tr>
</tbody>
</table>

*Westra et al. Nature Genetics 2013 45, 1238–43*
Discussion

- Expression of \textit{FOS}: neuronal activation of vasomotor areas
- Blockade of \textit{FOS} expression attenuates high BP in HTN induced and spontaneously HTN mice
- PPP1R15A and DUSP1: no direct evidence of involvement in HTN or thiazides BP regulation
- DUSP1 inhibits ERK signaling \textit{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)

\textit{TH}: Tyrosine Hydroxylase

*ERK: Extracellular Regulated Kinase


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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