

Supplementary Table 1. The clinical characteristics of the affected members of the kindreds CAD-2001. Kindred ID's corresponds to those in Figure 1A. LDL, HDL, triglyceride, and glucose were measured after an overnight fast. †, Deceased (also denoting age of death); 3VD, significant stenosis of all three major coronary arteries; MI, myocardial infarction; CABG, coronary artery bypass graft PTCA, percutaneous transluminal coronary angioplasty; CTA, computed tomography angiogram; TG, triglyceride; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; A1C, Hemoglobin A1C; T2D, type II diabetes; HTN, hypertension; BMI, body mass index; - 3 vessel disease; NA, not available. * indicates age at which last medical information was obtained. ** indicates the last measured LDL (Baseline LDL levels before the initiation of statins were not available).

| | M/F | Living | CAD status | Age of event | HTN | T2D | A1C | TC | LDL** | HDL | TG | BMI | Genotype |
|--------------|-----|--------|-------------------------------|-------------------------|-----------------|---------------|------|------------|------------|----------------|------|------|----------|
| Normal range | | | | | >140 S >90 D | >126 mg/dl | <6.0 | <200 mg/dl | <100 mg/dl | >50 F >40 M | <150 | <30 | |
| I-1 | M | N | MI† | 50 60† | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-1 | M | N | MI† | 50 67† | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-4 | F | N | MI | 52 75† | + | + | NA | NA | NA | NA | NA | NA | D121N |
| II-5 | M | N | MI x2, CABG† | 55 60† | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-7 | M | N | MI† | 29 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-8 | M | N | Unaffected | 72 | - | - | NA | NA | NA | NA | NA | NA | Wildtype |
| II-9 | M | N | MI† | 60 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-10 | M | Y | MI (multiple) † | 40's, 65 | NA | NA | NA | NA | NA | NA | NA | NA | Unknown |
| II-11 | F | N | MI† | 59 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-12 | M | N | MI x4† | 29, 38, 54, 61 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-14 | M | Y | MI x2, CABG | 42, 52 | + | + | 7.0% | 170 | 58 | 35 | 358 | 30.3 | D121N |
| II-16 | M | N | MI x3† | Late 30s | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-18 | M | N | MI† | 30s | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-20 | F | Y | Unaffected | 59* | - | - | NA | 196 | 115 | 64 | 84 | 29.3 | Wildtype |
| II-21 | M | N | CABG- 3 vessel disease† | 36, 48, 54 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| III-1 | M | N | MI x2† | 29, 34 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| III-3 | M | Y | MI x3† | 40's, 60 | + | + | NA | NA | NA | NA | NA | NA | Unknown |
| II-4 | F | N | Unaffected | 62 | - | - | NA | NA | NA | NA | NA | NA | Wildtype |
| III-6 | F | Y | CAD/MPI | Late 40's | + | + | 6.1% | 247 | 56 | 134 | 285 | 32.8 | D121N |
| III-7 | M | N | CABG 3VD | 29 | + | + | - | - | - | - | - | - | D121N |
| II-9 | F | Y | Unaffected | 68 | - | - | NA | NA | NA | NA | NA | NA | Wildtype |
| III-11 | F | Y | CABG | 37 | + | + | 6.5% | 169 | 94 | 35 | 235 | 37.9 | D121N |
| III-12 | M | Y | CABG | 45 | + | + | 6.9% | 124 | 39 | 44 | 207 | 42.0 | D121N |
| III-14 | F | Y | MI/PTCA | 45 | + | + | IGT | 251 | 154 | 29 | 359 | 40.4 | D121N |
| III-16 | M | Y | CABG 4VD | 56 | + | + | NA | NA | NA | NA | NA | NA | S121N |
| III-17 | M | Y | CABG, DES | 48, 53 | + | + | 8.2% | 154 | 66 | 28 | 299 | 24.9 | D121N |
| III-19 | M | Y | CAD by CTA | 52 | + | + | IGT | 133 | 51 | 26 | 280 | 45.1 | D121N |
| III-21 | F | Y | Unaffected | 59* | - | - | | 196 | 115 | 64 | 84 | 29.3 | Wildtype |
| III-23 | F | Y | Unaffected | 57* | - | - | | 155 | 80 | 50 | 129 | 33.1 | Wildtype |
| III-24 | M | Y | CAD/PTCA | 50 | + | + | 6.2% | 168 | 72 | 28 | 339 | 45.9 | D121N |
| IV-2 | F | Y | CAD/PTCA | 24 | + | - | 5.0% | 159 | 73 | 64 | 111 | 36.5 | D121N |
| IV-3 | F | Y | Unknown | 31* | + | - | No | - | - | 32 | 190 | 38.6 | D121N |
| IV-7 | F | Y | Unknown | 32* | + | - | 5.6% | 209 | 112 | 33 | 321 | 37.5 | D121N |
| IV-6 | F | Y | Unaffected | 44* | - | - | | 170 | 99 | 43 | 139 | 42.1 | Wildtype |
| IV-8 | F | Y | Unaffected | 43* | - | - | | 243 | 175 | 47 | 103 | 32.0 | Wildtype |
| IV-13 | M | Y | Unaffected | 40* | - | - | | 112 | 66 | 40 | 75 | 26.5 | Wildtype |

