Supplementary Methods

Study Subjects

All 1112 Chinese ICP patients were of Han origin. A clinical diagnosis of chronic pancreatitis was based on two or more of the following criteria as previously described [Zou et al., 2016]: (i) presence of a typical history of recurrent pancreatitis; (ii) radiological findings such as pancreatic calcification and/or pancreatic irregularities revealed by endoscopic retrograde pancreatography or by magnetic resonance imaging of the pancreas; and (iii) pathological sonographic findings. ICP was defined as having neither reported family history of the disease nor recognized precipitating factors such as alcohol abuse, trauma, medication, infection and metabolic disorders.

Cell Culture and Transfection

HEK 293T cells (GenHunter, Nashville, TN) were cultured in 6-well tissue culture plates at a density of 1.5×10^6 cells per well, in Dulbecco's Modified Eagle Medium (DMEM) (Life Technologies, Grand Island, NY) supplemented with 10% fetal bovine serum, 4 mM glutamine and 1% penicillin/streptomycin at 37°C. Transfections were performed with 4 µg plasmid DNA and 10 µL Lipofectamine 2000 (Life Technologies) in 2 mL DMEM medium. After overnight incubation, the transfection medium was removed, cells were rinsed and covered with 2 mL OptiMEM reduced serum medium (Life Technologies). Conditioned medium was harvested 48 hours after the addition of OptiMEM.

Measurement of Procarboxypeptidase Secretion

Protein levels of CPA1 zymogen in the conditioned medium were measured by SDS-PAGE, Coomassie staining and densitometry. An aliquot (200 µL) of the medium was precipitated with 10% trichloroacetic acid (final concentration), the precipitate was recovered by centrifugation, dissolved in 20 µL Laemmli sample buffer containing 100 mM DTT, and heat-denatured at 95°C for 5 min. Samples were electrophoresed on 15% SDS-polyacrylamide mini gels and proteins were stained with Coomassie Blue (Brilliant Blue R-250). Quantitation of bands was carried out with the GelDocXR+ gel documentation system and Image Lab 3.0 software (Bio-Rad, Hercules, CA).

Measurement of CPA1 Activity

CPA1 zymogen was activated with 100 nM human cationic trypsin and 50 nM human CTRC, for 1 h at 37°C. The 40 µL activation mixture contained 20 µL conditioned medium, 0.1 M Tris-HCl (pH 8.0), 1 mM $CaCl_2$, and 0.05% Tween 20 (final concentrations). Carboxypeptidase activity was then measured by adding 50 µL assay buffer (0.1 M Tris-HCl (pH 8.0), 1 mM $CaCl_2$, 0.05% Tween 20) and 10 µL of 600 µM N-[4-methoxyphenylazoformyl]-L-phenylalanine substrate to the activation mix (100 µL final volume, 60 µM final substrate concentration). The decrease in absorbance was followed at 350 nm for 2 min. Rates of substrate cleavage were calculated from fits to the initial linear portion of the curves and were expressed as percent of the wild-type rate.

Exon 1

Exon1_F CGGTCCTGGGAGGGTTTAAAA
Exon1_R TCTGTCTGTCTCCTCTACTGGTTG

ccttctccgctacccagtgggcaaacagaaccgcagctttagggtgtgggcaggcagagtcctggctgggactccaggaggcctcgagcccc
cgctgaccctcaggccccgctggccccagatggtcgggggtggagctctggcttatctctccagctgcccagttccctgccactttatcatggag
ggtgagagggtgtcagagctcAGAACTCCCACCCCAGCCTCCCCGTGGGACAGGACCCAGGTGCTGGGG
GAGAACAGACCTCGGGAGCAGCCAGGAGTCCT**CGGTCCTGGGAGGGTTTAAAAG**CCAGGGGG
CCGTCTCGACCTCAGTCTGACCTTCCCTCCCGGCAGCAGCATGCGGGGGTTGCTGGTGTTGAGT
GTCCTGTTGGGGGCTGTCTTTGGCAAGGAGGACTTTGTGGGGTAGGGATGTGGAGAGGAGGGG
GTGCCCTCTGAGGGTGATGGGGAGGACTCAGCCCC**CAACCAGTAGAGGAGACAGACAGA**CAG
ATACATGGCAACACAGCCAGAGAGGATGGCCTGGCACCACCTGGGACAGCTGGCAGATAAGCAA
CCAGGGTTGGGAAGAGGTTGTGTCTCCCAAGACAGTCTCCTGAGCCCTGGAGAAACCTGAGCTC
TGAGGAGGAGTTTTCAGGAGAGGAGAAAGGAGGA

