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Molecular diagnosis of cystic fibrosis in South African populations

To the Editor: Cystic fibrosis (CF) is present in all South African population groups. In a significant proportion of patients a diagnosis of CF can be confirmed by DNAanalysis and the detection of two CF transmembrane conductance regulator (CFTR) mutations, using the panels of mutations developed in this study. The index of suspicion will also be raised in patients with a single CFTR mutation. DNAtesting is important, especially in regions without access to reliable sweat tests, and should be considered an aid to diagnosis. In addition to receiving appropriate treatment, patients and their families can receive more accurate genetic counselling, CF carrier testing and prenatal diagnosis.

CF is one of the commonest autosomal recessive disorders among white South Africans, with a prevalence of 1 in 2 000; prevalence in the coloured population is 1 in 12 000.[1] CF was initially thought to be extremely rare in African blacks but a recent study showed a carrier frequency of 1 in 34 and a calculated incidence of 1 in 4 624 births.[2]

CF is characterised by pancreatic insufficiency, chronic pulmonary disease, elevated sweat chloride levels and a number of other features. It can be difficult to diagnose because of the great variability of clinical presentation and severity. The UK CF Foundation Consensus Panel suggests confirmation of diagnosis only after two positive sweat test results on separate occasions in a patient with suggestive clinical features.[3] However, as a diagnostic test the sweat test is not ideal. It requires extreme technical rigour by experienced staff using standardised methods. In large parts of South Africa such services are not readily available.

An alternative method of diagnosis became possible with the cloning of the CFTR gene.[4] CF is caused by mutations in the CFTR gene — patients have two mutations and carriers have one. Over 1 000 mutations have been identified.[5] Patients may have two identical mutations (homozygotes) or two different mutations (compound heterozygotes), but the identification of two CF mutations in a patient confirms the diagnosis of CF.

Given the number of CF-causing mutations and the impracticality of screening the large CFTR gene, testing for mutations that are common in a particular population makes genetic testing useful as a diagnostic tool. The aim of this study was to improve the sensitivity and efficiency of diagnostic genetic testing for CF in South Africa through the development of customised panels of mutations for different South African population groups. Atotal of 201 white, 43 coloured and 14 black CF patients with confirmed diagnoses were included in this project for CFTR mutation analysis.

White and coloured patients were tested for 24 mutations including △F508, 394delTT, Q493X, 3272-26A → G, 3120+1G→ A, R117H, 3659delC, G542X, G551D, R553X, 621+1G → T, W1282X, N1303K, 1717-1G → A, R1162X, R334W, 3849+10kbC → T, A455E, 2183AA → G, 1078delT, △I507, R347P, S1251N, and E60X. Five coloured patients in whom small amounts of DNA were available from buccal scrapes were only tested for the △F508 mutation. Black patients were initially tested for the 3120 +1G →A mutation. Those black patients whose mutations were still unidentified were tested for the △F508 mutation. Mutation detection assays have been described previously.[6]

Significant differences in the CFTR mutation distribution were found between groups, supporting the notion that population-specific panels of mutations are required when using genetic tests to diagnose CF (Table I). Sixteen mutations were detected in the South African white population, accounting for 91% of all CFTR mutations in this population. In the coloured population, the △F508 and 3120+1G→Amutations occur at appreciable frequencies and account for 74.4 % (64/86) of mutations. In the black population, 60.7% of mutations (17/28) were identified,

Table I. Frequency of common CFTR mutations in cystic fibrosis patients from different South African population groups

Mutation	White (*N* = 201)*	Coloured (*N* = 43)*	Black (*N* = 14)*
△F508	0.76	0.500	-
3272-26A → G	0.040	0.012	-
3120+1G → A	0.005	0.174	0.464
394delTT	0.037	-	-
G542X	0.017	0.023	-
R553X	0.01	-	-
W1282X	0.01	-	-
N1303K	0.01	-	-
G551D	0.008	0.023	-
R117H	0.0025	-	-
Q493X	0.0025	-	-
S549N	0.0025	-	-
621+1G → T	0.0025	-	-
1717-1G → A	0.0025	-	-
2789+5G → A	0.0025	-	-
3659delC	0.0025	-	-
R1162X	-	0.012	-
G1249E†	-	-	0.036
3196del54†	-	-	0.036
-94G → T†	-	-	0.036
2183delAA†	-	-	0.036
Unknown	0.086	0.256	0.393
Total mutation detection	0.910	0.744	0.607

* *N* = number of patients studied.
† These patients were reported previously. [5,6]
- = not observed.

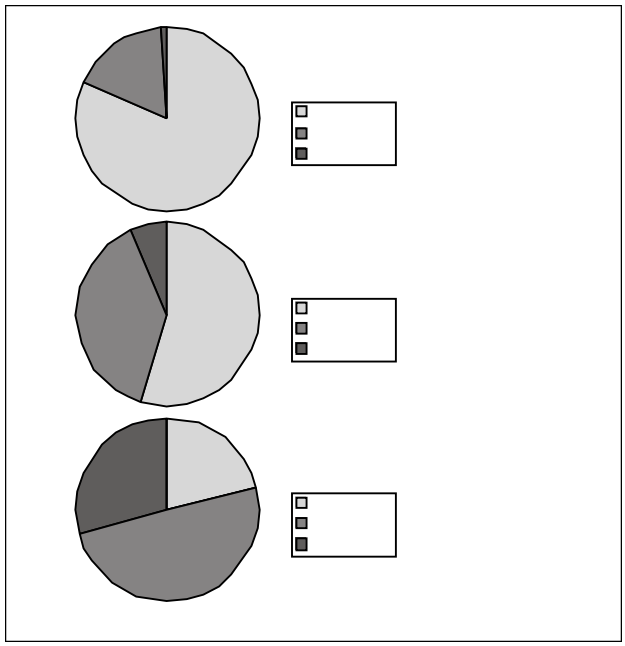

Fig. 1. Pie charts illustrating the proportion of South African CF patients who can be diagnosed by DNA analysis when testing for the common mutations included in the diagnostic panels. (a) white CFTR mutation panel: 15 mutations (91% mutation detection); (b) coloured CFTR mutation panel: 16 mutations (74% mutation detection); (c) black CFTR mutation panel: 3120+1G → A (46% mutation detection). M= mutation identified; U= mutation unknown; M/M = two identified CFTR mutations; M/U = one identified CFTR mutation; U/U = no identified CFTR mutations.

including five different mutations. The most common mutation is 3120+1G→A, which occurs at a frequency of 46% (13/28). Four patients were homozygous for this mutation. Four other mutations (each on a single chromosome) have been identified.[6]

Fig. 1 shows the breakdown of the expected proportion of CFTR genotypes after testing a suspected CF patient using customised panels of mutations developed in this project. In the white population, 83% of CF patients will have two identifiable mutations (M/M) confirming a diagnosis of CF. Similarly, after DNA analysis alone, 55% of coloured but only 21% of black CF patients can be definitively diagnosed as having CF. The remaining CF patients will have either one identified mutation (M/U) or no identified mutations (U/U). In black CF patients, 71% will show at least one 3120+1G → Amutation after DNAanalysis, thus assisting the clinician in making a diagnosis. Confirmation of the diagnosis in such patients will only be possible with clear clinical features and/or two positive sweat tests.

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