Ala92 Type 2 Deiodinase Allele Increases Risk for the Development of Hypertension

Olga Gumieniak, Todd S. Perlstein, Jonathan S. Williams, Paul N. Hopkins, Nancy J. Brown, Benjamin A. Raby, Gordon H. Williams

Abstract—Accumulating evidence suggests that genes of the hypothalamic–pituitary–thyroid pathway influence susceptibility to hypertension. Type 2 iodothyronine deiodinase is responsible for the conversion of thyroxine to triiodothyronine for use in peripheral tissues. The present study evaluated whether a type 2 iodothyronine deiodinase nonsynonymous polymorphism, threonine 92 to alanine (Thr92Ala), is a determinant of hypertension susceptibility. A total of 372 euthyroid subjects were genotyped for Thr92Ala polymorphism using the Sequenom MassARRAY platform. Associations with hypertension and hypertension-related intermediate phenotypes were performed with generalized estimating equations. Type 2 iodothyronine deiodinase Thr92Ala allele frequencies differed significantly between hypertensive and normotensive subjects, with an excess of Ala92 carriers in hypertensive compared with normotensive subjects (64.8% versus 47.1%; \( P = 0.011 \)). Adjusted for age, gender and race, the estimated odds ratio for hypertension in Ala92 allele carriers compared with Thr92 homozygotes was 2.11 (95% CI: 1.15 to 3.89). Among euthyroid adults, the common Ala92 allele of the type 2 iodothyronine deiodinase increases risk for the development of hypertension. These data support an important role for genetic variation in the hypothalamic–pituitary–thyroid pathway in influencing susceptibility to hypertension. (Hypertension. 2007;49:461-466.)

Key Words: hypertension ■ genetics ■ genetic predisposition to disease ■ thyroid hormones ■ iodothyronine deiodinase type 2

Accumulating evidence suggests that genetic variations in the hypothalamic–pituitary–thyroid axis influence susceptibility to hypertension. In 1 animal model of essential hypertension, the spontaneously hypertensive rat, both blood pressure elevation and high-normal serum thyroid-stimulating hormone (TSH) concentrations are mediated by thyroid hormone within the euthyroid range was also associated with vascular dysfunction. Because thyroid hormone is a vasodilator, these observations suggest that the subtle variation in circulating thyroid hormone concentrations may contribute to hypertension susceptibility, or, alternatively, that high-normal TSH in hypertensive individuals may be a phenotypic marker for genetic variants affecting both blood pressure and serum TSH. The presence of familial aggregation of high-normal TSH values in hypertensive families and the influence of hypertension family history on serum TSH levels in healthy normotensive individuals provide additional support for an important role of hypothalamic–pituitary–thyroid pathway genes in blood pressure regulation through their influence on circulating and/or intracellular thyroid hormone levels or through other, currently unknown, mechanisms.

Type 2 iodothyronine deiodinase (Dio2) generates triiodothyronine (T3) for local use in tissues with some of the Dio2-generated T3 exported to the plasma. Pituitary Dio2 plays a critical role in feedback regulation of TSH secretion. A trend for an association between serum TSH and a common nonsynonymous Dio2 single nucleotide polymorphism, resulting in Thr92Ala substitution, has been observed in healthy individuals, suggesting that it may be important in regulation of circulating thyroid hormone levels. Dio2 expression in human aortic and coronary artery smooth muscle cells suggests a role in maintaining vascular tone and blood pressure.

Given the biological plausibility of Dio2 to influence blood pressure regulation, the present study evaluated whether...
Thr92Ala Dio2 is a determinant of hypertension susceptibility in a cohort of 372 generally healthy euthyroid hypertensive and normotensive individuals. As a promoter region, −221G→C polymorphism of the TRH receptor has been associated with essential hypertension, and an uncommon Asp727Glu polymorphism in the TSH receptor has been reported to influence serum TSH levels; these 2 polymorphisms were also examined. Our data suggest that the Ala92 Dio2 allele increases hypertension susceptibility.

Methods

Subjects

Included in this report are 304 hypertensive and 68 normotensive subjects who had Thr92Ala Dio2 genotypes available. Subjects in this report were studied by the Hypertensive Pathotype (HyperPath) Group, an international collaboration involving 5 participating centers: the Brigham and Women’s Hospital, University of Utah Medical Center, Vanderbilt University Hospital, Broussais (Paris, France), and University La Sapienza (Rome, Italy).