Exon 2

Exon2_1_F ACAGCGTCTAGAAGTTTCTAAAGATGG
Exon2_1_R AGCTCCTTCACCTTCTGTACCT
Exon2_2_F CAGGTGCTCCGAATCTCTGTAG
Exon2_2_R AGAGTCAATTCCATGTCTCCTTGTTG

GGCCTGGCTGGCTTGGAACAGAGAAATAGTCCAAACTGGGATTGAGATAGTA**ACAGCGTCTAGA**
AGTTTCTAAAGATGGGGAGAGAAGAGGTGAGGGAGCCCAGGCCTCTCCTTGTTGAGACCCTTG
GTGCTGTCCCCTGCCCAGCCCAGAGGACGAGGCCCAGTCTGGGGATTCTGGGCTGCTGCCTCC
CTCCTGCACCTGGGGAGTGCTTGTGGCCAGGGCAGGTGCAGCTTGGGTGCTCACTCCCCACTC
CCACTCTGCCCAGGCAT**CAGGTGCTCCGAATCTCTGTAG**CCGATGAGGCCC**AGGTACAGAAGG**
TGAAGGAGCTGGAGGACCTGGAGCACCTGCAGGTCAGAAGAGGGGAGAAGGGCTCTCTGAGG
CCCCAGGGTATCAGCTGGGGCCACCCCAGGTCCCCAGCGGCCAACTGTGCCTGGGCTGTCTCC
ACC**CAACAAGGAGACATGGAATTGACTCT**GTTAGGAAGCGACTTCAAGCCCCCAGCTCCAGAG
CCTTGCTGCCCTTGAGCACCTGGGCAAGGGGCCGGGCCCCTTTCCAGTTCCTCCCTCTGCCTTG
CTGTCTCAAAGGCCCCTCACTCTGCTCCTGGGCCATTTCCCTGACCACACTGGACTCTC

Exon 3

Exon3_1_F CCAATTATATGAGAACTTCTGGCACCAA
Exon3_1_R CTCGATCATGGTCTCATAGCTGATG
Exon3_2_F CCAGGCGGTCAAGATCTTTCTG
Exon3_2_R TAGGTGGCGTAGTTAAAAGTGTCG
Exon3_3_F CAGGAGCAGATGTTCGCCTT
Exon3_3_R CAATGGAGCTACGACCACACA

GAGCCTTGCTGCCCTTGAGCACCTGGGCAAGGGGCCGGGCCCCTTTCCAGTTCCTCCCTCTGCC
TTGCTGTCTCAAAGGCCCCTCACTCTGCTCCTGGGCCATTTCCCTGACCACACTGGACTCTCCAG
TCCCCAGGGTTTCCCCGTATTTCTCTGGCCCTATTACCCCTGACCTATCC**CCAATTATATGAGAA**
CTTCTGGCACCAACAGCCCCTCCCACGCAGGCCCTGTCCCTGCCTGCTGTCCTGGCTGGTGCC
CCCAGCCCGCTGTGACCGTGCCGGCTCTTGTCCTCCCCAGCTGGACTTCTGGCGGGGGCCTGC
CCACCCTGGCTCCCCCATCGACGTCCGAGTGCCCTTCCCCAGCAT**CCAGGCGGTCAAGATCTTT**
CTGGAGTCCCACGG**CATCAGCTATGAGACCATGATCGAG**GACGTGCAGTCGCTGCTGGACGAG
GAG**CAGGAGCAGATGTTCGCCTT**CCGGTCCCGGGCGCGCTCCAC**CGACACTTTTAACTACGCC**
ACCTACCACACCCTGGAGGAGGTGAGGGCGCCCCTAGCGGCCGCTCCCTGCAGCCACCAGCTC
TTCATCATGGCTGGTAGAACGCGGTAGGGCCAAGGCCAGGGCCAGCCTGGGTGTGCGCAGCGC
CTGCTCTGTTTCCATGTGGCC**TGTGTGGTCGTAGCTCCATTG**CAGGGCTCGCAGCAGGCTGGGA
CGGTG

Exon 4

Exon4_F TCTGGGTGCCCAGAAGCTATTA
Exon4_R TGTTCCCTGGTACCATGATTTCC

GGGCTGCTAAGGGAAGCA**TCTGGGTGCCCAGAAGCTATTA**AGGCCAGTGGTCTCTTCTTTCACA
CCTCAGATCTATGACTTCCTGGACCTGCTGGTGGCGGAGAACCCGCACCTTGTCAGCAAGATCC
AGATTGGCAACACCTATGAAGGGCGTCCCATTTACGTGCTGAAGGTAACATCCACATGTGGACAT
ACACAGGGGAGAATGGACCCACACGTGGCATCCGTGATGGGCGTGGGCTCTCCCGG**GGAAATC**
ATGGTACCAGGGAACACGCTGTTAAATGGACTCCCCATGCAGACATTTGGAAAGGCCTGAGTCT
CCACCCTGGTCTTGGCGTGTGCACTCCTGCCCAT

