# Salt balance via CFTR and evolution of *CFTR gene* in Japanese

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Summary

Chronic pancreatitis is regarded as non-classic form of cystic fibrosis (CF). In order to understand the genetic background for chronic pancreatitis in Japanese, we examined twenty common CF-causing mutations in Europeans, nine CF-causing mutations in Japanese, and three polymorphisms (poly T, TG repeats, and M470V) of the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene in 65 patients with chronic pancreatitis (51 alcoholic and 14 idiopathic) and 162 normal subjects. None of the 29 CF-causing mutations were detected. The 7T was the most common (97.5%) haplotype and hence the 7T/7T was a dominant genotype in Japanese. Compared with Caucasians, the 5T and 9T were very rare. 6T was found in 4 normal subjects. The (TG)11 and (TG)12 were dominant haplotypes in Japanese and the ratio was roughly 1:1. Frequencies of the (TG)11/11 (24%), (TG)11/12 (53%), and (TG)12/12 (21%) in normal subjects were significantly ($p=0.044$) different from alcoholic and idiopathic pancreatitis. The ratio of methionine (M-type) and valine (V-type) at position 470 in exon 10 was 2:3 in normal subjects. Genotype analysis revealed two major haplotypes, the (TG)12-M470 (31%) and (TG)11-V470 (51%); the former expresses a smaller amount of intact CFTR proteins and the latter produces proteins with lower intrinsic activity. Hence, CFTR function predicted from the genotypes in the majority of Japanese (97%) is lower (53~75%) than that in Caucasians with the wild type *CFTR* gene. Both secretory diarrhea caused by the activation of the CFTR $Cl^-$ channel and sweat fluid and electrolytes loss caused by the warm and humid climate of Japan might have acted as selective pressure on the *CFTR* gene. Eight patients (12.1%) had Q1352 H (1.9% in control) and three (4.6%) had R1453W (1.9% in control). Association of a mild form of mutation, such as Q1352H, may further reduce CFTR function by as much as 75%. These genetic backgrounds probably explain the association of CFTR dysfunction and chronic pancreatitis in Japan where CF is very rare.