Hypertensive and normotensive subjects were recruited by advertisement from the general public and from the clinic populations. The study was conducted according to the principles of the Declaration of Helsinki and all applicable local regulations related to protection of human subjects. The institutional review boards of the respective institutions approved the study, and all of the subjects gave written informed consent before enrollment.

Hypertension was defined either as a seated diastolic blood pressure of ≥100 mm Hg off antihypertensive medications, ≥90 mm Hg while taking ≥1 medication, or treatment with ≥2 medications. Assessment was made on an unrestricted sodium diet. Subjects with hypertension requiring ≥4 medications were excluded. Siblings of hypertensive subjects were invited to participate. For siblings, hypertension was defined either as a seated diastolic blood pressure ≥90 mm Hg off antihypertensive medications, diastolic blood pressure of ≥80 mm Hg on 1 antihypertensive medication, or treatment with ≥2 agents. Normotensive subjects had a seated blood pressure ≤120/80 mm Hg and no first-degree relative diagnosed with hypertension before 60 years of age.

All of the subjects underwent a screening history, physical examination, and laboratory tests. Those with secondary forms of hypertension, diabetes mellitus, obesity (body mass index >34 kg/m²), renal insufficiency, alcohol intake >12 oz per week, or any significant medical or psychiatric illnesses were excluded. All of the antihypertensive medications were stopped 2 to 4 weeks before the study. Subjects were between 18 and 65 years of age; race was self-defined.

A total of 406 subjects had Thr92Ala Dio2 genotypes available. Twenty-one subjects with TSH values outside of laboratory reference range, 2 subjects with normal TSH values but on levothyroxine replacement therapy, 4 subjects with missing information about race, and 7 Asian subjects were excluded from all of the analyses. Therefore, 372 subjects (321 white and 51 black) were included in analyses of the association with hypertension. Of these, 242 subjects had serum TSH, 231 subjects had free thyroxine index, and 294 subjects had fasting plasma glucose and insulin values available. In analyses correlating the genotype with homeostasis model assessment (HOMA), 3 subjects with diabetes mellitus and 2 with fasting insulin levels >3 SD above the mean insulin value were excluded.

Protocol

All of the subjects underwent the following protocol, described in detail previously. Subjects consumed ≥200 mmol sodium diet as outpatients for 4 to 7 days. On the final day of the diet, subjects were admitted to the general clinical research center and remained fasting and supine overnight. All of the hemodynamic and laboratory assessments were made in the morning after overnight bed rest. Reported systolic and diastolic blood pressures are the means of 3 consecutive readings (by Dinamap, Critikon, Inc) separated by 5 minutes each, measured at bed rest in the morning. Serum TSH, T4, and thyroid hormone binding ratio assays were performed centrally at the Brigham and Women’s Hospital core laboratory as described previously. The reference range for serum TSH was 0.5 to 5.0 mIU/L. Plasma glucose and insulin were assayed as described previously.

Genotyping

The Thr92Ala polymorphism was identified from the public single nucleotide polymorphism database dbSNP (rs225014, available online at http://www.ncbi.nlm.nih.gov/projects/SNP/). Genomic DNA was extracted from stored peripheral leukocytes using standard procedures.

Genotyping using genomic DNA was performed with the SEQUENOM MassARRAY matrix-assisted laser desorption ionization-time of flight mass spectrometry platform (Sequenom). Primers were designed using a semiautomated method (SPECTRODESIGNER, Sequenom). Genotyping quality control consisted of ≥90% successful calls, confirming concordance among repeat genotyping in ~10% of genotypes and documentation of Hardy–Weinberg equilibrium.

Statistical Analysis

Statistical analyses were performed using SAS 8.2 (SAS Institute). Hardy–Weinberg equilibrium was assessed for each single nucleotide polymorphism using χ² tests. Generalized estimating equations, which can account for potential nonindependence of observations

