

Cystic Fibrosis Screening

Two case reports and discussion of a screening algorithm

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Objectives

Preconception and prenatal screening for cystic fibrosis (CF) was recommended in 2001 by ACOG and physicians are increasingly ordering CF testing and interpreting results. CF mutations are relatively common, with about 1 in 29 Caucasians being carriers of a CF mutation. One of the greatest challenges of CF screening is that there are over 1300 known mutations in the CFTR gene. The frequency of particular mutations varies by population, many mutations are private (unique to a single family), and new mutations continue to be identified.

CF carrier screening during the preconception and prenatal period presents exciting new opportunities and challenges for physicians and patients. This paper reviews the guidelines for screening and provides an algorithm for CF carrier screening in specific situations, utilizing two case examples that illustrate the complexities of CF screening.

Background

Cystic fibrosis (CF) is a genetic condition that results in the production of very thick mucus that disrupts the respiratory and digestive system. It can also lead to chronic infections, lung disease, pancreatic difficulties, growth problems and infertility. Most people with CF are diagnosed as infants, but a few are diagnosed much later. Some people are only mildly affected, while others have a more severe case of the disease. Currently, people with CF typically live into their mid-30s.

CF is inherited in an autosomal recessive fashion, meaning that both parents have to be carriers for a CF mutation in order to have an affected child. While the carrier rate is highest in Caucasians, a person of any ethnic group can be a carrier for CF. The only way to determine carrier status is to have carrier screening.

In 1989, the gene causing CF was cloned (CFTR, located on chromosome 7). The gene comprises 27 exons and spans more than 230 kilobases. Population-wide screening for CF was suggested based on the fact that many carriers are unaware of their status and because the carrier frequency is high enough to warrant population screening in certain ethnic groups. In addition, there are clear reproductive implications for carriers.

Cystic fibrosis screening is complicated and the results need to be carefully interpreted considering the donor's ethnicity, number of mutations screened for, and the carrier status of the partner.

Case reports

These case reports illustrate the complexities of CF screening.

Case #1 is a 28 yo G0 woman affected with CF and her husband, who are undergoing IVF with surrogacy, both whom had been inadequately screened for CF. The proband had 1 identifiable mutation on a 25 mutation panel screening. The partner had been screened with a 25 mutation panel test. Upon gene sequencing, the second mutation was found in the proband and the partner was found to have no identifiable mutation with 99% accuracy. This additional testing allowed them to move forward with a pregnancy with confidence.

Case #2 is a 45 yo G1P0T1 woman and her partner undergoing IVF. The proband has 2 brothers who were recently found to have congenital bilateral absence of the vas deferens (CBAVD). They each have one delta F508 mutation for CF. The proband had not been screened. She was screened for the F508 mutation and found to be a carrier. Her partner had been screened for the 25 common mutations and was negative. The availability of sequencing of the CF gene for the proband's partner was discussed, the couple elected this additional testing and the partner was found to be heterozygous for the deleterious mutation R1066H. Thus the couple is at 25% risk to have an affected child and can take advantage of PGD

Current CF screening

The American College of Medical Genetics recommends using a CF screening test that consists of 24 known mutations in the CF gene, including the delta F508 mutation that represents about 70% of all CF mutations. The addition of the additional 25 mutations in the panel brings the detection rate up to 90% in Caucasians of Northern European descent. The sensitivity of testing using this European descent, the sensitivity is 80% and in Ashkenazi Jews, it is 97%. In persons of African origin, the sensitivity is 69%, and in Hispanics, it is 57%. In persons of Asian origin, the sensitivity is unknown but thought to be even lower, with one pilot study identifying 49% of mutations in Asians. The conclusion regarding CF testing in any ethnic or racial group, however, is that no test will identify all carriers of CF. Although testing will allow refined risk assessment, negative test results reduce the risk but do not eliminate it. This concept is challenging to convey to patients and requires careful genetic counseling.

Sequencing of the CF gene has a sensitivity reported as 99% across ethnic groups. This testing can be useful in certain high-risk situations, such as:

- One partner is a CF carrier
- One partner is affected with CF
- One partner is non-Caucasian and is being screened for CF
- Male with CBAVD

Conclusions

The availability of professional genetic counseling and appropriate screening options can help insure that couples undergoing IVF can take full advantage, when indicated, of technologies such as PGD.

Working in partnership with a genetic counselor can benefit IVF centers and donor agencies by making sure that appropriate state-of-the-art testing is being ordered and that results are being interpreted correctly.

References

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