Association of $\beta_2$-Adrenoceptor Gln27Glu Variant With Body Weight But Not Hypertension

Ruby C.Y. Lin, John O. Ericsson, Adam V. Benjafield, and Brian J. Morris

$\beta_2$-Adrenoceptor ($\beta_2$-ADR) mediates vasodilatation and lipolysis in response to epinephrine. A C79G (Gln27Glu) variant of $\beta_2$-ADR has shown association with overweight or obesity,2–6 elevation in systolic blood pressure (BP),7,8 and hypertension (HT).7,9 Suggestive linkage with HT exists near $\beta_2$-ADR8,10 (5q32-q34) and Gln27 is associated with lower baseline blood flow, attenuated increase in forearm blood flow in response to isoproterenol,11 and $\beta_2$-ADR downregulation.12 However, other investigators find no association13–15 or linkage16 with overweight or obesity, nor an association16 or linkage17,18 with BP, nor an association with HT16,19,20

Here we address this controversy in a cohort of white Australian patients of Anglo-Celtic origin with strong genetic predisposition to HT (two HT parents).

Methods

Subjects

Ascertainment and characteristics were as described previously.21–24

Genotyping

The genotyping was done by polymerase chain reaction-restriction fragment length polymorphism using 30 ng of genomic DNA, primers: 5’-atggggcacaacgcggagcgc-3’ and 5’-agtcacattttcataagaat-3’. 0.1 U AmpliTaqTM (Perkin-Elmer, Applied Biosystems, Norwalk, CT), followed by 1 U TseI (New England BioLabs, Beverly, MA) at 65°C for 1 h.

Statistical Analyses

$\chi^2$ and ANOVA used StatView (Abacus Concepts, Berkeley, CA). Relative risk, odds ratio,25 power,26 and Bonferroni correction27 were calculated as described.

Results

Hardy Weinberg equilibrium was observed. Gln27 frequency was similar in each group (Table 1) and did not differ between sexes. Power to detect association with HT was 72%. In overweight HT (body mass index [BMI] ≥25 kg/m²) $\beta_2$-ADR variant is associated with overweight, BMI, and hypertension. $\beta_2$-ADR variant is associated with overweight, BMI, and hypertension. $\beta_2$-ADR variant is associated with overweight, BMI, and hypertension. $\beta_2$-ADR variant is associated with overweight, BMI, and hypertension.
plasma lipids, BP, or any other parameter after Bonferroni correction.

**Discussion**

Like other researchers, we saw no association of the Gln27Glu variant with HT. Our data support, however, findings of a contribution to overweight or obesity. Discrepancies in the literature could be contributed by ethnicity. For example, the Glu27 variant confers attenuated vasodilatation in response to epinephrine agonists in African, but not in white, Americans, and could contribute to elevated mortality from HT cardiovascular disease in the former. Furthermore, the Glu27 allele is protective against vascular hyperreactivity, and correlates with lower mortality in advanced heart failure. This could explain the higher prevalence of Glu27 in whites as opposed to African Americans.

Although our data do not support a role for the Gln27Glu variant in HT, they do not exclude a role for other variants in or near ADRB2, nor involvement of Gln27Glu in other populations.

The association of Glu27 with overweight in HT is seen in different ethnic groups. Glu/Glu was associated with obesity in Swedish women, and obesity and fat distribution in Japanese; German and Austrian reports were, however, negative, as were studies of Swedish and Danish men. In a French study, Gln/Gln was associated with obesity in men. Gender-specific variations could explain discrepancies, given higher Glu27 frequency in obese Swedish women, whose genetic background should be similar to Danes. A sex-specific effect could also explain lack of association in Japanese men. Because association with overweight was confined to our HT group, HT might have to exist for an association to become apparent, and could explain disparities between studies.

β2-ADR subtypes differ in effect on fat accumulation and lipolysis. β1-ADR, like β1-ADR, is expressed primarily in subcutaneous fat, whereas β2-ADR is the major β-adrenoceptor in visceral adipose tissue. Because women tend to accumulate fat subcutaneously, whereas men do so visceraally, an alteration of the β2-ADR might be likely to affect lipolysis in subcutaneous adipose tissue of women more than men. In our study the Gln27 variant was associated with overweight in HT of both sexes. However, we did not determine fat distribution in our

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**Table 1.** Association analysis of ADRB2 variant in hypertensive versus normotensive subjects, and after subdivision into lean (BMI < 25 kg/m²) and obese (BMI ≥ 25 kg/m²) groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Genotype Frequencies</th>
<th>Allele Frequencies</th>
<th>χ²</th>
<th>P</th>
<th>C</th>
<th>G</th>
<th>χ²</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>CG</td>
<td>GG</td>
<td></td>
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<td>Frequency</td>
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<td>Frequency</td>
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<td>Frequency</td>
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</tr>
<tr>
<td>NT</td>
<td>141</td>
<td>54 (0.38)</td>
<td>55 (0.39)</td>
<td>32 (0.23)</td>
<td>1.9</td>
<td>0.39</td>
<td>163 (0.58)</td>
<td>119 (0.42)</td>
<td>0.05</td>
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<tr>
<td>HT</td>
<td>108</td>
<td>38 (0.35)</td>
<td>51 (0.47)</td>
<td>19 (0.18)</td>
<td>1.2</td>
<td>0.27</td>
<td>127 (0.59)</td>
<td>89 (0.41)</td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>43</td>
<td>22 (0.51)</td>
<td>15 (0.35)</td>
<td>6 (0.14)</td>
<td>8.1</td>
<td>0.017</td>
<td>59 (0.69)</td>
<td>27 (0.31)</td>
<td>6.4</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td>62</td>
<td>15 (0.24)</td>
<td>34 (0.55)</td>
<td>13 (0.21)</td>
<td>0.7</td>
<td>0.69</td>
<td>64 (0.51)</td>
<td>61 (0.49)</td>
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</tr>
<tr>
<td>NT BMI &lt; 25</td>
<td>46</td>
<td>16 (0.35)</td>
<td>19 (0.41)</td>
<td>11 (0.41)</td>
<td>0.7</td>
<td>0.69</td>
<td>51 (0.55)</td>
<td>41 (0.45)</td>
<td>3.3</td>
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<tr>
<td>BMI ≥ 25</td>
<td>62</td>
<td>25 (0.42)</td>
<td>24 (0.40)</td>
<td>11 (0.18)</td>
<td>0.7</td>
<td>0.69</td>
<td>74 (0.68)</td>
<td>35 (0.32)</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; NT = normotensive; HT = hypertension.

Units for BMI are kg/m². Values in parentheses are fraction of total.

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**FIG. 1.** Tracking of Glu27 allele of the Gln27Glu variant of ADRB2 with elevation in body mass index (BMI) in hypertensive patients.
subjects, so we cannot comment on genotypic effect in different adipose regions.

In conclusion, the $\beta_2$-ADR Gln27Glu polymorphism is not a risk factor for HT in our population, but is associated with overweight and increased BMI.

References