### TABLE 1. Characteristics of Subjects With Complete Thr92Ala Dio2 Genotypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (n=372)</th>
<th>Hypertensive (n=304)</th>
<th>Normotensive (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.3±10.1</td>
<td>47.6±8.5</td>
<td>35.2±10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7±4.2</td>
<td>28.1±4.0</td>
<td>25.8±4.9</td>
<td>0.0007</td>
</tr>
<tr>
<td>High-sodium SBP, mm Hg</td>
<td>142±24</td>
<td>150±20</td>
<td>110±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High-sodium DBP, mm Hg</td>
<td>85±15</td>
<td>90±12</td>
<td>66±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, %</td>
<td>43.6</td>
<td>40.8</td>
<td>55.9</td>
<td>0.028</td>
</tr>
<tr>
<td>Black, %</td>
<td>13.7</td>
<td>12.5</td>
<td>19.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Serum FTI, μg/dL*</td>
<td>6.89±1.43 (n=231)</td>
<td>6.77±1.41 (n=189)</td>
<td>7.43±1.42 (n=42)</td>
<td>0.006</td>
</tr>
<tr>
<td>Serum TSH, mIU/L†</td>
<td>1.74±0.87 (n=242)</td>
<td>1.76±0.87 (n=198)</td>
<td>1.65±0.92 (n=44)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Plus-minus values are mean±SD. P value is for hypertensive versus normotensive subjects. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FTI, free thyroxine index.†Log-transformed values used for analyses.
among siblings, were used to evaluate the relationship between each polymorphism and hypertension and potential intermediate phenotypes, adjusting for age, gender, and race. Because free T4 measurements were not available, free thyroxine index was calculated by multiplying total T4 by thyroid hormone binding ratio. High-normal TSH was defined as serum TSH levels >2.0 mIU/L as described previously.14 HOMA of insulin resistance was calculated as [fasting plasma glucose (mmol/L) \times fasting plasma insulin (\mu U/ml)]/22.5. Natural-log transformation was applied to serum TSH, HOMA, and serum insulin values to achieve normality. All of the reported \( P \) values are based on 2-sided tests.

**Results**

Baseline characteristics of 372 subjects with complete Thr92Ala Dio2 genotypes are shown in Table 1. The mean age of subjects was 45.3±10.1 years and 43.6% were female, 13.7% were black, and 81.7% were hypertensive.

Genotype and allele frequency distributions are shown in Table 2 and in the Figure. The allele frequencies for Thr92Ala Dio2 polymorphism were similar to those reported previously.17,22 All of the distributions were in Hardy–Weinberg equilibrium.

Dio2 genotype frequencies differed significantly between hypertensive and normotensive subjects (\( P = 0.011 \)), with excess representation of Ala92 alleles among hypertensive compared with normotensive subjects (Figure, panel A). Dio2 genotype frequencies were very similar in white and black subjects (Figure, panels B and C), and the association between the Thr92Ala genotype with hypertension was not modified by race (\( P = 0.86 \) for an interaction).

Multivariable logistic regression analysis (adjusted for age, gender, and race), demonstrated that the association of the Dio2 Thr92Ala with hypertension was most consistent with a dominant genetic model: compared with Thr92 homozygotes, Ala92 heterozygote carriers and homozygotes were at higher odds of having hypertension (adjusted odds ratio: 2.11; 95% CI: 1.15 to 3.89; \( P = 0.016 \); Table 3). Of note, the dominant genetic model for Thr92Ala Dio2 is consistent with a previous report.22 Results of logistic regression analyses, stratified by race, are also shown in Table 3.

Neither the −221G→C TRH receptor nor the Asp727Glu TSHR variants were associated with hypertension or circulating thyroid hormone levels in the present study. There were no significant differences in serum TSH or free thyroxine index by Thr92Ala Dio2 genotype in all of the subjects (Table 4), with no effect modification by hypertension status (\( P = 0.91 \) for an interaction term for the effect on free thyroxine index; \( P = 0.73 \) for an interaction term for the effect on TSH). We have reported previously that high-normal TSH values, defined as serum TSH >2.0 mIU/L but \( \leq 5.0 \) mIU/L, aggregate in hypertensive families, supporting the hypothesis that high-normal TSH in hypertensive individuals may be a phenotypic marker for certain genetic variants influencing blood pressure regulation.14 We, therefore, examined whether Thr92Ala Dio2 genotype frequencies differed by high-normal versus normal TSH status. Thr92Ala genotype frequencies in hypertensive subjects with normal TSH were very similar to the overall hypertensive population (Table 5). However, representation of the Ala92 allele was numerically higher in hypertensive subjects with high-normal TSH compared with those with normal TSH, although the difference was not statistically significant (Table 5), suggesting that Thr92Ala
Dio2 may be 1 of the genetic variants affecting both serum TSH levels and blood pressure regulation, but the latter is not a consequence of altered circulating thyroid hormone levels. Thr92Ala Dio2 has been associated with insulin resistance in obese individuals. We examined the relationship between Thr92Ala Dio2 with insulin sensitivity using the HOMA index. Our results are consistent with the findings of Men-tucia et al., with the Ala92 allele being associated with insulin resistance in a dominant mode (Table 6). Our results did not achieve statistical significance, however. No effect modification by the hypertension status of the relationship between Thr92Ala Dio2 with HOMA was present (P = 0.43 for an interaction).

