Letters to the Editor

Am. J. Hum. Genet. 46:394–395, 1990

Is Population Screening for Cystic Fibrosis Appropriate Now?

To the Editor:

The exciting recent discovery of the gene responsible for cystic fibrosis (CF) and the molecular characterization of a common CF mutation (Kerem et al. 1989) have led, perhaps inevitably, to calls for population screening to detect carriers of this recessive gene mutation (Goodfellow 1989). Such screening, at this time, would be a mistake and a disservice to the clinical genetics community. Until assays to detect the abnormal CF protein or probes specific for all CF mutations are available, such testing would have a significant false-negative rate. The potential problems that this may cause, in counseling and medical liability, are enormous. The possibility that the public's perception, or acceptance, of genetic testing may be negatively affected by unrealistic expectations of such testing is real.

In the initial survey (Kerem et al. 1989), some 70% of CF chromosomes were found to contain a single, defined mutation. It was already known that there was significant linkage disequilibrium between CF and particular RFLPs recognized by probes tightly linked to the CF locus on chromosomes 7 (Beaudet et al. 1989). It was found by Kerem et al. (1989), that the vast majority (over 90%) of CF chromosomes containing the defined mutation, in their survey, also contained a particular pattern of RFLPs for two probes, XV-2c and KM-19. But it is clear, as well, that the percentage of CF chromosomes marked by this particular pattern of XV-2c and KM-19 RFLPs varies between racial and ethnic subpopulations and that the between-population variance can be as great or greater when CF and specific RFLPs recognized by other linked probes, such as pJ3.11 and met, are compared (Estivill et al. 1988; Cutting et al. 1989; F. Gilbert, unpublished data). This means that the 70%/30% ratio of defined to unknown mutations for CF that applies to western Europeans almost certainly does not apply to eastern or southern Europeans or to American blacks.

Therefore, carrier risk estimates, based on combinations of linkage disequilibria data for selected RFLPs and for the presence/absence of the defined mutation, that are developed for one population may not be extrapolatable to another. Counseling in advance of any such testing, then, and after the results are in can be problematic and a potential nightmare for clinical geneticists and genetic counselors. Geneticists already have experience with confusion arising from the interpretation of high and low values for maternal serum alpha-fetoprotein in screening for neural tube defects in second-trimester pregnancies. And that is in a test for which definitive follow-up studies (high-resolution ultrasound and amniocentesis) to detect affecteds are available. (No definitive test to independently confirm a predicted diagnosis of CF in a fetus or abortus is available.)

Given that there are approximately 4×10^6 pregnancies/year in the United States, that approximately 1 in 20 (Caucasian) individuals is a CF carrier, and that about 70% of all carriers can be picked up by screening for the defined mutation, this means that screening all

0002-9297/90/4602-0020$02.00

pregnancies would result in the identification, each year, of about 300,000 couples in which one or both partners is a likely CF carrier. Who will be responsible for counseling couples in advance of the testing, and who will interpret the results and discuss further testing options for such couples? Does one limit counseling post-testing to couples in which both partners are identified as carriers of the defined mutation, or should all couples in which one partner is identified as a likely carrier be offered amniocentesis for microvillar enzyme analysis (an approach to CF prenatal diagnosis with its own false-positive and false-negative rates [Mulivor et al. 1987]). Is it sufficient to screen couples for the presence/absence of the defined mutation, or should the study be extended to include probes for closely linked markers? Given that only some 70% of CF chromosomes are identifiable by assaying for the defined mutation (Kerem et al. 1989), only some 44% of CF-homozygous affecteds would be prenatally detectable using this approach (Stewart 1989). Over one-half of all CF affecteds would, therefore, be missed using this approach alone for prenatal diagnosis (adding microvillar enzyme analysis to prenatal testing would increase the detection rate of affecteds to 90% or greater). How will liability for false negatives (missed affecteds) be handled? Can the cost to patients and medical insurers for all of the testing (including amniocentesis) be justified?

The opportunity to immediately offer population screening, via probes specific for the common mutation and other linked markers, to identify a significant fraction of CF carriers and CF affecteds in utero, must be balanced against the logistical problems of the testing itself (screening millions with the gene probes, hundreds of thousands with other linked probes, and performing perhaps hundreds of thousands of amniocenteses for microvillar enzyme analysis), the complicated counseling required (for which available personnel may be insufficient), and the reality of an appreciable false-negative rate. Might not the whole cumbersome process so turn off patients and obstetricians that even when all CF mutations are characterized and the predictive accuracy of the testing approaches 100%, interest in population screening for CF will have dissipated? And a bad experience with CF testing may deter attempts in the immediate future to introduce population testing for other disorders.

It would seem most appropriate at this time to limit testing to determine CF status to those with a family history of CF (with or without a living CF-affected relative for comparison) and to the spouses of CF carriers or affecteds. It would be prudent to wait until more is known about the mutant protein, the range of mutations possible, and the new mutation rate before population screening to identify CF carriers is attempted. It is also necessary that the questions raised by the possibility of general population screening for any genetic disorder—including plans for the delivery of counseling, guidelines for counseling, quality control for testing, levels of reimbursement for testing, and medical liability—be discussed in the genetics community before that possibility becomes a reality.

FRED GILBERT

Genetics
Cornell University Medical College
New York

References

Beaudet AL, Feldman GL, Fernbach SD, Buffone GJ, O'Brien WE (1989) Linkage disequilibrium, cystic fibrosis, and genetic counseling. Am J Hum Genet 44:319–326

Cutting GR, Antonarakis SE, Buetow KH, Kasch LM, Rosenstein BJ, Kazazian HH Jr (1989) Analysis of DNA polymorphism haplotypes linked to the cystic fibrosis locus in North American black and Caucasian families supports the existence of multiple mutations of the cystic fibrosis gene. Am J Hum Genet 44:307–318

Estivill X, Farrall M, Williamson R, Ferrari M, Seia M, Guinta AM, Novelli G, et al (1988) Linkage disequilibrium between cystic fibrosis and linked DNA polymorphisms in Italian familes: a collaborative study. Am J Hum Genet 43:23–28

Goodfellow P (1989) Steady steps to the gene. Nature 341: 102–103

Kerem B-S, Rommens J, Duchanan H, Markiewicz D, Cox T, Chakravarti A, Buchwald M, et al (1989) Identification of the cystic fibrosis gene: genetic analysis. Science 245: 1073–1080

Mulivor RA, Cook D, Muller F, Boué A, Gilbert F, Menutti M, Pergament E, et al (1987) Analysis of fetal intestinal enzymes in amniotic fluid for the prenatal diagnosis of cystic fibrosis. Am J Hum Genet 40:131–146

Stewart A (1989) Screening for cystic fibrosis. Nature 341:696

Am. J. Hum. Genet. 46:395–396, 1990

Rapid Nonradioactive Detection of the Major Cystic Fibrosis Mutation

To the Editor:

The gene for cystic fibrosis (CF) has recently been