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Genetic screening in cystic fibrosis

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Keywords

CFTR, cystic fibrosis, genetic testing, genotype analysis, mutational analysis

Context

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane regulator (CFTR). To date, more than 800 mutations in CFTR have been described. The most commonly available commercial assay identifies less than 100 of the known CFTR mutations. When a CF patient undergoes genotype analysis, occasionally one or both of their mutations remain unidentified. As allele-specific therapeutics are developed, identification of both of an individual's mutations will increase in importance. The currently accepted standard for comprehensive screening of *CFTR* mutations is the labor-intensive denaturing gradient gel electrophoresis. The authors propose using a modified version of single strand conformation polymorphism and heteroduplex analysis (SSCP/HA) to identify mutations undetected by the commercial assay. The aims of this study are to verify the SSCP/HA detects known mutations not identified by commercial screening.

Significant findings

SSCP/HA was tested on the 20 CF alleles from 10 patients with typical CF, four of which alleles had been identified by commercial screening, and the 14 alleles from 7 patients with at least one symptom of CF but normal or borderline sweat chloride concentrations (so-called 'atypical CF'), one of which was identified by commercial screening were also identified by SSCP/HA. 11 of 16 CF alleles (69%) not identified by commercial screens were identified by SSCP/HA. Of 13 alleles from the 'atypical CF patients' not identified by commercial screen, three were found, by SSCP/HA, to be CFTR mutants. Extrapolation to the rest of the Center population indicates that commercial screening plus SSCP/HA would detect 95 % of CF alleles, similar to the more expensive and time consuming denaturing gradient get electrophoresis.

Comments

It is important to note that these results apply to this CF study center. Results may vary in other populations, especially those in which the most common mutations are not easily identified by SSCP/HA, such as mutations that lie outside the coding region. With respect to diagnosis, determination of an abnormal sweat chloride concentration remains the most cost-effective and technically simple method of demonstrating laboratory evidence of an abnormality in CFTR. As such, SSCP/HA plays little role in the routine diagnosis of CF. However, as allele-specific therapeutics become available, comprehensive screening of *CFTR* mutations, by other methods including SSCP/HA, will become more important.

Methods

Single strand conformation polymorphism and heteroduplex analysis, PCR

Additional information

References

1. Wine JJ, Kuo E, Hurlock G, Moss RB: Comprehensive mutation screening in a cystic fibrosis center. Pediatrics. 2001, 107: 280-286.