**Discussion**

One of the major challenges in investigating genetic determinants of essential hypertension is its heterogeneity, which results in individual hypertensive patients having unique combinations of genes contributing to their blood pressure elevation. The findings of the present study add to the body of evidence that hypothalamic–pituitary–thyroid pathway genes, specifically Dio2, are important determinants of hypertension susceptibility.

The present study demonstrated that a nonsynonymous Dio2 polymorphism, Thr92Ala, is a determinant of hypertension susceptibility with the odds of having hypertension being twice as great among the Ala92 heterozygote careers and homozygotes compared with Thr92 homozygotes. Therefore, homozygosity for the Thr92 Dio2 allele seems protective against the development of hypertension. TSHR Asp727Glu and TRH receptor −221G→C polymorphisms were not associated with hypertension in the present study.

Thyroid hormone has multiple effects on the cardiovascular system, and, of particular relevance to the pathogenesis of hypertension, both thyroxine and tri-iodothyronine are direct vasodilators. The Dio2 gene, localized on chromosome 14q24.3, is expressed in vascular smooth muscle cells suggests a role in maintaining vascular tone. There was a nonsignificant trend for an association between Thr92Ala Dio2 with serum TSH in healthy individuals, suggesting that Thr92Ala may be important in the regulation of circulating thyroid hormone levels.

Representation of the Ala92 allele was numerically higher in hypertensive subjects with high-normal TSH compared to normal TSH.

**TABLE 3. Association Between Thr92Ala Dio2 and Hypertension**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hypertensive (n, %)</th>
<th>Normotensive (n, %)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>N = 304</td>
<td>N = 68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>crude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thr/Thr</td>
<td>107 (35.2%)</td>
<td>36 (52.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Thr/Ala + Ala/Ala</td>
<td>197 (64.8%)</td>
<td>32 (47.1%)</td>
<td>1.92 (1.22 to 3.52)</td>
<td>2.11 (1.15 to 3.89)</td>
</tr>
<tr>
<td>White subjects</td>
<td>N = 266</td>
<td>N = 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>crude</td>
<td>97 (36.5)</td>
<td>29 (52.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Thr/Ala + Ala/Ala</td>
<td>169 (63.5)</td>
<td>26 (47.3)</td>
<td>1.86 (1.08 to 3.23)</td>
<td>1.79 (0.94 to 3.41)</td>
</tr>
<tr>
<td>Black subjects</td>
<td>N = 38</td>
<td>N = 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>crude</td>
<td>10 (26.3%)</td>
<td>7 (53.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Thr/Ala + Ala/Ala</td>
<td>28 (73.7%)</td>
<td>6 (46.2%)</td>
<td>2.30 (0.75 to 7.09)</td>
<td>10.1 (1.75 to 58.2)</td>
</tr>
</tbody>
</table>

*P value represents an overall significance (crude and adjusted) of the association between hypertension and Thr92Ala Dio2 genotypes for a dominant genetic model. OR indicates odds ratio.

*Analyses adjusted for age and gender in analyses in white and black subjects and for age, gender, and race in analyses in all subjects.

**TABLE 4. Association of Thr92Ala Dio2 With TSH and FTI**

<table>
<thead>
<tr>
<th>Thyroid Function Tests</th>
<th>Thr/Thr</th>
<th>Thr/Ala</th>
<th>Ala/Ala</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTI, μg/dL</td>
<td>6.97±0.11</td>
<td>6.60±0.13</td>
<td>7.00±0.26</td>
<td>0.49</td>
</tr>
<tr>
<td>(n = 85)</td>
<td>(n = 114)</td>
<td>(n = 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>1.69±0.08</td>
<td>1.75±0.09</td>
<td>1.81±0.15</td>
<td>0.78</td>
</tr>
<tr>
<td>(n = 88)</td>
<td>(n = 121)</td>
<td>(n = 33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus–minus values are mean±SEM. FTI indicates free thyroxine index.

*P value represents a significance of the differences in FTI and TSH values among Thr/Thr versus Thr/Ala + Ala/Ala Dio2 genotypes.