Exon 5

Exon5_1_F	AAGCAGAGCCTCTACCTGAGAT
Exon5_1_R	GCCTTACCTTCTTTGCAAACCAGA
Exon5_2_F	CAGTAAGCGTCCAGCCATCT
Exon5_2_R	CCACAGCAATGGACACCTTTC

GCCCCAC**AAGCAGAGCCTCTACCTGAGAT**ACACAGAGAGCAGGTGGTCTCTGGCCCAGGTCGG
GGTCTCCTTCAGGGCAGCAAGATGAGGCCTCAGCTGTGAAATTGCCTCTGATCACTCCCCTGCC
TCCTCTCCAGTTCAGCACGGGGGG**CAGTAAGCGTCCAGCCATCT**GGATCGACACGGGCATCCA
TTCCCGGGAGTGGGTCACCCAGGCCAGTGGGG**TCTGGTTTGCAAAGAAG****GTAAGGC**CGGGGA
GGTGAGGAGGGCTCTCACCTGGTGGGGCATTGGTGTCCAAGGCCCACAGAAGCCCGGGCCTCC
CTTTGCCCATCCAGAAGCAGTGACCACAGAGGACATGGG**GAAAGGTGTCCATTGCTGTGG**CTTG
GCAGATGCCTGGCCCAGCCTGCGCTGCCCCTCTGCTCC

Exon 6

Exon6_F	GGGAAAGGTGTCCATTGCTGT
Exon6_R	GGGTGAACTACTTGTGCAGCTT

ACAGAAGCCCGGGCCTCCCTTTGCCCATCCAGAAGCAGTGACCACAGAGGACATG**GGGAAAGG**
TGTCCATTGCTGTGGCTTGGCAGATGCCTGGCCCAGCCTGCGCTGCCCCTCTGCTCCTCTAACC
CCCCAGATCACTCAAGACTACGGGCAGGATGCAGCTTTCACCGCCATTCTCGACACCTTGGACAT
CTTCCTGGAGATCGTCACCAACCCTGATGGCTTTGCCTTCACGCACAGCACGGTACCGGCCTTCT
CCTGTCCTTGGGGGAAGCAGGATGGGCCTCTGGCTTCT**AAGCTGCACAAGTAGTTCACCC**CTAA
TCTCAAGCCCCAGAAGTCAAGGGAGGGGCAATCAGA

Exon 7

Exon7_F	CCAATCAGGGCACTTGTGTTG
Exon7_R	CATCCTTGCTCCCAAGACACT

CCGACAACCAGCTGGGAGTGGATCCCATCCCAAGCTGTGCCTGCAGCTCAGCTT**CCAATCAGGG**
CACTTGTGTTGAGGGCTTCCACCTCCAGGGAGCCCTCCCCTCAGTCCACTCTGCTCTCTGCAGC
CTCTGAACCACCCCCCACCCAGCACTGTGACAAGCGTCACACGTGCCTCGGGGTGGCTGATCCC
ATTTCCTTCCTCAGAATCGCATGTGGCGCAAGACTCGGTCCCACACAGCAGGCTCCCTCTGTATT
GGCGTGGACCCCAACAGGAACTGGGACGCTGGCTTTGGGTGTAAGGCCCAG**AGTGTCTTGGGA**
GCAAGGATGGGATGGCCTCGAATGGCTCCTCACCACTGCTCTTGCTCCCCGCCTCTCTCCTGCC
CCTGCAGTGAGGGGAGGGTTGGGGGTGGCAGCTCTGC

Exon 8

Exon8_1_F	GGTTATAGAAGGCCTTTGGGCTT
Exon8_1_R	GGTCCTTCACAAAGTCTACAATGGA
Exon8_2_F	GGCAAGTTTGCCAATTCCGAAG
Exon8_2_R	TGTGCCTTAAGCAGGTCTGATG

