CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated?

In chronic pancreatitis (CP), alterations in several genes have so far been described, but only small cohorts have been extensively investigated for all predisposing genes. 660 patients with idiopathic or hereditary CP and up to 1758 controls were enrolled. PRSS1, SPINK1 and CTRC were analysed by DNA sequencing, and cystic fibrosis transmembrane conductance regulator (CFTR) by melting curve analysis. Frequencies of CFTR variants p.R75Q, p.I148T, 5T-allele and p.E528E were comparable in patients and controls. We identified 103 CFTR variants, which represents a 2.7-fold risk increase (p<0.0001). Severe cystic fibrosis (CF)-causing variants increased the risk of developing CP 2.9-fold, and mild CF-causing variants 4.5-fold (p<0.0001 for both). Combined CF-causing variants increased CP risk 3.4-fold (p<0.0001), while non-CF-causing variants displayed a 1.5-fold over-representation in patients (p=0.14). CFTR compound heterozygous status with variant classes CF-causing severe and mild represented an OR of 16.1 (p<0.0001). Notably, only 9/660 (1.4%) patients were compound heterozygotes in this category. Trans-heterozygosity increased CP risk, with an OR of 38.7, with 43/660 (6.5%) patients and 3/1667 (0.2%)
controls being trans-heterozygous (p<0.0001). Accumulation of CFTR variants in CP is less
pronounced than reported previously, with ORs between 2.7 and 4.5. Only CF-causing variants
reached statistical significance. Compound and trans-heterozygosity is an overt risk factor for the
development of CP, but the number of CFTR compound heterozygotes in particular is rather low. In
summary, the study demonstrates the complexity of genetic interactions in CP and a minor influence
of CFTR alterations in CP development.