

**Table S1:** Sequencing primers

|   | Details                                  | FWD primer                                          | REV Primer                                          |
|---|------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| 1 | <i>plod3</i> cDNA amplification          | 5'-TAGCGACGGGAAAACCTGAAC-3'                         | 5'-CAAATCTGATGGAGGGAGGA-3'                          |
| 2 | <i>mgt</i> <sup>m635</sup> cDNA mutation | 5'-CAGCTGTTCTACACACGCATC-3'                         | 5'-CAACGTAGCGAGTCTCTCCAG-3'                         |
| 3 | <i>plod3</i> CRISPR mutation             | 5'-GCCTTTATAGTGTGCGTGTTTG-3'                        | 5'-GAAATTAAGTCGCTGCAGtggtg-3'                       |
| 4 | hPLOD3 cDNA                              | Clal<br>(5'atcgatATGACCTCCTCGGGGCC T-3')            | XhoI<br>(5'ctcgagTCAGGGGTCGACAAA GGA-3')            |
| 5 | zebrafish <i>PLOD3</i> (zPLOD3) cDNA     | Clal 5'-actc <u>ATCGATT</u> AGCGACGGGAAAA CTGAAC-3' | XhoI 5'-actc <u>CTCGAG</u> CAAATCTGATGGA GGGAGGA-3' |

**Table S2:** Q5® site-directed mutagenesis

|   | Mutation                                        | FWD primer                          | REV Primer                          |
|---|-------------------------------------------------|-------------------------------------|-------------------------------------|
| 1 | 1354C>T (Arg452 to stop)<br>Truncating Mutation | 5'GCAGCGGAAGtGAGTGG<br>GTGT-3'      | 5'ACCAGCTCCACGTAGT<br>CC-3'         |
| 2 | 1354C>T<br>(Arg452_Val453del)<br>2 AA Deletion  | 5'GGTGTGTGGAATGTACC<br>ATACATC-3'   | 5'CTTCCGCTGCACCAG<br>CTC-3'         |
| 3 | 1880T>C (Leu627Pro)<br>Missense mutation        | 5'-<br>CTGCAGCTGCcGCGGACG<br>TAT-3' | 5'-<br>GCCACCTCCCTCATAGT<br>CCAG-3' |
| 4 | 2071delT (Cys690 to<br>frameshift)              | 5'-<br>GCCGCTTCCTGCGCTACG-<br>3'    | 5'-<br>GCCACCTCCCTCATAGT<br>CCAG-3' |

**Table S3:** Primary and secondary Antibodies

|           | Antibody Name                          | Catalog Number   | Manufacture                                | Conc               |
|-----------|----------------------------------------|------------------|--------------------------------------------|--------------------|
| 1.        | PLOD3 Antibody                         | 11027-1-AP       | Proteintech                                | 1:500              |
| 2.        | Collagen Type II Antibody WB           | 600-401-104-0.1  | Rockland                                   | 1:500              |
| 3.        | Collagen Type II Antibody IF           | II-II6B3         | DSHB                                       | 1:500              |
| 4.        | Anti-Collagen I antibody [EPR7785] WB  | ab138492         | abcam                                      | 1:500 WB,          |
| 5.        | Anti-Collagen I antibody IF            | ab34710          | abcam                                      | 1:200 IF           |
| 6.        | eIF2 $\alpha$ Antibody                 | #9722            | CST                                        | 1:500              |
| 7.        | Phospho-eIF2 $\alpha$ (Ser51) Antibody | #9721            | CST                                        | 1:500              |
| 8.        | ATG5 antibody                          | ab108327         | abcam                                      | 1:500              |
| 9.        | Anti-SQSTM1 / p62 antibody             | ab155686         | abcam                                      | 1:500              |
| 10.       | LC3A/B Antibody                        | PA1-16931        | Thermo                                     | 1:500, 1:200 IF    |
| 11.       | Cathepsin B Antibody                   | M1506-1          | Huabio                                     | 1:500              |
| 12.       | ATF4                                   | PA5-72620        | Thermo                                     | 1:500              |
| 13.       | LAMP1                                  | Ab24170          | abcam                                      | 1:500 WB, 1:200 IF |
| 14.       | CHOP                                   | 2895             | CST                                        | 1:500              |
| 15.       | ERp57                                  | <b>MA5-31366</b> | Thermo                                     | 1:200              |
| 16.       | GM130                                  | 610822           | BD-Biosciences                             | 1;200              |
| 17.       | PDI                                    | P7496            | Sigma                                      | 1:200              |
| 18.       | P44/42 MAPK                            | 4696             | CST                                        | 1:500              |
| 19.       | Phospho P44/42 MAPK                    | 9106             | CST                                        | 1:500              |
| Secondary |                                        |                  |                                            |                    |
| 20.       | Anti-alpha Tubulin Antibody            | ab40742          | abcam                                      | 1:3000             |
| 22.       | Anti-Rabbit IgG (H+L), HRP Conjugate   | W4011            | Promega                                    | 1:3000             |
| 23.       | Anti-Mouse IgG (H+L), HRP Conjugate    | W4021            | Promega                                    | 1:3000             |
| 21.       | GFP (Chicken IgY )                     | A10262           | Vanderbilt Molecular and Cell Biology Core | 1:500              |
| 22.       | Chicken IgY-Alexa488                   | A11039           | Invitrogen                                 | 1:500              |
| 23.       | WGA-488                                | W11261           | Invitrogen                                 | 1:500              |
| 22.       | Anti-mouse GFP-488                     | A21121           | Invitrogen                                 | 1:500              |

