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.

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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)

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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

agree. Describing dysmorphologic disorders by eponyms was appropriate when the responsible genes were not known, but little purpose is served in preserving these terms once the molecular genetics and cell biology are delineated. Although one may wish to honor investigators with eponyms, such nosology inhibits understanding of mechanisms: "post-streptococcal glomerulonephritis" may be less euphonious than "Bright's disease" but is more specific and informative.

Cragun and Hopkin raise questions about the patient initially described by Antley and Bixler and about several other reported cases. Clearly, it is difficult (if not impossible) to make or exclude a diagnosis retrospectively. Lacking the individual's DNA, we cannot know the molecular lesion in the patient described by Antley and Bixler (but we'd be happy to study it!). Whereas Cragun and Hopkin lament the paucity of published photographs and clinical detail in many case reports, we lament the poor descriptions of the external genitalia and the incomplete hormonal evaluations in most patients with "ABS." Careful steroidal evaluation is crucial: mass spectrometric analysis of urinary steroids is highly reliable but not widely available; appropriate evaluation of pre- and poststimulation plasma steroids is equally reliable. The data available to Reardon et al. (2000) were insufficient to establish or exclude a steroidogenic disorder for several of their patients; hence, their report does not provide evidence for the suggestion that *POR* (P450 oxidoreductase) mutations might cause a skeletal disorder associated with normal genitalia. Thus, we believe that our conclusion that "aside from the genital anomalies attributable to disordered steroidogenesis, no dysmorphological feature distinguished patients with *POR* mutations from those with *FGFR* mutations" (Huang et al. 2005, p. 736) is well supported by the data in table 1 of Huang et al. (2005, p. 731). For convenience, we have compiled the clinical data from table 1 and the genetic data from table 4 (p. 737) in the table shown here. More-refined observations may identify other anatomic features distinguishing *POR* from *FGFR* mutations in infants with craniosynostosis; however, our data clearly show that dysmorphologists must pay very close attention to the external genitalia in these children and consider evaluation of steroid secretion before and after tropic stimulation with adrenocorticotropic hormone.

Deficient POR activity can cause a broad spectrum of human disease (Flück et al. 2004; Miller 2004; Huang et al. 2005), and clearly the patients described by us and others who have POR lesions without skeletal defects do not have ABS. Thus, we do not think it is reasonable to follow the suggestion of Cragun and Hopkin to use the term "ABS" for patients with the more severe form of POR deficiency associated with skeletal anomalies. If, as they propose (and we agree), all *FGFR*-based craniosynostosis disorders should be grouped together, then it is logical to group all *POR* disorders together. Regardless of whether the clinical genetics community agrees to discard eponyms in favor of a term such as "FGFR hyperactivity," we believe that "POR deficiency," which is a newly described monogenic disease, should be dissociated from the term "Antley-Bixler Syndrome."

Table 1

Genotype/Phenotype Correlations Collated from the Data in Tables 1 and 4 of Huang et al. (2005)

	No. of Patients with Mutation			
Genotype	1 *POR* ($n = 4$)	2 *POR* ($n = 15$)	*FGFR2* ($n = 9$)	None Found ($n = 4$)
Craniosynostosis	4/4	14/15	8/8	3/3
Brachycephaly	…	7/10	5/5	1/2
RU/RH[a] synostosis	4/4	13/15	6/7	2/3
Femoral bowing	3/3	9/13	3/6	2/2
Femoral fractures	0/1	2/10	2/3	1/2
Midface hypoplasia	2/2	9/10	8/8	2/2
Proptosis	1/1	9/11	8/9	3/3
Rocker-bottom feet	…	4/9	0/1	1/1
Arachnodactyly	2/2	7/11	0/3	1/1
Camptodactyly	…	3/6	2/5	…
Choanal atresia	1/1	7/9	7/8	3/3
Abnormal steroids	***2/2***	***8/8***	…	…
Abnormal genitalia	***2/2***	***10/10***	…	…

Note—The column designations (from table 4 of Huang et al. [2005]) indicate whether a mutation was found on only one of the two *POR* alleles (1 *POR*), both alleles (2 *POR*), on one allele of *FGFR2*, or whether no mutation was found on either gene. The clinical findings are from table 1 (Huang et al. 2005); since each finding was not commented on in all the case histories, the denominators vary. Of the findings described in the available clinical data, only the presence of an abnormality in steroidogenesis or in genital development distinguished the patients with *POR* mutations from those with *FGFR2* mutations.

