Letters to the Editor

Am. J. Hum. Genet. 77:327–328, 2005

Use of the Term "Antley-Bixler Syndrome": Minimizing Confusion

To the Editor:

We read with great interest the publication by Huang et al. (2005), which made a number of significant contributions to our understanding of the biochemistry and molecular genetics of a newly described, highly variable, autosomal recessive condition referred to as "cytochrome P450 oxidoreductase (POR [MIM 124015]) deficiency." We agree with the authors that what has been termed "Antley-Bixler syndrome" (ABS [MIM 207410]) in the scientific literature is genetically heterogeneous with at least two distinct disorders, (1) ABS without disordered steroidogenesis, which appears to be a variant of the autosomal dominant fibroblast growth factor receptor (*FGFR)*–related craniosynostosis syndromes, and (2) ABS with disordered steroidogenesis, which appears to be caused by severe mutations in *POR*. However, we disagree with the authors' proposition "that the term 'ABS' be reserved for those patients with the skeletal dysmorphologic findings initially reported by Antley and Bixler (1975) but who have normal genitalia and normal steroidogenesis, and that patients with the skeletal dysmorphologic phenotype plus evidence of disordered steroidogenesis be referred to as having 'POR deficiency'" (Huang et al. 2005, p. 745).

Although the female patient first described by Antley and Bixler did not have ambiguous genitalia or any reported steroid anomalies, there are a number of reasons why these facts do not provide sufficient justification to reserve the term "ABS" for patients with *FGFR* mutations. These include:

1. To our knowledge, the patient described by Antley and Bixler (1975) has not had molecular testing for mutations in *FGFR2* or *POR*. Therefore, POR deficiency cannot be ruled out for this patient.
2. Steroid abnormalities associated with POR deficiency and ABS are not always recognized without the use of urinary steroid profiling (Shackleton et al. 2004). In fact, Huang et al. (2005) found *POR* mutations in both alleles of two female patients with ABS who were initially believed not to have steroid abnormalities when first reported by Reardon et al. (2000).
3. The presence of ambiguous genitalia is not necessary for making a diagnosis of POR deficiency. This is illustrated by the two females with ABS and normal genitalia who are reported by Huang et al. (2005) to have mutations in *POR*. In addition, we have published a family with classic ABS in which a male child had ambiguous genitalia but his sister did not (Cragun et al. 2004). Both children had evidence of abnormal steroid metabolism, and mutations in *POR* have subsequently been confirmed.

Because of similarities with respect to phenotype, molecular findings, and pattern of inheritance, patients with *FGFR* mutations should be grouped with those with the other autosomal dominant *FGFR*-related craniosynostosis syndromes. This proposal is supported by others who have questioned the diagnosis of ABS for a patient who has *FGFR2* mutations (Gorlin 1999; Gripp et al. 1999). Even Huang et al. (2005) admit that the diagnosis of ABS was reconsidered in some of the patients they report with *FGFR* mutations.

Clarifying which individuals represent classic ABS has been difficult because few pictures of patients with ABS and known *POR* or *FGFR* mutations have been published, and the clinical descriptions of these patients often lack detail. However, some subtle features—including a pear-shaped or bulbous nose, low-set and dysplastic ears, arachnodactyly, and/or rockerbottom feet—are often present in patients with ABS who are known or suspected to have POR deficiency; these features are not described in patients with known *FGFR* mutations. Interestingly, the patient reported by Antley and Bixler (1975) had a bulbous nose, low-set dysplastic ears, and arachnodactyly. In addition, that patient also had significant camptodactyly, which is described in patients who likely have POR deficiency more commonly than in those with *FGFR* mutations. Compared with cases of ABS that are suspected or known to be caused by POR deficiency, patients with *FGFR* mutations generally have more-severe proptosis and facial dysmorphism that is more similar to that of patients with Pfeiffer syndrome or Crouzon syndrome (two *FGFR*-related craniosynostosis syndromes). On the basis of this evidence, the authors' conclusion—that "aside from the genital anoma-

lies attributable to disordered steroidogenesis, no morphologic feature distinguished patients with *POR* mutations from those with *FGFR* mutations" (Huang et al. 2005, p. 736)—may not be warranted.

Continuing to use the term "ABS" for patients with *FGFR* mutations will only contribute to the confusion that is already present in the literature. The concern is that this confusion may interfere with proper patient management and counseling, both of which depend on the ability of clinicians and researchers to clearly recognize, understand, and convey to patients the differences between POR deficiency and *FGFR*-related craniosynostosis syndromes.

