Letters to the Editor

care. We urge that in addition to correcting the lot issues it has defined, Roche reevaluate (at a minimum) subsets of the key research sample sets to ensure that: (a) there is no need to recalculate the 99th percentile value that is the cornerstone of the Universal Definition of Myocardial Infarction, and (b) the data upon which the metrics proposed for the use of this assay are correct. Such a reevaluation should be conducted immediately with appropriate clarifications, as necessary, in the journals in which the index reports were published. We strongly encourage editors of all journals to ensure that all submitted manuscripts in this area identify the lot of reagent used and that authors be able to document that the presented data reflect the reformulated, new-calibration lots.

Author Contributions: All authors confirmed they have contributed to the intellectual 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.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: F.S. Apple, Clinical Chemistry, AACC.

Consultant or Advisory Role: F.S. Apple, Instrumentation Laboratory, T2 Biosystems, and Alere; A.S. Jaffe, Beckman Coulter, Ortho Clinical Diagnostics, Alere, Abbott Laboratories, Critical Diagnostics, Amgen, and Roche.

Stock Ownership: None declared.

Honoraria: F.S. Apple, Instrumentation Laboratory, T2 Biosystems, and Beckman Coulter.

Research Funding: F.S. Apple, large majority of manufacturers of cardiac troponin assays, including Roche Diagnostics.

Expert Testimony: None declared.

Patents: None declared.

Other Remuneration: A.S. Jaffe, Radiometer.

References


Fred S. Apple1,2* Allan S. Jaffe3

1 Hennepin County Medical Center
Department of Laboratory Medicine and Pathology

2 University of Minnesota Department of Laboratory Medicine and Pathology, Minneapolis MN

3 Mayo Clinic
Rochester, MN

*Address correspondence to this author at:
Clinical Laboratories P4
Hennepin County Medical Center
701 Park Ave.
Minneapolis, MN 55415
Fax 612-904-4229
E-mail apple004@umn.edu

Previously published online at
DOI: 10.1373/chchem.2012.194985

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

To the Editor:
The defective CYP21A21 (cytochrome P450, family 21, subfamily A, polypeptide 2) genes downstream of the TNXB (tenasin XB) gene in congenital adrenal hyperplasia (CAH)2 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), nt 707–714del, 1127N, cluster E6 (1236N, V236E, and M239K), V281I, F306AL307insT, Q318X, and R356W. The chimeric CYP21A1P/CYP21A2 and TNXA/TNXB genes, which are caused due to 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 1 pseudogene (serine/threonine kinase 19) located on chromosome 6, and C4B is the complement component 4B (Chido blood group) gene] (1) and a deletion of the RP2–C4B–CYP21A2–1/XTNXB gene array (1).

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.

2 Nonstandard abbreviations: CAH, congenital adrenal hyperplasia; nt, nucleotide(s); 1/X, uncertain fraction of the gene sequence.
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 ampli-

> con 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, 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/XTNXB gene array, the allele exhibited haplotypes of C4A–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 and downstream of the TNXA gene. The TNXA/TNXB-1 chimeric for-

mation (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 83 897 to approximately nt 83 475, which do not extend to the duplicated TNXA gene (5).

Chen et al. (4) successfully characterized 252 patients with CAH by a comprehensive molecu-

lar 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.

Author Contributions: All authors confirmed they have contributed to the intellectual 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.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

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Hsien-Hsiung Lee*

School of Chinese Medicine
College of Chinese Medicine
China Medical University
Taichung, Taiwan

*Address correspondence to the author at:
School of Chinese Medicine
College of Chinese Medicine
China Medical University
91 Hsueh-Shih Rd.
Taichung 404, Taiwan
Fax +886-3-9389073
E-mail hhlee@mail.cmu.edu.tw or
lehhsienhsiu@gmail.com

Previously published online at DOI: 10.1373/clinchem.2012.190769

In Reply

In his letter, Lee questions our classification of a group of large CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) deletion alleles into a new CH-8 designation because of concern that the CH-8 group we described may be the CYP21A1P

1 Human genes: CYP21A2, cytochrome P450, family 21, subfamily A, polypeptide 2; CYP21A1P, cyto-

chrome P450, family 21, subfamily A, polypeptide 1 pseudogene; TNXB, tenasin XB; TNXA, tenasin XA (pseudogene).