CCCCA**GGTTATAGAAGGCCTTTGGGCTT**TCCTGAATCCAGGGGTGGGAGTGAGCCCTTCCATAC
CACCTCACCCCCAACTCCATGCAAAGAACTGGATTCCAGAAGCCACAGAAGCTGGAGGAGCCAC
ACCGCCATGCCCTCTGTCCCCCCACAGTGTCCGGAGCCAGCAGTAACCCCTGCTCGGAGACTTA
CCAC**GGCAAGTTTGCCAATTCCGAAG**TGGAGGTCAAG**TCCATTGTAGACTTTGTGAAGGACC**AT
GGGAACATCAAGGCCTTCATCTCCATCCACAGCTACTCCCAGCTCCTCATGTATCCCTATGGCTA
CAAAACAGAACCAGTCCCTGACCAGGATGAGCTGGTAGGCACTGACCTCGGCTTGCCCCCTCGT

CCCCAAGGTGGCTTCGGACAGGCCCAGGCTTTCCCC**CATCAGACCTGCTTAAGGCACA**GACAC
CTCCAGAGTACCTGACACCCTTCCTTCCCTGATGGCTTGGGAAGACCAGCGGGTGGACTAACCA
TTTTTTCTGGGAAACTGAGGCACAGGAGTGATGGAGTCACTTCTGTAATGTGACAGAGCAAGGGG
CAGGGCTAGACTTCGAT

Exon 9

Exon9_F GACTACCCTGGACATGCTGTTC
Exon9_R GATACTCCCTCGGTCAGGAAGA

TGTGCTCCCTGCTGGAGGCCCACTTCTGCAGGGTGCTTCTCCTAGGCTCCCCTGCCAGCCCCCA
GACTACCCTGGACATGCTGTTCCAGGAGCCTGGCCATGACAGGTGGCTTTGCTTGGTGTTTTGT
CCAGGATCAGCTTTCCAAGGCTGCTGTGACAGCCCTGGCCTCTCTCTACGGGACCAAGTTCAAC
TATGGCAGCATCATCAAGGCAATTTGTAAGTGGCCGTAGGGTCTCTCTTGATGGGCCTGCGAGG
AACATCTGCTGGC**TCTTCCTGACCGAGGGAGTATC**CCTCATGGAAGGAAGTAGCCAAGGGCACC
CAGATCTG

Exon 10

Exon10_1_F CTCTTTGGACCTCTTGGCTTAGA
Exon10_1_R AGCTCGAAGGTGAAGGAGTACTT
Exon10_2_F GAAGCACTATTGACTGGACCTACA
Exon10_2_R CTCAAACTTTATTTGGTTGCCTGGAT

AGAGACTTCCTTGCATCCCCTAGTGAATAGGGGAACCATTGCTGGTCTC**CTCTTTGGACCTCTTG**
GCTTAGACCTTTTAGTGGGAGTTTCTTGGAAGTGAGGCTGCTTGGTCAACAGCAGACCTTAGTAG
ACACTGACTCCACTCAGCATTGCACAAGGCACAGAGCTTTGGACAGGGTTGGATCGTTAACCCAA
CCCGTGTAAATATTCCCAAAGTGATTGACCCTTTCTCTCCTATTTTACTCCTGCCCCAGATCAAGC
CAGTG**GAAGCACTATTGACTGGACCTACA**GCCAGGGCATC**AAGTACTCCTTCACCTTCGAGCT**C
CGGGACACTGGGCGCTATGGCTTCCTGCTGCCAGCCTCCCAGATCATCCCCACAGCCAAGGAGA
CGTGGCTGGCGCTTCTGACCATCATGGAGCACACCCTGAATCACCCCTACTGAGCTGACCCTTT
GACACCCTTCTTGTCCTCCTCTCTGGCCCC**ATCCAGGCAACCAAATAAAGTTTGAG**TGTACCAG
GAACAGAATCCTGGGGCTTGCAtgtggagtgtctgcctcttcaagctggggcaaaagtgatttaattcctgcaggcctcactggaa
atgtgtgggtggttggactagatgacccctacattcccctgcattccaacatcctgtgaagtcgtatccaagtggcgtctgttttaattagaccaccct
gagttcagctcaccagtgggatgatttgttcataccttagtagcaagcagcagcaacagctgctaaccaaatgcccggcaccccacagtggtgt
ggaattcggcgtgtacaaaggtctagctagctgtgtcca

Supplementary Figure S1. Sequence information pertaining to the targeted sequencing of the *CPA1* gene. The sequences of the 16 primer pairs are first provided, followed by an illustration of their respective locations within the *CPA1* genomic sequence using different underlines, in the context of the 10 exons. Coding sequences are highlighted in blue. The *CPA1* genomic sequence was obtained from human GRCh37/hg19.

