**LETTERS TO THE EDITOR**

5' Polymorphism of the CYP17 Gene is Not Associated with Serum Testosterone Levels in Women with Polycystic Ovaries*

To the editor:

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine disorder characterized by hyperandrogenemia and is the most common cause of anovulatory infertility and hirsutism (1–3). Despite the variable clinical presentation a consistent finding is the presence of elevated serum androgens (4, 5), suggesting an underlying disorder of androgen biosynthesis in PCOS, for which there appears to be a genetic basis (6, 7).

Previous studies had suggested that there may be an abnormal regulation of the enzyme P450c17α in women presenting with PCOS. This enzyme is thought to catalyze the rate-limiting step in androgen biosynthesis in the ovaries and the adrenals and was therefore regarded as a good candidate for involvement in the etiology of PCOS (8). In a previous study, we carried out linkage analysis on the gene CYP17, coding for P450c17α, on chromosome 10q24, in twenty PCOS/male pattern baldness (MPB) pedigrees (9). Clear exclusion of this locus as a primary genetic defect in PCOS/MPB was obtained. However, sequencing analysis of the CYP17 promoter region identified a base pair change that creates an additional SPl-type promoter element. This also created an MspA1 restriction enzyme cleavage site that allowed a simple screening assay to be set up. The frequency of this variant (A2) allele was investigated in the pedigrees and in a small, case-control data-set (n = 68) comprising consecutively identified caucasians with polycystic ovaries and normal controls. Preliminary results showed an association of the A2 allele with PCOS (odds ratio = 3.57, *P* = 0.03). We proposed that this extra promoter element may up-regulate the expression of CYP17, resulting in an increased synthesis of androgens.

We have now extended our case-control data-set (n = 96) and have obtained data on total serum testosterone levels. To confirm our hypothesis we have used this data-set to examine the association of the A2 allele with serum testosterone levels. New samples were typed for the CYP17 polymorphism as described previously (9). All individuals (affected and control) were then allocated to three groups according to their genotypes, A1/A1, A1/A2, and A2/A2. Analysis of variance (ANOVA) was used to compare mean serum testosterone levels in the different groups (Fig. 1). No significant difference was found between the means of the groups (*P* = 0.82).

Consequently, we have used this extended data-set to reevaluate the association of the A2 allele with PCOS. A phase square contingency table was used to test for any significant difference between the groups. The results are summarized in Table 1. We could no longer find an association between the A2 allele and PCOS (*P* = 0.30). Previously we had found the frequency of individuals with this allele to be 74% and 38% for PCOS affected and normal control respectively, however our results in this larger series of subjects now show frequencies of 67% and 62% respectively.

The results of this follow-up study have shown that there is no significant association between CYP17 and PCOS, suggesting that this gene does not play a major role in the etiology of hyperandrogenemia. These findings are in keeping with data reported in another recent study of hyperandrogenemic women (10). The discrepancy between the previous and present results is probably due simply to the relatively small number of normal controls in the original data-set. We may therefore conclude that this base-pair change identified in the promoter region of the CYP17 gene is a common polymorphism with no obvious role in the etiology of PCOS or hyperandrogenemia.

---

*Received July 25, 1996. Address correspondence to: Neda Gharani, Department of Molecular Genetics, Imperial College School of Medicine at St. Mary's, Norfolk Place, London, England W2 1PG.*

---

**TABLE 1. Results of screening for the presence of the A2 allele**

<table>
<thead>
<tr>
<th></th>
<th>A2/A2</th>
<th>A1/A2</th>
<th>A1/A1</th>
<th>% with A2 present</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS affected</td>
<td>11</td>
<td>22</td>
<td>16</td>
<td>67%</td>
</tr>
<tr>
<td>Normal control</td>
<td>5</td>
<td>24</td>
<td>18</td>
<td>62%</td>
</tr>
</tbody>
</table>

There was no significant difference between PCOS and controls in the allelic distribution.

Neda Gharani, Dawn M. Waterworth, Robert Williamson, Stephen Franks

Imperial College School of Medicine at St. Mary’s
London W2 1PG, UK

Murdoch Institute, Royal Children’s Hospital
Melbourne, Australia (R.W.)

**References**