Genomic Association Analysis Identifies Multiple Loci Influencing Antihypertensive Response to an Angiotensin II Receptor Blocker

To the Editor:

The interesting article by Turner et al.1 concerns the pharmacogenomics of the angiotensin receptor blocker Candesartan and the validation of the associated single-nucleotide polymorphisms by their opposite direction associations with blood pressure response to hydrochlorothiazide.

We are also performing a pharmacogenomic study of the angiotensin receptor blocker Losartan2 and hydrochlorothiazide in a slightly larger sample of white-only, essential hypertensives, carefully recruited and followed up by the Italian Network for Pharmacogenomics of Hypertension over several years. All patients have been genotyped within the HYPERGENES project.3 The major differences between our and Turner’s study are as follows: (1) the genotyping array: missing genotypes were obtained by imputing (imputation quality ≥ 87%); (2) we used Losartan 50 mg instead of Candesartan 16 to 32 mg, hydrochlorothiazide dose being the same (results in the Table). The major limitation of both studies is the small sample size, leading to low statistical power. Also, if the bulk of our data are still under analysis, we have not been able to reproduce Turner’s specific findings.

The present negative report is not at all against the importance of pharmacogenomics. It only poses a warning on the technical and methodological issues and indicates the absolute need of large consortia that share results to produce solid results.

Sources of Funding

This work was supported by the HYPERGENES project, grant HEALTH-2007–201550, funded by EU within the FP7 and from InterOmics PB05 (MIUR—CNR Italian Flagship Project).

Table. Data From the INPH. Genotyping Array: Illumina 1M

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>IMPUTING</th>
<th>r²</th>
<th>n</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>n</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>Frequency</th>
<th>ARB</th>
<th>HCTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13059339</td>
<td>3</td>
<td>Yes</td>
<td>0.87</td>
<td>264</td>
<td>0.1</td>
<td>0.24</td>
<td>0.625</td>
<td>364</td>
<td>−0.19</td>
<td>0.15</td>
<td>0.286</td>
<td>0.42</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>rs3758785</td>
<td>11</td>
<td>No</td>
<td>...</td>
<td>264</td>
<td>−0.22</td>
<td>0.16</td>
<td>0.265</td>
<td>364</td>
<td>−0.23</td>
<td>0.24</td>
<td>0.225</td>
<td>0.7</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>rs7113572</td>
<td>11</td>
<td>No</td>
<td>...</td>
<td>264</td>
<td>−0.22</td>
<td>0.25</td>
<td>0.481</td>
<td>364</td>
<td>−0.11</td>
<td>0.25</td>
<td>0.617</td>
<td>0.9</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>rs2113653</td>
<td>2</td>
<td>Yes</td>
<td>0.97</td>
<td>264</td>
<td>−0.099</td>
<td>0.17</td>
<td>0.607</td>
<td>364</td>
<td>−0.26</td>
<td>0.12</td>
<td>0.109</td>
<td>0.42</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>rs12313639</td>
<td>12</td>
<td>No</td>
<td>...</td>
<td>264</td>
<td>0.554</td>
<td>0.26</td>
<td>0.227</td>
<td>364</td>
<td>0.02</td>
<td>0.46</td>
<td>0.972</td>
<td>0.05</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>rs11649420</td>
<td>16</td>
<td>Yes</td>
<td>0.97</td>
<td>264</td>
<td>0.548</td>
<td>0.47</td>
<td>0.045</td>
<td>364</td>
<td>−0.19</td>
<td>0.17</td>
<td>0.356</td>
<td>0.16</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

INPH indicates Italian Network for Pharmacogenomics of Hypertension; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; SNP, single-nucleotide polymorphism; Chr, Chromosome; r² values, which indicate imputation quality, are missing for nonimputed SNPs. Data analysis as in reference 1. The first 10 principal components, age, and sex considered as covariates. To exclude any carry-over effect, only hypertensives that had been untreated for hypertension were recruited.


Disclosures

None.

Francesca Frau
Department of Health Sciences
University of Milano
Milano, Italy

Lorena Citterio
Division of Nephrology and Dialysis
San Raffaele Scientific Institute Milano
Milano, Italy

Maria Francesca Ortu
Roberta Zaninello
Hypertension and Related Diseases Centre—Azienda Ospedaliero-Universitaria
University of Sassari
Sassari, Italy


Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

(Hypertension. 2013;61:e5.)

© 2012 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPTENSIONAHA.112.201426
Genomic Association Analysis Identifies Multiple Loci Influencing Antihypertensive Response to an Angiotensin II Receptor Blocker
Francesca Frau, Lorena Citterio, Maria Francesca Ortu and Roberta Zaninello

*Hypertension*. 2013;61:e5; originally published online November 12, 2012; doi: 10.1161/HYPERTENSIONAHA.112.201426

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/1/e5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org/subscriptions/