Exons 1-2

ccttctccgctacccagtgggcaaacagaaccgcagctttagggtgtgggcaggcagagtcctggctgggactccaggaggcctcgagcc
cccgctgaccctcaggccccgctggccccagatggtcgggggtggagctctggcttatctctccagctgcccagttccctgccactttatcatgga
gggtgagagggtgtcagagctcAGAACTCCCACCCCAGCCTCCCCGTGGGACAGGACCCAGGTGCTGGG
GGAGAACAGACCTCGGGAGCAGCCAGGAGTCCTCGGTCCTGGGAGGGTTTAAAAGCCAGGGGG
CCGTCTCGACCTCAGTCTGACCTTCCCTCCCGGCAGCAGCATGCGGGGGTTGCTGGTGTTGAGT
GTCCTGTTGGGGGCTGTCTTTGGCAAGGAGGACTTTGTGGGGTAGGGATGTGGAGAGGAGGGG
GTGCCCTCTGAGGGTGATGGGGAGGACTCAGCCCCCAACCAGTAGAGGAGACAGACAGACAGA
TACATGGCAACACAGCCAGAGAGGATGGCCTGGCACCACCTGGGACAGCTGGCAGATAAGCAA
CCAGGGTTGGGAAGAGGTTGTGTCTCCCAAGACAGTCTCCTGAGCCCTGGAGAAACCTGAGCTC
TGAGGAGGAGTTTTCAGGAGAGGAGAAAGGAGGAGGCCTGGCTGGCTTGGAACAGAGAAATAG
TCCAAACTGGGATTGAGATAGTAACAGCGTCTAGAAGTTTCTAAAGATGGGGAGAGAAGAGGTGA
GGGAGCCCAGGCCTCTCCTTGTTGAGACCCTTGGTGCTGTCCCCTGCCCAGCCCAGAGGACGA
GGCCCAGTCTGGGGATTCTGGGCTGCTGCCTCCCTCCTGCACCTGGGGAGTGCTTGTGGCCAG
GGCAGGTGCAGCTTGGGTGCTCACTCCCCACTCCCACTCTGCCCAGGCATCAGGTGCTCCGAAT
CTCTGTAGCCGATGAGGCCCAGGTACAGAAGGTGAAGGAGCTGGAGGACCTGGAGCACCTGCA
GGTCAGAAGAGGGGAGAAGGGCTCTCTGAGGCCCCAGGGTATCAGCTGGGGCCACCCCAGGTC
CCCAGCGGCCAACTGTGCCTGGGCTGTCTCCACCCAACAAGGAGACATGGAATTGACTCTGTTA
GGAAGCGACTTCAAGCCCCCAGCTCCAGAGCCTTGCTGCCCTTGAGCACCTGGGCAAGGGGCC
GGGCCCCTTTCCAGTTCCTCCCTCTGCCTTGCTGTCTCAAAGGCCCCTCACTCTGCTCCTGGGC
CATTTC**CCTGACCACACTGGACTCTC**

Exons 3-4

GAGCCTTGCTGCCCTTGAGCACCTGGGCAAGGGGCCGGGCCCCTTTCCAGTTCCTCCCTCTGC
CTTGCTGTCTCAAAGGCCCCTCACTCTGCTCCTGGGCCATTTCCCTGACCACACTGGACTCTCCA
GTCCCCAGGGTTTCCCCGTATTTCTCTGGCCCTATTACCCCTGACCTATCCCCAATTATATGAGAA
CTTCTGGCACCAACAGCCCCTCCCACGCAGGCCCTGTCCCTGCCTGCTGTCCTGGCTGGTGCCC
CCAGCCCGCTGTGACCGTGCCGGCTCTTGTCCTCCCCAGCTGGACTTCTGGCGGGGGCCTGCC
CACCCTGGCTCCCCCATCGACGTCCGAGTGCCCTTCCCCAGCATCCAGGCGGTCAAGATCTTTC
TGGAGTCCCACGGCATCAGCTATGAGACCATGATCGAGGACGTGCAGTCGCTGCTGGACGAGG
AGCAGGAGCAGATGTTCGCCTTCCGGTCCCGGGCGCGCTCCACCGACACTTTTAACTACGCCAC
CTACCACACCCTGGAGGAGGTGAGGGCGCCCCTAGCGGCCGCTCCCTGCAGCCACCAGCTCTT
CATCATGGCTGGTAGAACGCGGTAGGGCCAAGGCCAGGGCCAGCCTGGGTGTGCGCAGCGCCT
GCTCTGTTTCCATGTGGCCTGTGTGGTCGTAGCTCCATTGCAGGGCTCGCAGCAGGCTGGGACG
GTGGGGCTGCTAAGGGAAGCATCTGGGTGCCCAGAAGCTATTAAGGCCAGTGGTCTCTTCTTTC
ACACCTCAGATCTATGACTTCCTGGACCTGCTGGTGGCGGAGAACCCGCACCTTGTCAGCAAGA
TCCAGATTGGCAACACCTATGAAGGGCGTCCCATTTACGTGCTGAAGGTAACATCCACATGTGGA
CATACACAGGGGAGAATGGACCCACACGTGGCATCCGTGATGGGCGTGGGCTCTCCCGGGGAA
ATCATGGTACCAGGGAACACGCTGTTAAATGGACTCCCCATGCAGACATTTGGAAAGGCCTGAGT
CTCCACCCTGGTCTTG**GCGTGTGCACTCCTGCCCAT**