|      |                     |        |            |        |
|------|---------------------|--------|------------|--------|
| 23.  | Anti-mouse GFP-555  | A21127 | Invitrogen | 1:500  |
| 24.  | Anti-rabbit GFP-488 | A11034 | Invitrogen | 1:500  |
| 25.  | Anti-rabbit GFP-555 | A21428 | Invitrogen | 1:500  |
| Dyes |                     |        |            |        |
| 26.  | DAPI                | D1306  | Invitrogen | 1:5000 |
| 27.  | LysoTracker         | L7528  | Thermo     | 50 nM  |

**Table S4:** Primers

| Name             | Forward                | Reverse               |
|------------------|------------------------|-----------------------|
| $\beta$ -actin 1 | CCATGGATGAGGAAATCGCTGC | GTCACACCATCACCAGAGTCC |
| zAtf4            | TTAGCCATTGCTCCGATAGC   | GCTGCGGTTTTATTCTGCTC  |
| zAtf6            | CTGTGGTGAAACCTCCACCT   | CATGGTGACCACAGGAGATG  |
| zDdit3           | AAGGAAAGTGCAGGAGCTGA   | TCACGCTCTCCACAAGAAGA  |
| Zplod3           | CGACGGGAAAACCTGAACTGAC | GCCATCGAACCTTCTGACCT  |
| Col2             | TTACAAGAAGCAGACTGCGC   | ACCTGAAGAAGGCCATTCTG  |
| $\beta$ -actin 2 | ACTGTATTGTCTGGTGGTAC   | TACTCCTGCTTGCTAATCC   |
| Bip              | AAGAGGCCGAAGAGAAGGAC   | AGCAGCAGAGCCTCGAAATA  |
| Suc1g1           | CAGCAAGCAGGAGTGAGACA   | TCACGGAGTTGAAGACTGGC  |
| sdhc             | CCTCCGAACACTCAAGCTCA   | ACTCTCCGGTAACACCAACG  |
| suc1g2           | CAAACCTTCTTGGACCTGGGC  | TTCCTTCGAGTCTGACCACC  |