[a] RH = radiohumeral; RU = radioulnar.

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0002-9297/2005/7702-0016$15.00

Am. J. Hum. Genet. 77:330–332, 2005

LRRK2 Haplotype Analyses in European and North African Families with Parkinson Disease: A Common Founder for the G2019S Mutation Dating from the 13th Century

To the Editor:

Parkinson disease [PD (MIM 168600)] is the second most common neurodegenerative disorder, characterized by resting tremor, rigidity, bradykinesia, and gait disturbances. The *LRRK2* gene (GenBank accession number AY792511) was recently identified as being responsible for autosomal dominant PD (Paisan-Ruiz et al. 2004; Zimprich et al. 2004). Several groups have reported that a single pathogenic G6055A substitution (G2019S) in the *LRRK2* gene was associated with 3%–6% and 1%–2% of familial and sporadic PD, respectively (Di Fonzo et al. 2005; Gilks et al. 2005; Kachergus et al. 2005; Lesage et al. 2005; Nichols et al. 2005). In addition, Kachergus et al. (2005) demonstrated that, in 13 families of European descent, G2019S-mutation carriers shared a small ancestral haplotype, suggestive of a common founder.

In our sample of 198 affected probands from families with PD that is compatible with autosomal dominant inheritance, mostly from France and North Africa, we identified a total of 13 *LRRK2* G2019S-mutation carriers, one of whom was homozygous for this mutation. Five were of European descent (two from France and one each from Portugal, Belgium, and The Netherlands), one was from North America, and seven were from North Africa. Surprisingly, one 60-year-old healthy French control individual also carried the same mutation.

To determine whether a common haplotype was also shared by the G2019S carriers in our series, all available family members of the 14 *LRRK2*-positive families were genotyped for the 17 chromosome 12q microsatellite markers and four SNPs, described elsewhere (Kachergus et al. 2005), that span a 16-Mb region that includes the *LRRK2* gene. Seven markers (three microsatellites and four SNPs) were located within the gene. A total of 62 individuals were analyzed: 40 G2019S carriers (23 affected and 17 unaffected) and 22 noncarriers, 2 of whom were affected. The microsatellites were genotyped by multiplexing appropriate labeled primers. The fluorescent PCR products were then pooled for analysis, in two runs, on an ABI 3730 automated sequencer. Results were analyzed with GeneMapper 3.5 software (Applied Biosystems). Two DNA samples from CEPH reference families 1331-01 and 1331-02 were used as external standards, to control for consistency between runs. The four *LRRK2* SNPs were genotyped by using the SnapShot multiplex kit (Applied Biosystems), in accordance with the manufacturer's instructions. Haplotypes were constructed using the Merlin program (Abecasis et al. 2002; Center for Statistical Genetics), and their frequencies were estimated with the expectation-maximization algorithm (Excoffier and Slatkin 1995). The difference in haplotype distribution between mutation carriers and noncarriers was evaluated by χ^2 and Fisher's exact tests. Marker-allele frequencies and marker positions were described elsewhere (Kachergus et al. 2005). The age of the mutation was evaluated by estimating the age of the most recent common ancestor of the G2019S-mutation carriers on the basis of information from their shared haplotypes (Genin et al. 2004).

The *LRRK2* haplotype that was associated with the G2019S mutation in all families originating from Europe and North Africa (fig. 1) was consistent with that described by Kachergus et al. (2005). However, the shared region was smaller than the 145–154 kb previously published, which reduces the common haplotype to only 60 kb. This minimal haplotype (T-254-A-G-A-154) consisting of six adjacent markers spanning the region between SNP *rs7966550* (Entrez SNP) in exon 22 of the *LRRK2* gene and microsatellite marker *D12S2518* in intron 45 flanking the G2019S mutation in exon 41 was determined in French family 030, in which 29 members in two generations were available for study. Parental phases could also be unambiguously determined in six other families. In the remaining families, the haplotype could not be reconstructed unambiguously from the shared region, but the genotypes were all compatible with the presence of the common haplotype. In the majority of families, the shared region extended farther than the minimal haplotype, particularly 3′ of the *LRRK2* gene, and independent of geographical origin. The common haplotype was also shared by five (24.7%) non-