Exons 5-6

GCCCCACAAGCAGAGCCTCTACCTGAGATACACAGAGAGCAGGTGGTCTCTGGCCCAGGTCGG
GGTCTCCTTCAGGGCAGCAAGATGAGGCCTCAGCTGTGAAATTGCCTCTGATCACTCCCCTGCC
TCCTCTCCAGTTCAGCACGGGGGGCAGTAAGCGTCCAGCCATCTGGATCGA
CACGGGCATCCATTCCCGGGAGTGGGTCACCCAGGCCAGTGGGGTCTGGTTTGCAAAGAAGGT
AAGGCCGGGGAGGTGAGGAGGGCTCTCACCTGGTGGGGCATTGGTGTCCAAGGCCCACAGAAG
CCCGGGCCTCCCTTTGCCCATCCAGAAGCAGTGACCACAGAGGACATGGGGAAAGGTGTCCATT
GCTGTGGCTTGGCAGATGCCTGGCCCAGCCTGCGCTGCCCCTCTGCTCCTCTAACCCCCCAGAT
CACTCAAGACTACGGGCAGGATGCAGCTTTCACCGCCATTCTCGACACCTTGGACATCTTCCTGG
AGATCGTCACCAACCCTGATGGCTTTGCCTTCACGCACAGCACGGTACCGGCCTTCTCCTGTCCT
TGGGGGAAGCAGGATGGGCCTCTGGCTTCTAAGCTGCACAAGTAGTTCACCCCTAATCTCAAGC
CCCAGAAGTCAAGGGAGGGGCAATCAGACCTGT**GCTCCTAGCCGAGGGTGTCT**

Exons 7-9

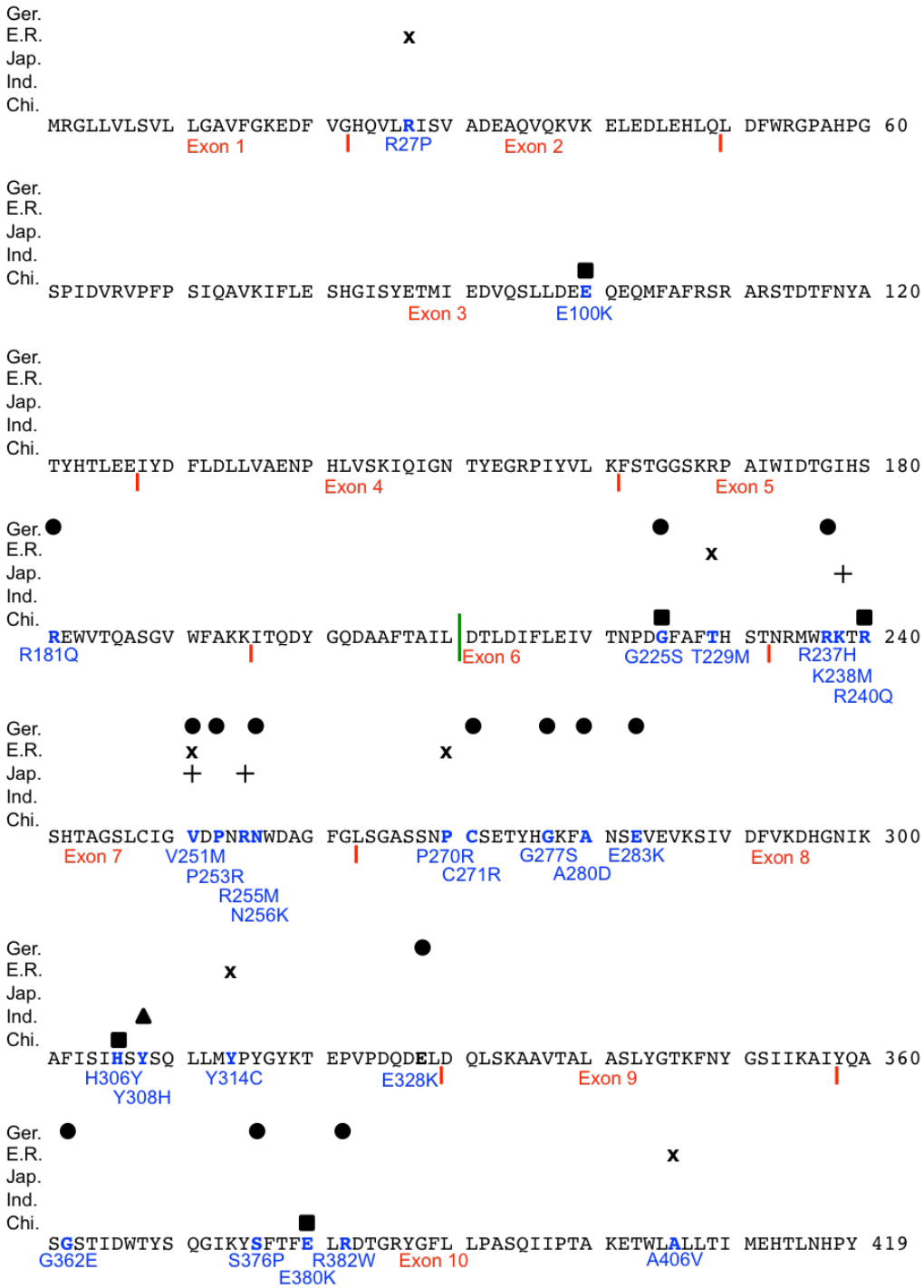
CCGACAACCAGCTGGGAGTGGATCCCATCCCAAGCTGTGCCTGCAGCTCAGCTTCCAATCAGG
GCACTTGTGTTGAGGGCTTCCACCTCCAGGGAGCCCTCCCCTCAGTCCACTCTGCTCTCTGCAG
CCTCTGAACCACCCCCCACCCAGCACTGTGACAAGCGTCACACGTGCCTCGGGGTGGCTGATCC
CATTTCCTTCCTCAGAATCGCATGTGGCGCAAGACTCGGTCCCACACAGCAGGCTCCCTCTGTAT
TGGCGTGGACCCCAACAGGAACTGGGACGCTGGCTTTGGGTGTAAGGCCCAGAGTGTCTTGGG

