Supplemental experimental procedures

Whole exome capture and sequencing

Using 1 ug of DNA Illumina paired-end pre-capture libraries were constructed according to the manufacturer's protocol (Illumina Multiplexing_SamplePrep_Guide_1005361_D) with modifications as described in the BCM-HGSC Illumina Barcoded Paired-End_Capture_Library_Preparation protocol. Four pre-capture libraries were pooled and then hybridized in solution to the HGSC CORE design (52Mb, NimbleGen) according to the manufacturer's protocol NimbleGen SeqCap EZ Exome Library SR User's Guide with minor revisions. The sequencing run was performed in paired-end mode using the Illumina HiSeq 2000 platform, with sequencing-by-synthesis reactions extended for 101 cycles from each end. With sequencing yields averaging ~9.3 Gb per sample and average coverage of 95.6x, the samples achieved 89% of the targeted exome bases covered to a depth of 20X or greater. Sequencing data mapping and alignment, and variant calling were performed using the in-house HGSC Mercury analysis pipeline (https://www.hgsc.bcm.edu/software/mercury).

Conservation Analysis

The absolute position of each exon on human chromosome 15 was determined and entered into the UCSC table browser as custom regions (https://genome.ucsc.edu/cgi-bin/hgTables). The non-coding region of exon 66 was excluded. In the USCS table browser, the group was set to comparative genomics

and the track to conservation. To obtain the PhyloP score for each exon, the 100 vertebrate conservation (phyloP100wayAll) table was selected. To obtain the percentage of conserved bases, the sum of bases in exons 1-64, in exons 65-66, and in exon 66 alone that had a score greater than 0 (i.e. bases that are conserved) was divided by the sum of all bases in those exons, respectively. Numbers are expressed in percent conserved bases.

Hyperinsulinemic-euglycemic clamp

In brief, a micro catheter was inserted into the jugular vein by survival surgery followed by a 4-5 day wait for complete recovery. Studies were then performed in conscious mice. 18 hour fasted conscious mice received a priming dose of HPLC-purified [3-3H] glucose (10μCi) and then a constant infusion (0.1μCi/min) of the same for ~1.5-2.0 hours. Blood samples were collected from the tail vein at 0, 50 and 60 min to measure the basal glucose production rate. After 1 hour of infusion, mice were primed with regular insulin followed by continuous insulin infusion (2.5 mU/kg/min) for 2 hours. Using a separate pump, 25% glucose was used to maintain the blood glucose levels at 100-140 mg/dl, as determined every 6-9 min using a glucometer (LifeScan, NJ). Hepatic glucose production under clamp conditions and peripheral glucose disposal rates were then measured from collected plasma. At the end of the clamp mice were sacrificed and tissues were snap frozen as required in liquid nitrogen.

***In vivo* imaging using SPECT scans**

200 ug recombinant asprosin was iodinated by a modification of the Chloramine-T method using 8 mCi of [125]-NaI by ViTrax, Inc. The labeled protein was isolated by passage through a PD-10 column (Sephadex G-25, 1.45 x 5.0 cm) equilibrated with distilled water (Invitrogen, Ultra Pure). 5.55 Mbq (150 uCi) of either I^{125}-asprosin, I^{125}-asprosin that was boiled for 5 minutes, or free I^{125}-Na was injected into the tail vein of each of the imaged mice. All mice were intravenously injected with Bismuth (MVIVO medilumine) at 350mg/kg body weight as a hepatic contrast agent. Imaging was done using Inveon Siemens scanner (Knoxville,TN). Following injection, mice were anesthetized with ~2% isoflurane in oxygen, adjusted to maintain a rate of 30-40 breaths/minute (BioVet, Newark, NJ, USA), and placed prone on the bed. A CT scan was acquired using the following protocol: 220 projections acquired covering 220º, with a source-to-detector distance of 320.76 mm and a source-to center of rotation distance of 223.87 mm. The x-ray tube voltage was set to 75 kVp and the current to 500 μA, with an exposure time of 800 ms per projection. The pixels in the detector were binned in groups of 2x2 for an effective detector pitch of 41.66 μm. After the CT scan, a SPECT image was acquired using both detectors in the Inveon Multimodality scanner, configured for the 35 keV photons emitted by the I^{125}. A total of 60 frames were acquired for 50 seconds each, with the gantry rotating 6º between frames. For the liver images, the 5-MWB-1.0 collimators were used (mouse whole body collimators with five 1.0 mm pinholes each), and a radius of rotation of 35 mm.

Image processing

The reconstruction of the CT images was done using a proprietary Feldkamp algorithm provided by Siemens as part of their Inveon Acquisition Workplace software. A downsampling of 2 was used to achieve isotropic voxels of size 83 μm. The SPECT images were reconstructed using the OSEM3D algorithm with 16 iterations and 6 subsets. The PSF model was used, and corrections for photon attenuation and scattering were applied.

FBN1 and GFP Adenoviruses

Adenovirus carrying human *FBN1* cDNA (*FBN1* pAdenoG-His) was custom built under control of the CMV promoter by Applied Biological Materials (Richmond, BC). The adenovirus passed quality control measures instituted by ABM and was validated by us for overexpression of full-length profibrillin protein *in vitro* and *in vivo*. The corresponding GFP adenovirus was obtained from the Vector Development Core at Baylor College of Medicine.

RNA Analysis

We used standard RNA extraction procedures (RNeasy Mini Kit from Qiagen). Reverse transcription was carried out using the High Capacity RNA-To-cDNA kit (Applied Biosystems Inc.) using the manufacturer's protocol. For gene expression analysis, QPCR was performed using sequence-specific primers and probes from Roche (Universal Probe Library). GAPDH was used as an internal control for all gene-expression assays. All QPCR primers are available upon request.

For analysis of human *FBN1* mRNA expression across all tissues, GTEx GTC RPKM file (v 6), containing all genes currently available in the database, was downloaded from the genotype-tissue expression project (GTEx) database (http://www.gtexportal.org). Data for *FBN1* was extracted and merged with sample IDs to get tissue-/organ-specific information. Tissue-specific relative expression (RPKM - reads per kilobase per million) was plotted on a logarithmic scale for all tissues.