**Table S5:** Succinic-acid targets

| N  | Succinic-acid targets (Broad Institute data portal) |                                                        |
|----|-----------------------------------------------------|--------------------------------------------------------|
| 1  | PLOD1                                               | procollagen-lysine,2-oxoglutarate 5-dioxygenase 1      |
| 2  | PLOD3                                               | procollagen-lysine,2-oxoglutarate 5-dioxygenase 3      |
| 3  | SDHA                                                | succinate dehydrogenase complex flavoprotein subunit A |
| 4  | SDHB                                                | succinate dehydrogenase complex iron sulfur subunit B  |
| 5  | SDHC                                                | succinate Dehydrogenase Complex Subunit C              |
| 6  | SDHD                                                | succinate dehydrogenase complex, subunit D             |
| 7  | ALDH5A1                                             | aldehyde dehydrogenase 5 family member A1              |
| 8  | ASPH                                                | aspartyl/asparaginyl beta-hydroxylase                  |
| 9  | BBOX1                                               | gamma-butyrobetaine hydroxylase 1                      |
| 10 | HSD17B6                                             | hydroxysteroid 17-beta dehydrogenase 6                 |
| 11 | OXCT1                                               | 3-oxoacid CoA-transferase 1                            |
| 12 | OXCT2                                               | 3-Oxoacid CoA-Transferase 2                            |
| 13 | P3H1                                                | prolyl 3-hydroxylase 1                                 |
| 14 | P3H2                                                | prolyl 3-hydroxylase 2                                 |
| 15 | P3H3                                                | prolyl 3-hydroxylase 3                                 |
| 16 | P4HA1                                               | prolyl 4-hydroxylase subunit alpha 1                   |
| 17 | P4HA2                                               | prolyl 4-hydroxylase subunit alpha 2                   |
| 18 | SLC13A1                                             | solute carrier family 13 member 1                      |
| 19 | SLC13A2                                             | solute carrier family 13 member 2                      |
| 20 | SLC13A3                                             | solute carrier family 13 member 3                      |
| 21 | SLC25A10                                            | solute carrier family 25, member 10                    |
| 22 | SUCLA2                                              | succinate--CoA ligase [ADP-forming] subunit beta       |
| 23 | SUCLG1                                              | succinate-CoA ligase GDP/ADP-forming subunit alpha     |
| 24 | SUCLG2                                              | succinate-CoA ligase [GDP-forming] subunit beta        |
| 25 | SUCNR1                                              | succinate receptor 1                                   |
| 26 | TMLHE                                               | trimethyllysine hydroxylase, epsilon                   |

**Table S6:**

| BCARD Phenotype     |                                                                                                                                                                                                                                                                         |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Organ               | Phenotype                                                                                                                                                                                                                                                               |
| Muscle              | Reduced muscle mass,<br>Muscle atrophy,<br>Joint contractures (elbows, fingers),<br>Club foot (TEV),<br>Diaphragmatic Eventration                                                                                                                                       |
| Skeleton            | Osteopenia, Low Bone Mineral Density,<br>Fractures,<br>Scoliosis, Kyphoscoliosis,<br>Flat Vertebrae (Platyspondyly),<br>Small capital femoral epiphyses,<br>Prominent knees,<br>Midfacial hypoplasia, Shallow orbits,<br>J-shaped sella turcica,<br>Teeth abnormalities |
| Dysmorphic features | Low set, simple ears,<br>Long philtrum, Short nose, anteverted nares,<br>Downturned corners of the mouth,<br>Decreased palmar creases,<br>Dysplastic nails and tapered fingers,<br>Coarse hair                                                                          |
| Ear                 | Sensorineural hearing loss                                                                                                                                                                                                                                              |
| Eye                 | Cataracts, Retinal thinning,<br>Optically empty vitreous<br>Myopia                                                                                                                                                                                                      |
| Neurologic          | Developmental delay,<br>Speech deficits,<br>Ptosis                                                                                                                                                                                                                      |
| CV                  | Aneurysms (hemorrhage),<br>Bruisability and blistering of skin                                                                                                                                                                                                          |

**Table S8:** ER Stress Inhibitors

| No | Catalog no | Name                         |
|----|------------|------------------------------|
| 1  | HY-15654   | Sodium phenylbutyrate        |
| 2  | HY-19696A  | Tauroursodeoxycholate Sodium |
| 3  | HY-12837   | EN460                        |
| 4  | HY-101455  | CDN1163                      |
| 5  | HY-15486   | Salubrial                    |
| 6  | HY-17537   | APY29                        |
| 7  | HY-13820   | GSK2656157                   |
| 8  | HY-15845   | STF-083010                   |
| 9  | HY-19710   | MKC3946                      |
| 10 | HY-12825   | BHPI                         |
| 11 | HY-100545  | BAPTA-AM                     |