To the Editor:

The defective CYP21A2 (cytochrome P450, family 21, sub-family A, polypeptide 2) genes downstream of the TNXB (tenasin XB) gene in congenital adrenal hyperplasia (CAH) fall into 3 categories: (a) small-scale conversions from the CYP21A1P (cytochrome P450, family 21, subfamily A, polypeptide 1 pseudogene) gene, (b) spontaneous mutations, and (c) chimeric RCCX modules that include the chimeric CYP21A1P/CYP21A2 genes and chimeric genes of TNXA [tenasin XA (pseudogene)] and TNXB (1). Most of the CYP21A2 mutations of the 15 loci identified thus far are due to small-scale conversions from CYP21A1P during both meiosis and mitosis (2). These mutations account for approximately 70% to 80% of CAH cases. These 15 mutational loci include nucleotide (nt) −126 (C>T), nt −113 (G>A), nt −110 (T>C), nt −103 (A>G), P30L, nt 655 (A>C>G), nt 707–714del, I172N, cluster E6, V281L, F306L, L307insT, Q318X, and R356W. The chimeric CYP21A1P/CYP21A2 and TNXA/TNXB genes, which are caused by unequal crossing over (or deletions) during meiosis (2) and occur in approximately 20% of CAH alleles in most populations (1, 3) reflect, respectively, the deletion of the 1/XCYP21A1P–TNXA–RP2–C4B–1/XCYP21A2 gene array [where 1/X indicates an uncertain fraction of the gene sequence, RP2 is the retinitis pigmentosa 2 (X-linked recessive) gene, and C4B is the complement component 4B (Chido blood group) gene] (1) and a deletion of the RP2–C4B–CYP21A2–1/XTXB gene array (1).

I read with interest the recent report by Chen et al. (4), in which the authors described an analysis of the CYP21A1P/CYP21A2 chimeric gene with a 3.2-kb TaqI-produced fragment prepared from the amplification amplified with the primer pair CYP779 and Tena32F (5). Chen et al. found 2 novel phenotypes of the chimeras, which they termed “CH-8” and “CH-9.” According to the authors, CH-8 (Table 1) carried the 15 mutational loci in the defective CYP21A2 gene, but they obtained no data from an analysis of the 3’ end of the gene, owing to a lack of variants to distinguish between CYP21A2 genes (4). A report of a prior study by Lee et al. (5) pointed out, however, that the defective CYP21A2 gene is a CYP21A1P gene that carries the 15 mutational loci. When the defective CYP21A2 gene was combined with the TNXA/TNXB-1 chimeric form, which is due to a deletion of the RP2–C4B–CYP21A2–1/XTXB gene array, the allele exhibited haplotypes of C4–CYP21A1P–TNXA/TNXB (1, 5). Therefore, in my view CH-8 may be the CYP21A1P gene and should not be classified into a series of the chimeric CYP21A1P/CYP21A2 gene, because there was no further analysis of the 3’ end sequence of CYP21A1P adjacent to the downstream of the TNXA gene. The TNXA/TNXB-1 chimeric formation (1) is a product that contains CYP21A1P with the 15 mutational loci and presents the polymorphic sites in the 3’ end of CYP21A1P in nt 83479 to approximately nt 83475, which do not extend to the duplicated TNXA gene (5).

Chen et al. (4) successfully characterized 252 patients with CAH by a comprehensive molecular genetic analysis, in which the well-established CYP779/Tena32F amplicon (5) is an unequivocal strategy for detecting attenuated chimeric CYP21A1P/CYP21A2 genes and the junction site (4). I believe that a better understanding of the underlying genetic mechanisms will contribute to more-precise diagnoses. I suggest that preparing the PCR products with a full CYP21A2 gene containing the downstream sequence of the TNXB gene (5) can faultlessly and accurately detect the molecular defect in CYP21A2 gene of the RCCX module that causes the 21-hydroxylase deficiency in CAH.

Table 1. Analysis of the mutational locus in CH-8 and TNXA/TNXB-1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mutations</th>
<th>3’ End sequence</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>White and Speiser (3)</td>
<td>15 Loci</td>
<td>TNXA sequence</td>
<td>CYP21A1P</td>
</tr>
<tr>
<td>Chen et al. (4)</td>
<td>15 Loci</td>
<td>Not done</td>
<td>CH-8 (?)</td>
</tr>
<tr>
<td>Lee et al. (5)</td>
<td>15 Loci</td>
<td>TNXA sequence</td>
<td>CYP21A1P, TNXA/TNXB-1</td>
</tr>
</tbody>
</table>

* The 15 loci include nt −126 (C>T), nt −113 (G>A), nt −110 (T>C), nt −103 (A>G), P30L, nt 655 (A>C>G), nt 707–714del, I172N, cluster E6, V281L, F306L, L307insT, Q318X, and R356W.

#CH-8 Phenotype in Steroid 21-Hydroxylase Deficiency: Fact or Fancy?

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1 Human genes: CYP21A2, cytochrome P450, family 21, subfamily A, polypeptide 2; TNXB, tenasin XB; CYP21A1P, cytochrome P450, family 21, subfamily A, polypeptide 1 pseudogene; TNXA, tenasin XA (pseudogene); RP2, retinitis pigmentosa 2 (X-linked recessive); C4B, complement component 4B (Chido blood group).

2 Nonstandard abbreviations: CAH, congenital adrenal hyperplasia; nt, nucleotide(s); 1/X, uncertain fraction of the gene sequence.
tual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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