CFTR structural rearrangements are not a major mutational mechanism in black and coloured southern African patients with cystic fibrosis

Candice Lee De Carvalho, Michele Ramsay

To the Editor: Exon copy number variants (CNVs) in the CFTR gene have been identified as a new type of mutation in cystic fibrosis (CF) patients.[1] Most of these mutations have been identified in CF patients of European origin; however, a deletion of the promoter and exons 1 and 2 of the CFTR gene was detected in two African American families.[2]

To increase the CFTR mutation detection rate in black and coloured South African CF patients for molecular diagnosis, we tested patients with a clinical phenotype of CF, and at least one unidentified CFTR mutation, for exon CNVs in the CFTR gene: 24 coloured patients (of Khoisan, Malay, European and African admixture), most of whom originate from the Western Cape, and 18 black patients (sub-Saharan African origin) were tested. Multiplex ligation-dependent probe amplification (MLPA) that detects deletions and duplications based on the principles of complementary probe binding, ligation and amplification with a comparison of patient data to control data, was used (CFTR P091 kit).[3] Controls were matched for ethnicity and geographical region of origin.

A heterozygous deletion of exon 2 was detected in a single black CF patient, using both MLPA and semi-quantitative fluorescent PCR. The deletion breakpoints were determined as c.54-1161_c.164+1603del2875 and a mutation mechanism was suggested based on a small direct repeat at the 5′ and 3′ breakpoints.[4] This mutation causes the deletion of amino acids 91 to 163, corresponding to the deletion of the first two transmembrane regions, two cytoplasmic topological domains and one extracellular topological domain of the chloride channel (http://www.expasy.org, http://www.genet.sickkids.on.ca/cftr/). The anticipated consequence would be complete loss of function. This patient had one positive sweat test and other symptoms suggestive of CF, including respiratory failure. He has since been lost to follow-up.

This mutation was not detected in any of the other patients, and may be unique to this family. No other CNVs were detected. It would therefore not be cost effective to include it in the diagnostic panel of mutations in black and coloured patients with symptoms suggestive of CF. Although the sample size was small, this report suggests that exon copy number variants of CFTR is not a major mutational mechanism giving rise to CF in black and coloured southern African CF patients.

Conflict of interest. The authors declare that there are no sources of conflict of interest to the above research.

Ethnic classification. The rationale for ethnic classification is that the study was done specifically to identify mutations in ethnic groups in which CFTR mutation detection in South Africa is low.

Division of Human Genetics, National Health Laboratory Service and School of Pathology, Johannesburg
Candice Lee De Carvalho, BSc (Agric), MSc
Michele Ramsay, PhD

Corresponding author: *C L De Carvalho (candiceleedc@gmail.com)*

References

1. Férec C, Casals T, Chuzhanova N, *et al*. Gross genomic rearrangements involving deletions in the CFTR gene: characterization of six new events from a large cohort of hitherto unidentified cystic fibrosis chromosomes and meta-analysis of the underlying mechanisms. *EJHG* 2006; 14(5): 567-576.
2. Hantash FM, Redman JB, Goos D, *et al*. Characterization of a recurrent novel large duplication in the cystic fibrosis transmembrane conductance regulator gene. *JMD* 2007; 9(4): 556-560.
3. Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens, F, Pals G. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *NAR* 2002; 30(12): e57.
4. des Georges M, Guittard C, Templin C, *et al*. WGA allows the molecular characterization of a novel large CFTR rearrangement in a black South African cystic fibrosis patient. *JMD* 2008; 10(6): 544-548.

Accepted 1 July 2009.