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CF-like lung disease associated with CFTR splicing variant

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Keywords

Cystic fibrosis, gene splicing, lung disease

Context

It is known that cystic fibrosis (CF) is caused by mutations in the gene CFTR. The level of CFTR protein normally required in each tissue necessarily affects the influence of CFTR mutations on that tissue (sweat glands, lung, pancreas, intestine, vas deferens). A functionally low level of CFTR protein may also arise due to alternative splicing of the CFTR transcript, and this has usually been seen in combination with CFTR mutations. One well characterised splice site in CFTR is in intron 8 (IVS8). The 9T allele of this intron results in the most efficient splicing, and the 5T and 7T variants result in a lower than normal level of full-length CFTR mRNA and presumably a decrease in mature, functional CFTR protein. The aim of this study was to investigate the CFTR genotype and CF characteristics of two patients with a history of idiopathic lung disease.

Significant findings

Two female patients presented with a history of lung disease. Full sequencing of the CFTR gene revealed one patient to be 5T/5T and the other to be ?F508/5T. The authors concluded: variations in the IVS8 polythymidine tract alone, with the added influence of the TG12 repeat sequence and the M470V polymorphism, are associated with defective CFTR function in sweat glands and airway epithelia, and late onset lung disease resembling that seen in CF.

Comments

This is the first report of CF-like lung disease associated with abnormal splicing of an unmutated CFTR gene. CF-like lung disease has been reported in patients that have only one mutant copy of CFTR whereas this report focusses on the influence of abnormal splicing. Since this study determined the level of CFTR in tissues usually affected by a CFTR mutation, it will help to characterise tissue CFTR dependency.

Methods

Sweat testing, DNA sequencing, RT-PCR

Additional information

References

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