tation in the remaining group (P. Fang et al., unpublished data).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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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])

References

American Society for Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee (1996) Diagnostic testing for Prader-Willi and Angelman syndromes: report of the ASHG/ACMG test and technology transfer committee. Am J Hum Genet 58:1085–1088

Beuten J, Sutcliffe JS, Casey BM, Hennekam RCM, Willems PJ, Beaudet AL (1996) Detection of imprinting mutations in Angelman syndrome using a probe for exon α of SNRPN. Am J Med Genet 63:414–415

Buiting K, Dittrich B, Grob S, Lich C, Buchholz T, Smith E, Reis A, et al (1998) Sporadic imprinting defects in Prader-Willi syndrome and Angelman syndrome: implications for imprint-switch models, genetic counseling, and prenatal diagnosis. Am J Hum Genet 63:170–180

Kishino T, Lalande M, Wagstaff J (1997) *UBE3* A/E6-AP mutations cause Angelman syndrome. Nat Genet 15:70–73

Kubota T, Das S, Christian SL, Baylin SB, Herman JG, Ledbetter DH (1997) Methylation-specific PCR simplifies imprinting analysis. Nat Genet 16:16–17

Malzac P, Webber H, Moncla A, Graham JM, Kukolich M, Williams C, Pagon RA, et al (1998) Mutation analysis of *UBE3A* in Angelman syndrome patients. Am J Hum Genet 62:1353–1360

Matsuura T, Sutcliffe JS, Fang P, Galjaard R-J, Jiang Y-H, Benton CS, Rommens JM, et al (1997) De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (*UBE3A*) in Angelman syndrome. Nat Genet 15:74–77

Meijers-Heijboer EJ, Sandkuijl LA, Brunner HG, Smeets HJM, Hoogeboom AJM, Deelen WH, van Hemel JO, et al (1992) Linkage analysis with chromosome 15q11-13 markers shows genomic imprinting in familial Angelman syndrome. J Med Genet 29:853–857

Sutcliffe JS, Nakao M, Christian S, Orstavik KH, Tommerup N, Ledbetter DH, Beaudet AL (1994) Deletions of a differentially methylated CpG island at the *SNRPN* gene define a putative imprinting control region. Nat Genet 8:52–58

Williams CA, Angelman H, Clayton-Smith J, Driscoll DJ, Hendrickson JE, Knoll JH, Magenis RE, et al (1995) Angelman syndrome: consensus for diagnostic criteria. Am J Med Genet 56:237–238

Yamamoto Y, Huibregtse JM, Howley PM (1997) The human E6-AP gene (UBE3A) encodes three potential protein isoforms generated by differential splicing. Genomics 41: 263–266

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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 intermarker spacings were 9.4 ± 3.6 cM; the marker heterozygosities were .78 ± .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 ϵ = .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.

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References

Boehnke M, Cox NJ (1997) Accurate inference of relationships in sib-pair linkage studies. Am J Hum Genet 61:423–429

Broman KW, Murray JC, Sheffield VC, White RL, Weber JL (1998) Comprehensive human genetic maps: individual and sex-specific variation in recombination. Am J Hum Genet 63:861–869

Yuan B, Vaske D, Weber JL, Beck J, Sheffied VC (1997) Improved set of short-tandem-repeat polymorphisms for screening the human genome. Am J Hum Genet 60:459–460

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