It is now generally believed that pancreatitis results from pancreatic autodigestion. An inappropriate conversion of pancreatic zymogens to active enzymes within the pancreatic parenchyma is thought to initiate the inflammatory process. A key role has been attributed to the activation of trypsinogen to trypsin, converting all proteolytic proenzymes to their active form. Several gain-of-function mutations in the cationic trypsinogen gene (PRSS1) have been identified in patients with chronic pancreatitis (CP). These mutations lead to enhanced intrapancræatic trypsinogen activation. In contrast, a variant in the anionic trypsinogen (PRSS2) gene, p.G191R, has been described that mitigates intrapancræatic trypsin activity and thereby plays a protective role. Beside trypsinogen mutations, loss-of-function variants in SPINK1, encoding a pancreatic trypsin inhibitor, are strongly associated with idiopathic CP. Approximately 15–40% of patients with so-called idiopathic CP carry p.N34S on one allele or on both alleles. Chymotrypsin C (CTRC) degrades all human trypsin isoforms with high specificity. Two CTRC alterations, p.R254W and p.K247_R254del, are significantly associated with idiopathic as well as alcohol-related CP. Functional analysis of the variants revealed impaired activity and/or reduced secretion. Thus, loss-of-function mutations in CTRC predispose to pancreatitis by diminishing its protective trypsin-degrading activity. Albeit the association between CFTR, the gene mutated in cystic fibrosis, and idiopathic CP is now well established, the pathogenic mechanisms are poorly understood.
Nearly 25–30% of patients carry at least one CFTR mutation, but few patients only were compound-heterozygous. Several patients, however, are trans-heterozygous for a CFTR alteration and a PRSS1, SPINK1, or CTRC variant, respectively.