AGCAAGGATGGGATGGCCTCGAATGGCTCCTCACCACTGCTCTTGCTCCCCGCCTCTCTCCTGC
CCCTGCAGTGAGGGGAGGGTTGGGGGTGGCAGCTCTGCCTCTGAGGGCTCTTGGGGATGGAG
GCTGTGCTCTGAGAGTTGGTTGTTACTCGCCTGCAAAAGGCAAGTTGCTTGCAAATGGGCTAAGG
TCTGAAATCCTACCTAGGGGGCTTCTAGCTTAACCTCAAGTCCTCCCGCCTTGGCCACGTCTCTG
TGAGAACTGGTCTCCACTGAGGAGCCCGTCTTCCCTCCCTGGGTGTGTCCATCAGCTCTGCCCA
AACCAGGCTGGGAGGGCAGTTCCCCCAGGTTATAGAAGGCCTTTGGGCTTTCCTGAATCCAGGG
GTGGGAGTGAGCCCTTCCATACCACCTCACCCCCAACTCCATGCAAAGAACTGGATTCCAGAAG
CCACAGAAGCTGGAGGAGCCACACCGCCATGCCCTCTGTCCCCCCACAGTGTCCGGAGCCAGC
AGTAACCCCTGCTCGGAGACTTACCACGGCAAGTTTGCCAATTCCGAAGTGGAGGTCAAGTCCAT
TGTAGACTTTGTGAAGGACCATGGGAACATCAAGGCCTTCATCTCCATCCACAGCTACTCCCAGC
TCCTCATGTATCCCTATGGCTACAAAACAGAACCAGTCCCTGACCAGGATGAGCTGGTAGGCACT
GACCTCGGCTTGCCCCCTCGTCCCCAAGGTGGCTTCGGACAGGCCCAGGCTTTCCCCCATCAGA
CCTGCTTAAGGCACAGACACCTCCAGAGTACCTGACACCCTTCCTTCCCTGATGGCTTGGGAAGA
CCAGCGGGTGGACTAACCATTTTTTCTGGGAAACTGAGGCACAGGAGTGATGGAGTCACTTCTGT
AATGTGACAGAGCAAGGGGCAGGGCTAGACTTCGATCTTAGGCACCACATGTGGAGGTGCATGT
GCCTGAAGGGCAGGGAAGGCCAGCCGGACACCCTGAAGGGCCAGAAAACTGTGCTGACAGGCT
CCCGGGCTGAGCTTCCAGGCTAAGCAGGCTCTGTGCTCCCTGCTGGAGGCCCACTTCTGCAGG
GTGCTTCTCCTAGGCTCCCCTGCCAGCCCCCAGACTACCCTGGACATGCTGTTCCAGGAGCCTG
GCCATGACAGGTGGCTTTGCTTGGTGTTTTGTCCAGGATCAGCTTTCCAAGGCTGCTGTGACAGC
CCTGGCCTCTCTCTACGGGACCAAGTTCAACTATGGCAGCATCATCAAGGCAATTTGTAAGTGGC
CGTAGGGTCTCTCTTGATGGGCCTGCGAGGAACATCTGCTGGCTCTTCCTGACCGAGGGAGTAT
CCCTCATGGAAGGAAGTA**GCCAAGGGCACCCAGATCTG**

