Supplementary Table e-1. General characteristics of patients with non-mitochondrial diseases

	ALS	Cardio-myopathy	Fibromyalgia	Lymphoma	mCRC	Non-agenarians	PBC	PSC	SM
n	9	22	32	20	20	30	29	30	14
age [years]	52,0 (11.9)	48.0 (12.2)	44.0 (11.2)	46.9 (12.5)	64.2 (7.0)	89.6 (0.5)	52.5 (10.1)	42.4 (13.6)	55.1 (12.1)
BMI [kg/m^2]	23.6 (2.6)	25.9 (4.6)	27.0 (5.2)	na	25.5 (4.8)	25.6 (4.0)	23.8 (2.9)*	22.0 (3.1)*	na
%males (n)	55.6 (5)	59.1 (13)	21.9 (7)	55.0 (11)	50.0 (10)	50.0 (15)	27.6 (8)**	50.0 (15)	50.0 (7)
fasting [h]	no	12	8-10	na	na	na	>2	>2	12
sample storage [°C]	-20	-80	-70	-70	-20	-70	-80	-80	-80

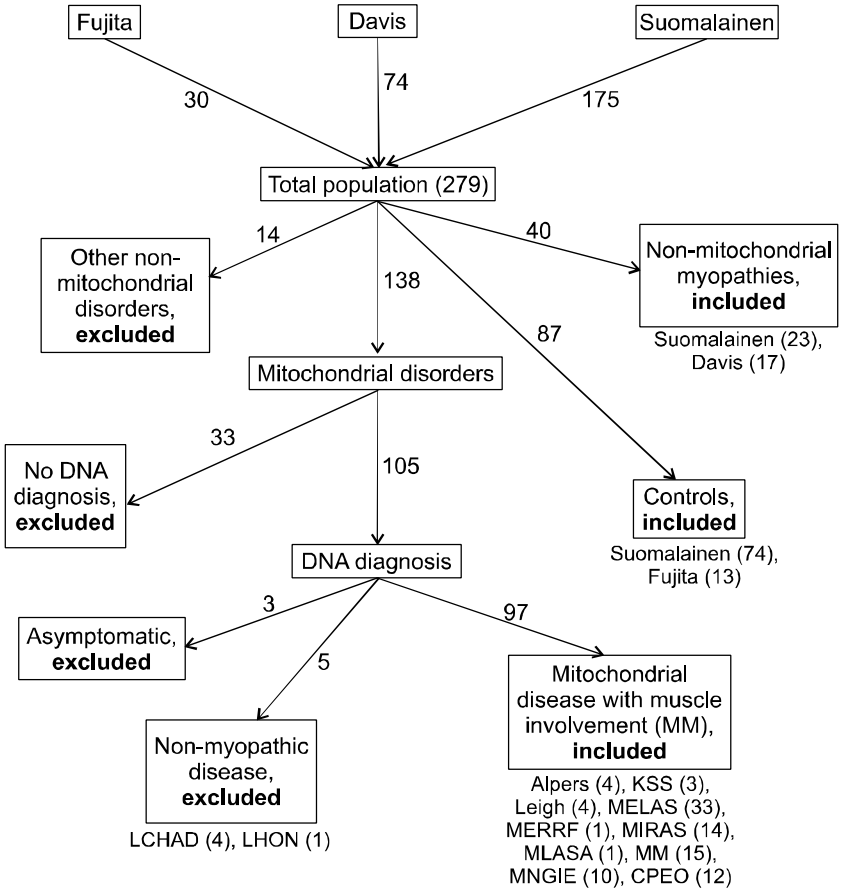
Brackets indicate the unit of each variable. Data presented as mean values (SD), na=not available, *calculated using ascites free weight. **As PBC is predominantly a female disease, we included all males transplanted in Finland between years 2000-2013 with this diagnosis. Abbreviations: ALS, amyotrophic lateral sclerosis; mCRC, metastasized colorectal cancer; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SM, statin-induced myalgia

Supplementary Table e-2. Association of S-FGF21 to liver dysfunction.