Supplementary Table 2. Lod scores for CAD associated traits. HTN, hypertension; CAD, coronary artery disease; T2D, Type2 diabetes.

| Phenotype | LOD Score | Odds of Linkage |
|------------------|------------------|------------------------|
| HTN | 7.483124 | 30,417,533:1 |
| CAD | 6.889799 | 7,758,879:1 |
| T2D | 3.417063 | 2613:1 |

Supplementary Table 3. Comparison of Metabolic Traits in CELA2A-D121N Carriers and Noncarriers. LDL, low density lipoprotein; TG, triglyceride; HDL, high density lipoprotein; BMI, body mass index; T2D, Type2 diabetes. n= 7 in each group, Statistical analyses were carried out using two-sided Student's t-test. Data presented mean +SEM. *, subjects are on lipid lowering drugs.

| | Mutation carriers | Noncarriers | P value(Student's t-test) |
|------------|--------------------------|--------------------|----------------------------------|
| LDL | 98.57±9.89(n=14) | 97±9.5(n=10)* | 0.91 |
| TG | 272.2±35.88(n=10) | 126.1±13.48(n=13) | 0.0004 |
| HDL | 44.36±0.5(n=11) | 5.33±4.24(n=6) | 0.61 |
| BMI | 38.0 ±1.5(n=11) | 28.43± 2.1(n=14) | 0.0020 |
| T2D | 9/12 | 0/20 | 0.00005 |

Supplementary Table 4. Proteins identified in 75kDa band of secreted human CELA2A.

| Score | Expectation | Protein ID | Protein Name | MW | % Coverage |
|--------------|--------------------|-------------------|----------------------------------------------------------------------------------------------|-----------|-------------------|
| 1286 | 5.60E-125 | GRP78_HUMAN | 78 kDa glucose-regulated protein OS=Homo sapiens GN=HSPA5 PE=1 SV=2 | 72288 | 41.9 |
| 1026 | 5.30E-99 | SF3B1_HUMAN | Splicing factor 3B subunit 1 OS=Homo sapiens GN=SF3B1 PE=1 SV=3 | 145738 | 29.9 |
| 1026 | 4.90E-99 | CELA2A_HUMAN | Chymotrypsin-like elastase family member 2A OS=Homo sapiens GN=CELA2A PE=1 SV=1 | 28869 | 42.8 |
| 912 | 1.30E-87 | PDIA4_HUMAN | Protein disulfide-isomerase A4 OS=Homo sapiens GN=PDIA4 PE=1 SV=2 | 72887 | 42.8 |
| 767 | 4.50E-73 | HS90B_HUMAN | Heat shock protein HSP 90-beta OS=Homo sapiens GN=HSP90AB1 PE=1 SV=4 | 83212 | 27.9 |
| 737 | 4.30E-70 | DHX15_HUMAN | Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15 OS=Homo sapiens GN=DHX15 PE=1 SV=2 | 90875 | 28.8 |
| 642 | 1.40E-60 | HS90A_HUMAN | Heat shock protein HSP 90-alpha OS=Homo sapiens GN=HSP90AA1 PE=1 SV=5 | 84607 | 23.6 |
| 556 | 5.50E-52 | DDX1_HUMAN | ATP-dependent RNA helicase DDX1 OS=Homo sapiens GN=DDX1 PE=1 SV=2 | 82380 | 36.8 |

Supplementary Table 5. Novel phosphorylation sites after rCela2a treatment of INS-1 cells.

