A family study describing second cousins with cystic fibrosis and no common ancestor who is a carrier

Vicki M Park, Maureen E Smith, M Teresa Knight, Michael J Rock

Abstract

We describe an extended pedigree in which second cousins are affected with cystic fibrosis (CF). Since the degree of relationship of the affected subjects is 1/32, common descent of one CF mutation was expected when the DNA laboratory undertook mutation analysis. Mutation testing showed that each CF mutation was introduced into the family by random mating and not by descent through a common ancestor. Implications for pedigree analysis and DNA testing are discussed.

(J Med Genet 1995;32:401-402)

When more than one lineage of a family exhibits the same genetic disease, the most likely explanation is inheritance of one allele from a common ancestor. Even in disorders such as CF, where the carrier frequency is quite high (approximately 1 in 25 in white populations), cousins are most likely to be carriers by common descent. We describe a large Italian pedigree with affected second cousins that is unusual in that no common ancestor is a CF

carrier. This pedigree illustrates how expectations regarding carrier status based on pedigree analysis could potentially lead to an inaccurate assessment of carrier risk.

The affected people are two brothers (IV·1 and IV·2) and their second cousin (IV·3) (figure). There are no other affected members of the family. Twenty-two family members underwent mutation analysis over a one year period as part of an institutional research protocol. Mutation testing was performed by standard methods and included evaluation of the following mutations: $\Delta F508$, G551D, G542X, R553X, and S549N.¹⁻³ One subject (III·11) was referred to the Kleberg DNA Diagnostic Laboratory, Baylor College of Medicine, where testing for 22 mutations was performed.

The first family members tested, IV·1 and IV·2, are both homozygous for $\Delta F508$. The mother (III·2) is a $\Delta F508$ carrier, and the father (III·1) was not available for testing. III·7 and III·8, the parents of the affected cousin, were tested next. (The affected cousin, IV·3, was not referred for DNA testing). Since III·7 is the first cousin of III·2, both were expected to carry the same mutation ($\Delta F508$). Instead, III·7 was found to carry the G551D mutation,

Department of Pediatrics, University of Tennessee, Memphis, 711 Jefferson Avenue, Room 429, Memphis, TN 38163, USA

V M Park
M E Smith
M T Knight
M J Rock*

Department of Obstetrics and Gynecology, University of Tennessee, Memphis, USA
V M Park

*Present address:
Department of Pediatrics, University of Wisconsin-Madison, 600 Highland Avenue, Madison, Wisconsin 53792, USA.

Correspondence to:
Dr Park.

Received 11 November 1994
Revised version
accepted for publication
23 December 1994

Pedigree of the four generations involved in DNA testing for cystic fibrosis.

while III·8 carries $\Delta F508$. At the time, a sample swap involving specimens from III·7 and III·8 was suspected, and repeat specimens were requested. Repeat analysis of the new samples confirmed the original results.

Study of additional family members elucidated the segregation of CF mutations in this family. Brothers II·3 and II·4 presumably are not CF carriers, but both married CF carriers (II·2 and II·5 carry $\Delta F508$ and G551D, respectively). These constitute random matings, since the two women not only carry different mutations, but are of different ethnic backgrounds. CF mutations were passed along to III·2 and III·7 (parents of the affected subjects), as well as to at least one other member of each sibship. III·2 and III·7 both married $\Delta F508$ carriers. Finally, both matings resulted in the birth of offspring affected with CF.

This family illustrates an unlikely pathway of CF inheritance. The probability of III·2 and III·7 both being carriers as a result of descent of a CF mutation from a common ancestor is $1/8$ (degree of relationship of first cousins). Given that their CF mutations were not inherited by common descent, the probability of both being carriers can be calculated as follows: $1/25 \times 1/2 \times 1/25 \times 1/2 = 1/2500$, where $1/25$ is the probability of each father mating with a CF carrier and $1/2$ is the probability of a CF mutation being passed from a carrier to her offspring. Thus, the probability of first cousins being CF carriers is 312 times less likely to

arise through random matings than through common descent. In this family, assumptions based on the more likely segregation pattern could have led to inaccurate assessment of carrier status in at risk people.

It is generally agreed that people with a family history of cystic fibrosis should be offered carrier testing.⁴ However, there is no consensus CF mutation panel to be used in all carrier screening.⁵ Given the relative frequency of CF mutations in the general population, family members at risk of being carriers of a particular CF mutation need to be counselled regarding the risk that other mutations may be segregating within the family. This family study illustrates the importance of careful pedigree analysis and comprehensive mutation testing.

We acknowledge the expert technical assistance of Ms Diane Woods and Ms Jody Lerner.

- 1 Ballabio A, Gibbs R, Caskey CT. PCR test for cystic fibrosis deletion. *Nature* 1990;343:220.
- 2 Friedman KJ, Highsmith WE, Silverman LM. Detecting multiple cystic fibrosis mutations by polymerase chain reaction-mediated site directed mutagenesis. *Clin Chem* 1991; 37:753-5.
- 3 Phillips OP, Elias S, Woods D, Hanissian AS, Schoumacher RA, Bishop C. Cystic fibrosis mutations in white and black Americans: an approach to identification of unknown mutations with implications for cystic fibrosis screening. *Am J Obstet Gynecol* 1993;168:1076-82.
- 4 American Society of Human Genetics Ad Hoc Committee on Cystic Fibrosis Carrier Screening. Statement of the American Society of Human Genetics on cystic fibrosis carrier screening. *Am J Hum Genet* 1992;51:1443-4.
- 5 Gilbert F. Cystic fibrosis carrier screening: comparability of data and uniformity of testing. *Am J Hum Genet* 1994;54: 925-7.