Spearman r	Bil	MELD	AST	AFOS	Alb	ALT	GT	INR	Prealb
r	0,48	0,37	0,36	0,22	-0,22	0,08	0,03	0,18	-0,15
95% confidence interval	0,25 to 0,66	0,12 to 0,59	0,04 to 0,61	-0,01 to 0,43	-0,48 to 0,07	-0,15 to 0,31	-0,24 to 0,29	-0,09 to 0,43	-0,43 to 0,15
p (two-tailed)	0,000	0,005	0,023	0,055	0,121	0,471	0,832	0,176	0,314
p value summary	***	**	*	ns	ns	ns	ns	ns	ns
Number of XY Pairs	58	56	40	78	50	78	58	58	47

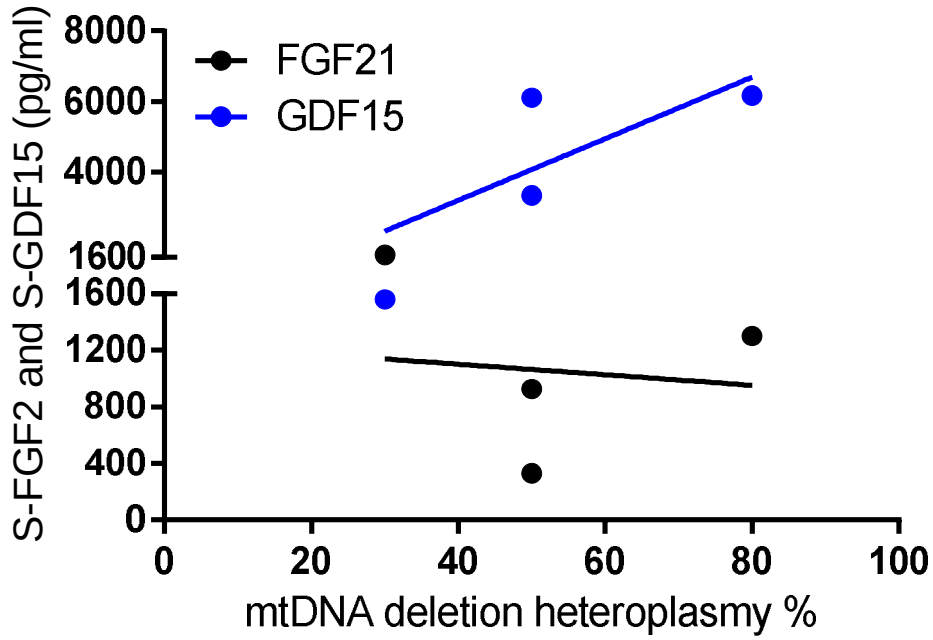
Bil = bilirubin, MELD = model for end-stage liver disease, AST = aspartate aminotransferase, AFOS = alkaline phosphatase, Alb = albumin, ALT = alanine aminotransferase, GT = gamma-glutamyl transferase, INR = international normalized ratio, Prealb = prealbumin, *p<0.05, **p<0.01, ***p<0.0001, ns=non-significant.

Supplementary Figure e-1. Flowchart of patient enrollment for meta-analysis.