**TABLE 5. Thr92Ala Dio2 Genotype Frequencies in Subgroups Based on Serum TSH**

<table>
<thead>
<tr>
<th>TSH Subgroup</th>
<th>Thr/Thr</th>
<th>Thr/Ala</th>
<th>Ala/Ala</th>
<th>Thr/Ala + Ala/Ala</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives with high-normal TSH (N = 55)</td>
<td>15 (27.3%)</td>
<td>32 (58.2%)</td>
<td>8 (14.5%)</td>
<td>40 (72.7%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Hypertensives with normal TSH (N = 143)</td>
<td>49 (34.3%)</td>
<td>76 (53.1%)</td>
<td>18 (12.6%)</td>
<td>94 (65.7%)</td>
<td></td>
</tr>
</tbody>
</table>
with those with normal TSH in the present study. These data suggest that Thr92Ala Dio2 may be 1 of the genetic variants affecting both blood pressure regulation and serum TSH levels, and high-normal serum TSH levels may be a phenotypic marker of hypertension mediated by Dio2 (likely in combination with other genetic variants).

Thyroid hormone induces GLUT4 expression in skeletal muscle, where Dio2 is also expressed. Ala92 Dio2 allele carriers had lower insulin sensitivity measured by the hyperinsulinemic–euglycemic clamp technique compared with Thr92 homozygotes. Because insulin resistance is a risk factor for the development of hypertension,17–21 the Thr92Ala Dio2 relationship with insulin sensitivity was explored as a possible mechanism of its association with hypertension. Although not statistically significant, the pattern of HOMA values in Ala92 Dio2 allele carriers and Thr92 homozygotes was consistent with the previous report.22 The failure to achieve statistical significance in the present study may have been because of the lower precision of the HOMA index compared with the hyperinsulinemic–euglycemic insulin clamp technique used in the previous investigation.22

Functional significance of the Thr92Ala Dio2 variant is not known. There were no differences in T4 deiodination between COS cells expressing wild-type or Thr92Ala Dio2 in 1 study. However, it is possible that the amino acid change would affect the Dio2 activity and function, including intracellular T3 generation and TSH feedback regulation. Alternatively, Thr92Ala Dio2 may affect enzyme expression rather than activity or be in linkage disequilibrium with the causative polymorphism in the Dio2 or another gene nearby. Finally, it is possible that for the Dio2 activity to be affected, an interaction is required between Thr92Ala with 1 additional polymorphism of the Dio2 gene. Exploring Dio2 haplotypes may help clarify the relationship between Dio2 and hypertension susceptibility.

The present findings should be interpreted in the context of study design. The present study had a relatively small sample size, particularly for black subjects. Therefore, our findings should be considered preliminary and require confirmation. Free T4 and free T3 levels, which would have been more sensitive measures of evaluating the effect of Thr92Ala Dio2 on plasma thyroid hormones, were not available; and an assessment of these levels could have provided a clue to the mechanism of Thr92Ala Dio2 function. This study has tested a single polymorphism in the Dio2 gene. Therefore, further interrogation of the Dio2 gene will be critical for a detailed characterization of its association with hypertension. There were missing TSH and HOMA values in approximately one third of subjects. However, because these values were missing randomly, it is more likely to bias toward the null hypothesis and not toward a false-positive result.

Perspectives
Among euthyroid adults not on thyroid hormone replacement therapy, the common Ala92 Dio2 allele approximately doubles the risk for the development of hypertension and is associated with higher serum TSH levels and lower insulin sensitivity. Given the relatively small sample size of the study, these results should be considered preliminary and require confirmation. Overall, these data support an important role for genetic variation in the hypothalamic–pituitary–thyroid pathway in influencing susceptibility to hypertension. Further work is needed to uncover the mechanisms by which Dio2 may affect hypertension susceptibility.

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Disclosures
None.

References

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TABLE 6. Association of Thr92Ala Dio2 With HOMA, Glucose, and Insulin

<table>
<thead>
<tr>
<th>Parameters of Insulin Sensitivity</th>
<th>Thr/Thr (n = 106)</th>
<th>Thr/Ala (n = 143)</th>
<th>Ala/Ala (n = 40)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA†</td>
<td>1.89±0.10</td>
<td>2.00±0.11</td>
<td>2.58±0.29</td>
<td>0.48</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL‡</td>
<td>88±1.1</td>
<td>91±1.1</td>
<td>96±2.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Fasting plasma insulin, μU/mL†‡</td>
<td>8.7±0.4</td>
<td>8.8±0.4</td>
<td>10.7±1.1</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*P value represents a significance of the differences in mean values between Thr/Thr and Thr/Ala+ Ala/Ala Dio2 genotypes.
†Log-transformed values were used for analyses.
‡Conversion factor for Systeme International units, multiply by 0.055.
§Conversion factor for Systeme International units, multiply by 7.175.


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