Exon 10

GGAAGTGAGGCTGCTTGGTCAACAGCAGACCTTAGTAGACACTGACTCCACTCAGCATTGCACA
AGGCACAGAGCTTTGGACAGGGTTGGATCGTTAACCCAACCCGTGTAAATATTCCCAAAGTGATT
GACCCTTTCTCTCCTATTTTACTCCTGCCCCAGATCAAGCCAGTGGAAGCACTATTGACTGGACC
TACAGCCAGGGCATCAAGTACTCCTTCACCTTCGAGCTCCGGGACACTGGGCGCTATGGCTTCC
TGCTGCCAGCCTCCCAGATCATCCCCACAGCCAAGGAGACGTGGCTGGCGCTTCTGACCATCAT
GGAGCACACCCTGAATCACCCCTACTGAGCTGACCCTTTGACACCCTTCTTGTCCTCCTCTCTGG
CCCCATCCAGGCAACCAAATAAAGTTTGAGTGTACCAGGAACAGAATCCTGGGGCTTGCAtgtggag
tgtctgcctcttcaagctggggcaaaagtgatttaattcctgcaggcctcactggaaatgtgtgggtggttggactagatgacccctacattcccct
gcattccaacatcctgtgaagtcgtatccaagtggcgtctgttttaattagaccaccctgagttcagctcaccagtgggatgatttgttcataccttag
tagcaagcagcagcaacagctgctaaccaaatgcccggcaccccacagtggtgtggaattcggcgtgtacaaa**ggtctagctagctgtgt**
cca

Supplementary Figure S2. Sequence information pertaining to the validation of targeted sequencing-derived *CPA1* variants by Sanger sequencing. Primer sequences used for amplifying the different exons are underlined. These primers were often used as sequencing primers. Further primers used for sequencing are indicated in red (forward) or green (reverse). Coding sequences are highlighted in blue. The *CPA1* genomic sequence was obtained from human GRCh37/hg19.



Supplementary Figure S3. Distribution of functionally impaired *CPA1* missense variants within the CPA1 amino acid sequence. Variants included those reported in this study as well as by Witt et al. [2013] irrespective of their occurrence in patients or controls. Variants found in different populations are indicated by different symbols, with their respective affected amino-acid positions highlighted in bold and blue. Short vertical bars in red indicate the exon boundaries. The long vertical line in green indicates the midpoint of the primary amino-acid sequence. The amino-acid sequence was derived from GenBank reference sequence NM_001868.3. Ger., E.r., Jap., Ind., and Chi. refer to the previously studied German, European replication, Japanese and Indian populations [Witt et al., 2013] and the currently studied Chinese population, respectively.

Supplementary Table S1. All Rare *CPA1* Variants in Chronic Pancreatitis Patients and Controls in Different Populations

Population	Disease subtype	Patients (%)	Controls (%)	OR	95% CI	*P* value
German	NACP	37/944 (3.92)	53/3,938 (1.35)	2.99	1.95-4.58	1.3×10^{-7}
Eur. rep.	NACP	15/600 (2.50)	39/2432 (1.60)	1.57	0.86-2.87	0.14
Indian	NACP	10/230 (4.35)	0/264 (0)	Undefined	Undefined	0.002
Japanese	NACP	6/247 (2.43)	0/341 (0)	Undefined	Undefined	0.005
Chinese	**ICP**	**20/1112 (1.80)**	**24/1580 (1.52)**	**1.19**	**0.65-2.16**	**0.57**

Data newly obtained in the Chinese population are highlighted in bold. Data from the other populations were derived from Witt et al. [2013].

Abbreviations: CI, confidence interval; Eur. rep., European replication; ICP, idiopathic chronic pancreatitis; NACP, nonalcoholic chronic pancreatitis; OR, odds ratio.