Lack of Association Between the Type 2 Deiodinase A/G Polymorphism and Hypertensive Traits: The Framingham Heart Study

To the Editor:

Thyroxine (T4) activation to T3 via the iodothyronine deiodinase type 2 allows for changes in intracellular thyroid status in a tissue-specific manner independent of serum T3. A single nucleotide polymorphism in type 2 deiodinase (DIO2) gene (A/G) in humans, in which a threonine changes to alanine at codon 92, has been associated with decreased enzyme activity and higher insulin resistance in type 2 diabetes patients.1 Nevertheless, these findings were not replicated in larger studies.2 Recently, Gumieniak et al3 reported that the alanine allele doubles the risk for development of hypertension in euthyroid subjects. Pituitary and hypothalamic type 2 deiodinase play a critical role in feedback regulation of thyroid-stimulating hormone (TSH) secretion, and higher serum TSH concentrations have been demonstrated in euthyroid hypertensive compared with normotensive control subjects.4 In this context, we thought it would be of interest to evaluate whether the previous reported association of Thr92Ala polymorphism and hypertension is also present in a large unselected, community-based population.

The present sample size consists of 1557 individuals who had complete phenotype and genotype information available drawn from a subset of unrelated individuals from the Framingham Heart Study offspring cohort, who had DNA collected between 1995 and 1998 (n = 2933). This study was approved by the institutional review boards of Boston University and Brigham & Women’s Hospital, and written informed consent was obtained from each subject. At each examination, blood pressure was measured twice in the left arm by an examining physician using a mercury column sphygmomanometer (Korotkoff phases I and V) after the subject had been at rest in the seated position for 5 minutes. Hypertension was defined as a systolic pressure (DBP) of ≥113 mm Hg in humans, in which a threonine changes to alanine at codon 92, has been associated with decreased enzyme activity and higher insulin resistance in type 2 diabetes patients.1 Nevertheless, these findings were not replicated in larger studies.2 Recently, Gumieniak et al3 reported that the alanine allele doubles the risk for development of hypertension in euthyroid subjects. Pituitary and hypothalamic type 2 deiodinase play a critical role in feedback regulation of thyroid-stimulating hormone (TSH) secretion, and higher serum TSH concentrations have been demonstrated in euthyroid hypertensive compared with normotensive control subjects.4 In this context, we thought it would be of interest to evaluate whether the previous reported association of Thr92Ala polymorphism and hypertension is also present in a large unselected, community-based population.

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The characteristics of study participants (n = 1557; 51.7% women) are presented in the Table. SBP, DBP, and hypertension status were assessed at examination cycles 1 and 7, and long-term average SBP and DBP were calculated over off-spring exams 1 to 7. Two-hundred individuals (12.9%) were homozygous for the alanine allele, 749 (48.1%) were heterozygous, and 608 (39.1%) were homozygous for the threonine allele. The genotypes were in Hardy-Weinberg equilibrium and the frequency of the minor allele (0.37) similar to that described previously.2,5,6 There were no significant associations (Table; all P > 0.38) for SBP, DBP, or hypertension status, either at examination cycles 1 or 7. The long-term average SBP and DBP were similar among the genotypes (P = 0.84 and P = 0.98, respectively). The risk of new-onset hypertension was also similar among the genotypes (138 cases; P = 0.94).

Despite previous data from the studies suggesting an association, we failed to demonstrate any significant association between hypertensive traits with the variant allele. Association studies offer a potentially powerful approach to identify genetic variants that influence susceptibility to common diseases. Nevertheless, caution is recommended in the interpretation of positive associations, especially those performed in relatively small or selected population samples. In fact, Gumieniak et al3 mention the small number of individuals as a specific limitation of the earlier study. To minimize such effect, it has been proposed that genetic association studies should include a large number of unselected participants, such as the present study. Another potential explanation for these apparently discrepant results refers to the definition of hypertension. Our definition of hypertension coincides with the definitions used in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and all of the subjects were evaluated on their regular medications. In the study by Gumieniak et al,3 patients with severe forms of hypertension were excluded, the cutoffs for hypertension were different from the usual, and antihypertensive medications were sus-

Table. Characteristics of Individuals Who Had Complete Phenotype and DIO2 Genotype Information and P Values for Blood Pressure–Related Traits Derived From a General Genetic Model, Adjusted for Age, Sex, Cigarette Smoking, and Body Mass Index

<table>
<thead>
<tr>
<th>Characteristic or Trait Exam 1</th>
<th>P Exam 7</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>36.6±8.96</td>
<td>62.9±8.79</td>
</tr>
<tr>
<td>Body mass index, mean±SD, kg/m²</td>
<td>25.5±4.34</td>
<td>28.1±5.12</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>645 (41.5)</td>
<td>197 (12.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean±SD, mm Hg</td>
<td>121.1±14.7</td>
<td>128.4±18.63</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean±SD, mm Hg</td>
<td>77.9±9.97</td>
<td>73.7±9.78</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>264 (16.7)</td>
<td>402 (25.8)</td>
</tr>
</tbody>
</table>

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pended for 2 to 4 weeks. Of note, another study performed in a sample of 315 patients with type 2 diabetes also failed to detect an association between this DIO2 polymorphism and hypertension.\textsuperscript{5,6} The present study has several strengths. We had a 96\% and 100\% power to detect a 5- or 10-mm Hg difference of SBP between genotypes, respectively. All of the subjects were white, thus reducing the risk of false-positive or -negative associations because of stratification bias. However, we only tested the association of 1 single nucleotide polymorphism in the DIO2 gene. It is possible that additional untested variants in this gene are associated with hypertension traits. Therefore, this study cannot rule out the DIO2 gene as a susceptibility gene for hypertension. In conclusion, the DIO2 Thr92Ala polymorphism is not associated with hypertensive traits in an unselected community-based population.

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\textbf{Disclosures}

None.

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