

tation in the remaining group (P. Fang et al., unpublished data). Thus, the risk of recurrence in families may be as high as 50% or may be relatively low, and the two circumstances are easily distinguished if a mutation is identified. In instances where no mutation is identified but where the clinical findings are typical of AS, considerable uncertainty prevails. Recurrence of AS is uncommon in this group but does occur.

To conclude, mutation analysis of *UBE3A* can be extremely informative for establishing a diagnosis of AS and for genetic counseling. If a disease-causing mutation is identified and is present in the mother, prenatal diagnosis is readily accomplished.

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TING-FEN TSAI,¹ ANNICK RAAS-ROTHSCHILD,²
ZIVA BEN-NERIAH,² AND ARTHUR L. BEAUDET¹

¹Department of Molecular and Human Genetics, Baylor College of Medicine and Howard Hughes Medical Institute, Houston; and ²Department of Human Genetics, Hadassah University Hospital, Jerusalem

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GenBank, <http://www.ncbi.nlm.nih.gov/Web/Genbank> (for human genomic *UBE3A* sequences [AF016703–AF016708 and X98032])

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/Omim> (for AS [MIM 105830] and for *UBE3A* [601623])

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Address for correspondence and reprints: Dr. Arthur L. Beaudet, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Room T619, Houston, TX 77030. E-mail: abeaudet@bcm.tmc.edu

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Estimation of Pairwise Relationships in the Presence of Genotyping Errors

To the Editor:

Boehnke and Cox (1997) described a likelihood method for the inference of pairwise relationships from data for a genome scan. This tool is useful for verification of the relationships in a linkage study, to identify pedigree errors, which, if undetected, could reduce the power to detect genes. While they showed that the method is robust for genotyping errors when the relationships full sibs, half sibs, and unrelated are inferred, a single genotyping error will lead to zero likelihood for the relationships MZ twins and parent/offspring. A simple modification of the method eliminates this problem and thus allows the accurate inference of the relationships MZ twins and parent/offspring, even in the presence of genotyping errors.

The crucial calculation in the method of Boehnke and

Cox (1997), with regard to genotyping errors, is $P(X_k | I_k = i)$, the probability that two individuals have genotypes $X_k = (X_{k1}, X_{k2})$ at locus k , given that they share i alleles identical by descent at the locus. To simplify the notation, let $p_i(x) = P(X_k = x | I_k = i)$. When two individuals share no alleles identical by state at a locus, $p_1(x) = p_2(x) = 0$, which results in a zero likelihood for relationships such as MZ twins and parent/offspring. If we allow $p_i(x) > 0$ for all possible x , this problem is eliminated.

In the calculation of the likelihood for a putative relationship, we propose to replace the values for $p_i(x)$ used by Boehnke and Cox (1997) with the following:

$$p_0^*(x) = p_0(x) ,$$

$$p_1^*(x) = (1 - \epsilon)p_1(x) + \epsilon p_0(x) ,$$

$$p_2^*(x) = (1 - \epsilon)p_2(x) + \epsilon p_0(x) ,$$

where ϵ denotes twice the approximate genotyping error rate.

To test this idea, we performed a computer simulation. By use of the 366 autosomal markers in Weber screening set version 9 (Yuan et al. 1997), 10,000 relative pairs were simulated for each of five relationships: MZ twins, parent/offspring, full sibs, half sibs, and unrelated. The sex-averaged map locations were taken from the study by Broman et al. (1998); allele frequencies were estimated by use of eight of the CEPH families. The inter-

marker spacings were 9.4 ± 3.6 cM; the marker heterozygosities were $.78 \pm .06$. Genotypes were simulated by use of an error rate of 2%. For each relative pair, the likelihood for the five relationships were calculated by use of $\epsilon = .02, .04$, and $.08$.

For the values of ϵ considered, all five relationships were classified correctly in all 10,000 replicates. Thus, our proposal is successful in extending Boehnke and Cox's (1997) method to the inference of MZ twins and parent/offspring pairs, in the presence of genotyping errors.

KARL W. BROMAN AND JAMES L. WEBER
Marshfield Medical Research Foundation
Marshfield, WI

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Address for correspondence and reprints: Karl W. Broman, Center for Medical Genetics, Marshfield Medical Research Foundation, 1000 North Oak Avenue, Marshfield, WI 54449. E-mail: BromanK@cmg.mfldclin.edu

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