Use of the term "ABS" to describe patients with POR deficiency who are at the more severe end of the phenotypic spectrum can be clinically useful in distinguishing them from patients with POR deficiency who have mild or no skeletal defects (Arlt et al. 2004; Flück et al. 2004; Fukami et al. 2004). We believe it would be better to reserve the use of the term "ABS" for patients with POR deficiency and clinically significant craniosynostosis and/or radiohumoral synostosis.

DEBORAH CRAGUN[1] AND ROBERT J. HOPKIN[1,2]
[1]*Cincinnati Children's Hospital Medical Center and* [2]*University of Cincinnati, Cincinnati*

Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for POR and ABS)

References

Antley R, Bixler D (1975) Trapezoidocephaly, midfacial hypoplasia and cartilage abnormalities with multiple synostoses and skeletal fractures. Birth Defects Orig Artic Ser 11:397–401

Arlt W, Walker EA, Draper N, Ivison HE, Ride JP, Hammer F, Chalder SM, Borucka-Mankiewicz M, Hauffa BP, Malunowicz EM, Stewart PM, Shackleton CH (2004) Congenital adrenal hyperplasia caused by mutant P450 oxidoreductase and human androgen synthesis: analytical study. Lancet 363:2128–2135

Cragun DL, Trumpy SK, Shackleton CH, Kelley RI, Leslie ND, Mulrooney NP, Hopkin RJ (2004) Undetectable maternal serum uE3 and postnatal abnormal sterol and steroid metabolism in Antley-Bixler syndrome. Am J Med Genet A 129:1–7

Flück CE, Tajima T, Pandey AV, Arlt W, Okuhara K, Verge CF, Jabs EW, Mendonca BB, Fujieda K, Miller WL (2004) Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome. Nat Genet 36:228–230

Fukami M, Horikawa R, Nagai T, Tanaka T, Naiki Y, Sato N, Okuya T, Nakai H, Soneda S, Tachibana K, Matsuo N, Sato S, Hom K, Nishimura G, Hasegawa T, Ogata T (2004) Cytochrome P450 oxidoreductase gene mutations and Antley-Bixler syndrome with abnormal genitalia and/or impaired steroidogenesis: molecular and clinical studies in 10 patients. J Clin Endocrinol Metab 90:414–426

Gorlin RJ (1999) Patient described by Chun et al. may not present Antley-Bixler syndrome. Am J Med Genet 83:64

Gripp KW, Zackai EH, Cohen MM Jr (1999) Not Antley-Bixler syndrome. Am J Med Genet 83:65–68

Huang N, Pandey AV, Agrawal V, Reardon W, Lapunzina PD, Mowat D, Jabs EW, Vliet GV, Sack J, Flück CE, Miller WL (2005) Diversity and function of mutations in P450 oxidoreductase in patients with Antley-Bixler syndrome and disordered steroidogenesis. Am J Hum Genet 76:729–749

Reardon W, Smith A, Honour JW, Hindmarsh P, Das D, Rumsby G, Nelson I, Malcolm S, Ades L, Sillence D, Kumar D, DeLozier-Blanchet C, McKee S, Kelly T, McKeehan WL, Baraitser M, Winter RM (2000) Evidence for digenic inheritance in some cases of Antley-Bixler syndrome? J Med Genet 37:26–32

Shackleton C, Marcos J, Malunowicz EM, Szarras-Czapnik M, Jira P, Taylor NF, Murphy N, Crushell E, Gottschalk M, Hauffa B, Cragun DL, Hopkin RJ, Adachi M, Arlt W (2004) Biochemical diagnosis of Antley-Bixler syndrome by steroid analysis. Am J Med Genet A 128:223–231

Address for correspondence and reprints: Dr. Deborah Cragun, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, E-5, MLC 4006, Division of Human Genetics, Cincinnati, OH 45229-3039. E-mail: Deborah.cragun@cchmc.org

0002-9297/2005/7702-0015$15.00

Am. J. Hum. Genet. 77:328–330, 2005

"Antley-Bixler Syndrome"—A Reply to Cragun and Hopkin

To the Editor:

Cragun and Hopkin (2005 [in this issue]) raise a series of points concerning use of the term "Antley-Bixler syndrome" (ABS), both in our recent paper in this journal (Huang et al. 2005) and elsewhere. We agree that it is useful to minimize confusion: the best way to do this may be to discard the term "ABS" and other eponymic terms once the molecular genetics and cell biology of a disease have been worked out. However, until such eponyms are discarded, as stated in our paper, "we propose that the term 'ABS' be reserved for those patients with the skeletal dysmorphologic findings initially reported by Antley and Bixler (1975) but who have normal genitalia and normal steroidogenesis" (Huang et al. 2005, p. 745). Cragun and Hopkin suggest that "patients with *FGFR* mutations should be grouped with those with other autosomal dominant *FGFR*-related craniosynostosis syndromes." We