Phosphorylation sites are shown in red.

| Protein | Peptide Sequence | Start | End | M/Z | Ion Mass | Ion Mass (calc) | phospho-sites |
|----------------|-----------------------------------------------------------------|-------|------|---------|----------|-----------------|---------------|
| CACANIA | K.SK T DLLNPEEAEDQLADIASVGSFAR.A + Phospho (ST) | 431 | 457 | 985.13 | 2952.37 | 2952.37 | 433 |
| CACANIA | R.EMGTDGYSD S EHYLPMEGQTR.A + Phospho (ST) | 2021 | 2041 | 828.32 | 2481.95 | 2481.94 | 2030 |
| CACNAID | K.TCFFADSDIVAEEDPAPCAFSGNGRQCAANG T ECR.S + Phospho (ST) | 300 | 334 | 990.89 | 3959.54 | 3959.56 | 331 |
| CACNAID | R.DW S ILGPHHLDEFKRIWSEYDPEAK.G + Phospho (ST) | 1517 | 1541 | 1078.15 | 3231.44 | 3231.47 | 1519 |
| PKA | R.TW T LCGTPEYLAPEIILSK.G + Phospho (ST) | 196 | 214 | 1136.55 | 2271.09 | 2271.08 | 198 |

Supplementary Table 6. Gene Enrichment analysis of significantly altered phosphoproteins in INS-1 cells after treatment with rCela2a. CACNA1A and CACNA1D are shown in bold. The P-values and Z-scores in the [Gene Ontology](#) view are determined using the hypergeometric probability distribution.

| Pathway | Fold Enrichment | P-value | Genes |
|----------------------------------|-----------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Membrane Fusion | 5.14 | 1.95E-02 | RABEP1, BAX, GOSR2, SLC25A46, VPS33B, YKT6, MFN1, TaSNAP29, STX7, VCIPI1 |
| Regulation of Insulin Secretion | 4.32 | 2.69E-02 | CACNA1D , BRSK2, SEC11C, ITPR1, CPT1A, NOV, ICA1, ADCY5, VAMP2, ISL1, SNAP25, CACNA1A , CDK16, PCSK1, UQCC2 |
| Exocytosis | 3.64 | 3.15E-02 | SOD1, PLG, SCR2, VPS33B, WASH1, YKT6, LIN7C, BRSK6, EXOC2, SDF4, EXOC5, CD63, SNAP29, RAB8A, VAMP2, SNAP25, CACNA1A , CDK16 |
| Protein Localization to Membrane | 3.13 | 1.97E-02 | SDCBP, PACSIN1, CDH2, PALM, BAX, TMED2, SSR3, NUP54, RAPGEF2, F11R, LIN7C, EHD3, SEC11C, PEX5, DPP6, RAB8A, RAE1, RPL35, VAMP2, MYO1C, FLOT2, CACNA1A , CHM |
| Oxidation-Reduction Process | 1.98 | 2.97E-02 | ACTC1, CDK7, BCKDHB, CHDH, ADAR, SOD1, CACNA1D , MINA, NDUFS4, CDH2, BAX, GSK3B, BLOC1S2, DOHH, CDK9, AKAP8, ARAF, DECR1, ADD2, COQ7, MTOR, HIGD1A, KCNAB12, GLY41, NSDHL, ADCY6, ATP2B2, CD63, ITPR1, PEX5, ALDH16A1, FAM213A, GNAS, ABCG2, MTFR1L, HSDL2, CPT1A, ECI2, GSTK1, RAE1, VAMP2, TXNRD2, BAP1, OGFOD3, RRM2, SNAP25, CACNA1A , TXNDC12, SCCPDH |
| Generation of Neurons | 1.90 | 2.06E-02 | NUMB, SOD1, STRN, SDCBP, STK24, CACNA1D , CNP, ATXN1, SIRT2, PACSIN1, ARHGAP11, RUFY3, MAP6, CDH2, PALM, BAX, MAPK9, GSK3B, BLOC1S2, ARF1, IST1, PSD, SMAD4, ARAF, RHOB, USH2A, RAPGEF2, TUBB2B, MTOR, ABLIM2, PLXNA3, BRSK2, STAR, ADNP, TCF12, MTPN, ADCY6, ATP2B2, PEX5, NOTCH3, MYH11, SEMA6B, ILK, THRB, CNTN1, RAB8A, ISL1, NUMBL, KRAS, F2, EML1, SNAP25, CACNA1A , CDK16, JAG2, SF3A2, SECISBP2, ALS2 |