Hereditary pancreatitis is caused by mutations in human cationic trypsinogen (PRSS1) which lead to increased autoactivation by altering chymotrypsin C (CTRC)-dependent trypsinogen activation and degradation. Exceptions are some cysteine mutations which cause misfolding, intracellular retention and endoplasmic reticulum stress. Clinical relevance of many PRSS1 variants found in patients with sporadic chronic pancreatitis is unknown but often assumed by analogy with known disease-causing mutations. Functional comparison of PRSS1 variants found in sporadic and hereditary cases is needed to resolve this dilemma. Here, we investigated the functional phenotype of 13 published PRSS1 variants with respect to autoactivation in the presence of CTRC and cellular secretion. Only mutation p.D100H increased trypsinogen autoactivation, but this gain in function was offset by a marked reduction in secretion. Five mutants (p.P36R, p.G83E, p.I88N, p.V123M, p.S124F) showed decreased autoactivation due to increased degradation by CTRC. Five mutants exhibited strongly (p.D100H, p.C139F) or moderately (p.K92N, p.S124F, p.G208A) reduced secretion, whereas mutant p.K170E showed slightly increased secretion. Mutant p.I88N was also secreted to higher levels but was rapidly degraded by CTRC. Finally, three mutants (p.Q98K, p.T137M, p.S181G) had no phenotypic alterations relative to wild-type trypsinogen. Rare PRSS1
variants found in sporadic chronic pancreatitis do not stimulate autoactivation but may cause increased degradation, impaired secretion or no functional change. Variants with reduced secretion are likely pathogenic due to mutation-induced misfolding and consequent endoplasmic reticulum stress.