

## **Association of polymorphism gene with clinical variability in cystic fibrosis patients**

Cystic fibrosis (CF) is an inherited disease, caused by a dysfunction (mutation) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This disease affects a numerous organs particularly the lungs and digestive system. CF is characterized by abnormalities affecting certain glands (exocrine) of the body especially those that produce mucus, saliva and sweat. There is a high degree of variability in the clinical manifestations of this disease. The severity of CF is not entirely explained by the CFTR genotype. In fact, besides the possible influence of the environment, other genes than CFTR gene (modifiers genes) can modulate clinical expression in CF patients. Among candidate modifiers gene TGFB1 (transforming growth factor b1) can be considered as a possible modulator of the clinical expression in CF patients. TGFB1 gene is located in the chromosome 19q13, and contains in the promoter region a polymorphism (sequence variation): -509C/T. The current study was undertaken to examine, for the first time in our population, a possible association between the -509C/T polymorphism of TGFB1 gene and phenotypic variability in CF. One hundred and eleven Tunisian CF patients (aged between 3 days to 29 years with a median of 5 months) and 100 Control subjects with mean age  $75.00 \pm 12.00$  months were studied. The sweat test is the standard diagnostic test for CF; it is an accurate, safe, and painless way to diagnose CF. This test is based on measuring the amount of chloride in the sweat and contains three phases: stimulation of the sweat glands by a pilocarpine solution; followed by the collection of the sweat and finally the determination of chloride concentration. Sweat chloride results are classified as normal (chloride levels less than 40mmol/L), intermediate (chloride levels between 40–59mmol/L), or abnormal (chloride levels > 60 mmol/L). This method is considered to be the most accurate method to diagnose CF. The -509C/T genotypes were performed by restriction fragment length polymorphism analysis (RFLP-PCR) method. Statistical analysis was performed using version 20.0 of the Statistical Package for the Social Science software: SPSS (SPSS Inc., Chicago, Illinois, USA).

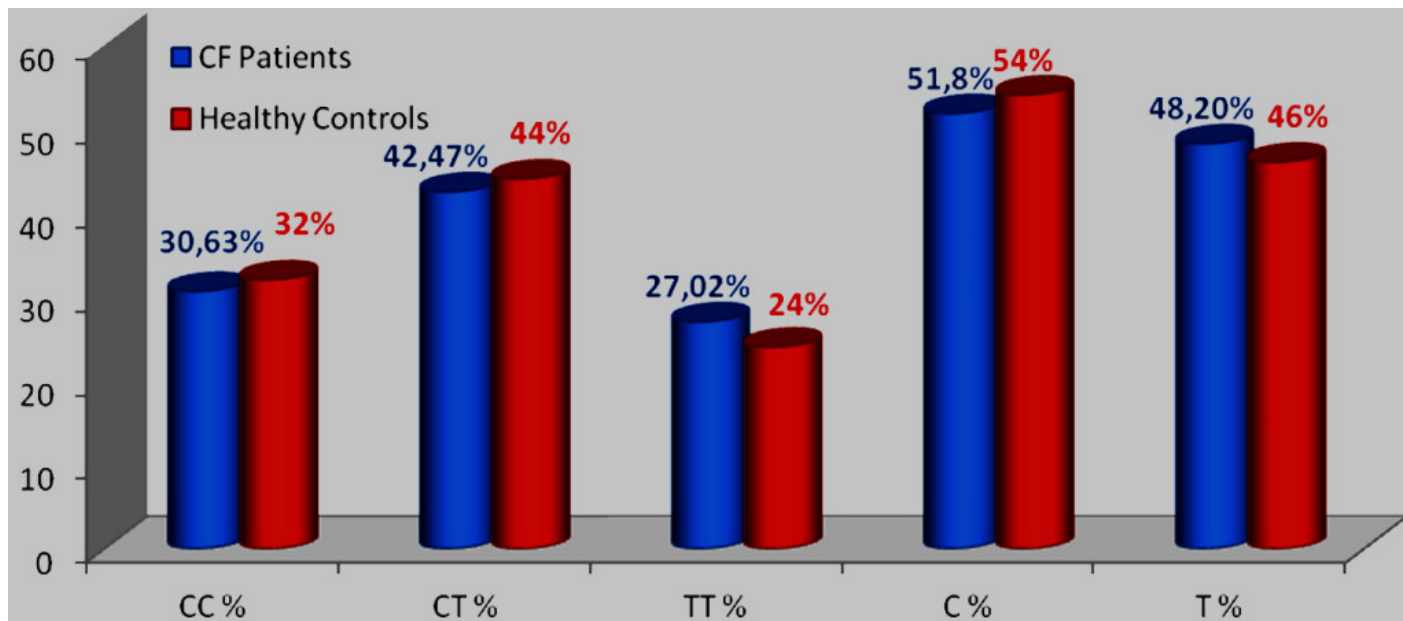


Fig. 1. Genotype and allele frequencies of the TGFB1 -509C/T polymorphism in CF patients and healthy controls.

The distribution of the TGFB1 -509C/T polymorphism was in Hardy-Weinberg equilibrium in both groups ( $\chi^2=2.566$ ,  $P=0.109$  in CF patients and  $\chi^2=1.307$ ,  $P=0.22$  in control). No significant difference in genotypes and alleles frequencies between the two groups was observed with respectively ( $\chi^2=0.253$ ,  $p=0.881$ ) and ( $\chi^2=0.204$ ,  $p=0.651$ ) (Fig. 1.).

In our work, we noted that patients with TT genotype were associated with an early inflammation and deterioration of lung disease with  $p=0.02$ , OR [CI 95%]=5.465 [1.748-17.088]). These data would be explained by an increase gene expression, TGFB1 secretion and circulating levels of TGFB1 protein. In fact, polymorphism at -509 position was found to be differentially related to transcriptional activity of TGFB1 and TGFB1 plasma concentration. Digestive symptoms, pancreatic insufficiency, meconium ileus and onset of manifestations seem not be modulated by the -509C/T polymorphism ( $p=0.944$ ,  $p=0.760$ ,  $p=0.262$ ,  $p=0.076$  respectively). Our results are in accordance with those found in other populations where studies characterized the -509C/T polymorphism as a potential factor in the severity of CF clinical expression. This association was not found in the sub-groups of patients with the most frequent mutation F508del at homozygous state ( $p=0.145$ ).

On the basis of the results of the present study and also of previous ones, the TGFB1 -509C/T gene polymorphism seems to be a modulate factor of CF lung disease expression. Further works are required to study the involvement of other polymorphisms located in TGFB1 gene, such as codon 10 and codon 25, as well as other genes in the clinical variability of CF patients.

## Publication

[Association of TGFB1 -509C/T polymorphism gene with clinical variability in cystic fibrosis patients: A case-control study.](#)

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*Pathol Biol (Paris)*. 2015 Sep