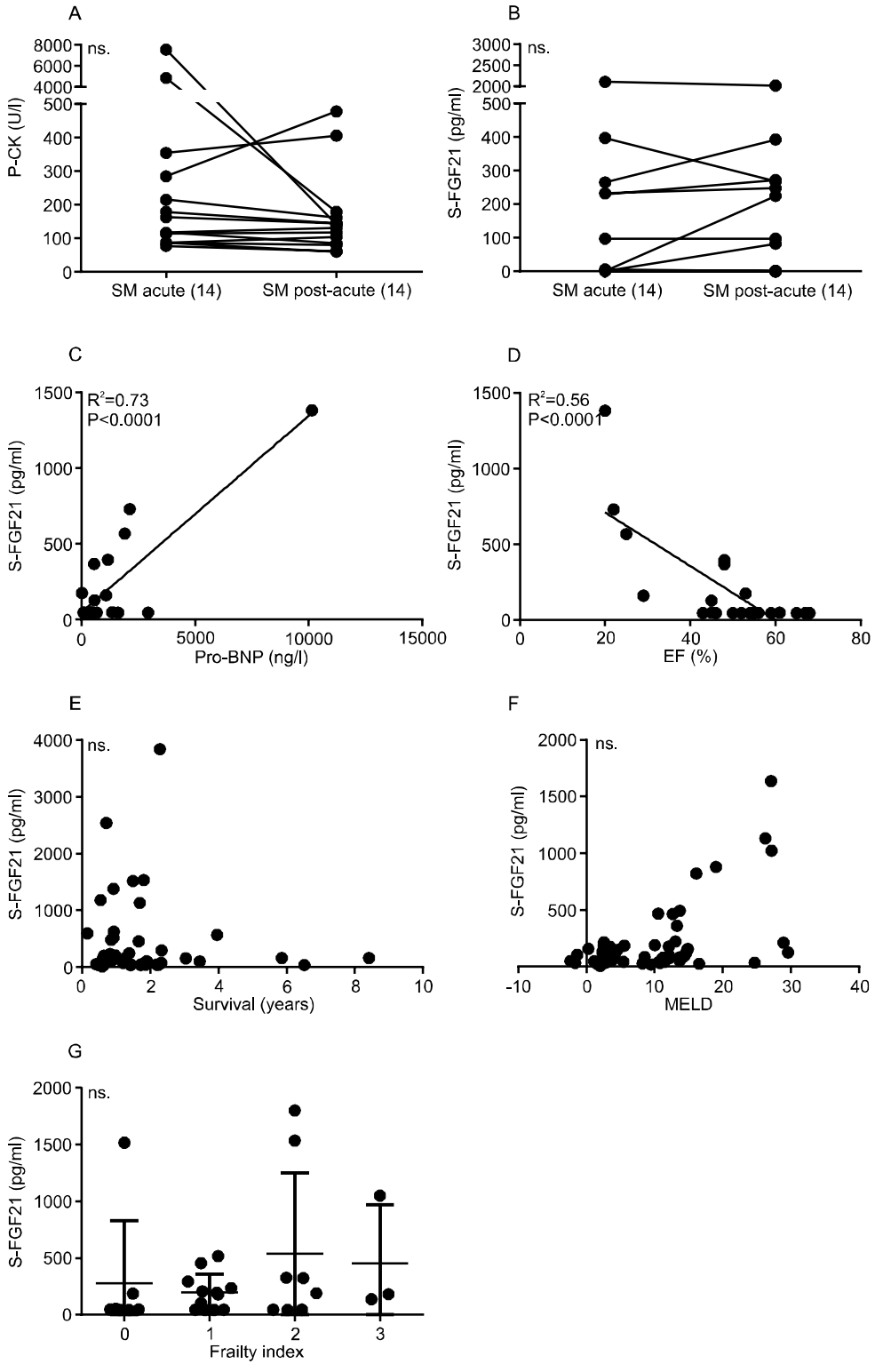
The chart depicts the inclusion criteria of mitochondrial myopathies, non-mitochondrial myopathies and controls collected from literature (Suomalainen et al. Lancet Neurol 2011;10:806-818; Davis et al. Neurology 2013;81:1819-1826; Fujita et al. Mitochondrion 2015;20:34-42) and analyzed as new samples. Numbers indicate individuals. Genetic causes of clinical syndromes with muscle manifestation are as follows: Alpers (POLG1), KSS (large mtDNA deletion), Leigh (ND3, SURF1, NDUFS7, ND1), MELAS (32x $tRNA^{Leu\text{-}UUR}$1x $tRNA^{Lys}$, MIRAS (POLG1), MLASA (YARS2), MM (11xtRNA, ND1, POLG, ND5, rRNA), MNGIE (TYMP), CPEO (5x Twinkle, 4x single mtDNA deletion, 2x POLG1, 1x tRNA). LCHAD=long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, LHON=Leber's hereditary optic neuropathy, KSS=Kearns-Sayre syndrome, MELAS=mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, MERRF=myoclonic epilepsy with ragged-red fibers, MIRAS=mitochondrial recessive ataxia syndrome, MLASA=myopathy with lactic acidosis, MM=mitochondrial myopathy, MNGIE=mitochondrial neurogastrointestinal encephalopathy, CPEO= progressive external ophtalmoplegia.

Supplementary Figure e-2. Association of mtDNA single deletion heteroplasmy-% to S-FGF21 and GDF15.



The lines indicate fitted linear regression lines on both datasets. R^2-value for FGF21 is 0.018 (non-significant) and for GDF15 0.6359 (non-significant).

Supplementary Figure e-3. Comparison of S-FGF21 to other disease parameters in non-mitochondrial diseases



Supplementary Appendix e-1. Amplification of *Fgf21* in mouse QF

β-actin primer sequences:
Forward 5'- ATG CTC CCC GGG CTG TAT- 3'
Reverse 5'- CAT AGG AGT CCT TCT GAC CCA TTC- 3'

Fgf21 primer sequences:
Forward 5'- CTG GGG GTC TAC CAA GCA TA -3'
Reverse 5'- CAC CCA GGA TTT GAA TGA CC -3'

Amplification protocol:
1. 95℃ 3min, 1 cycle
2. 95℃ 10sec, 60℃ 30sec, 45 cycles
3. 60℃ -95℃ in 0.5℃ intervals, 5sec in each, reading after each temperature change, 1 cycle

Supplementary references

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