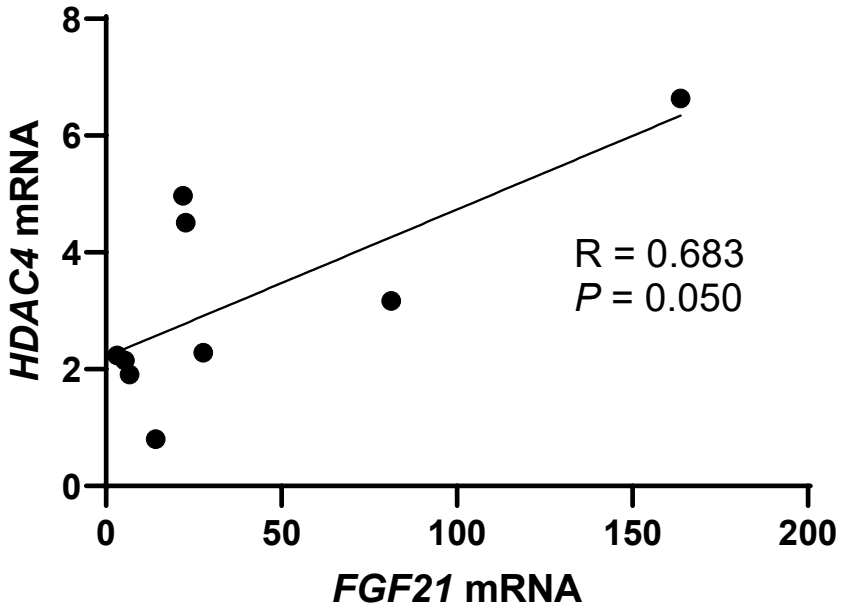
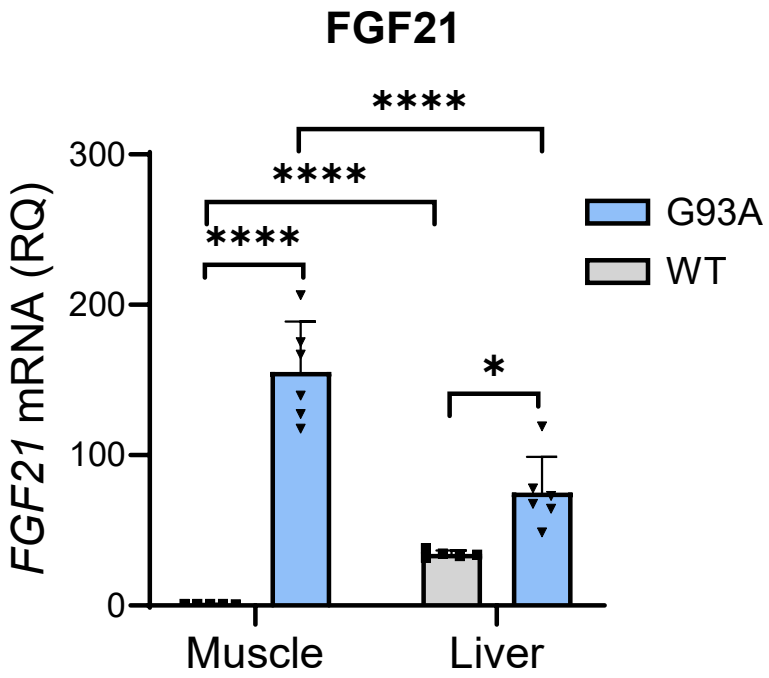
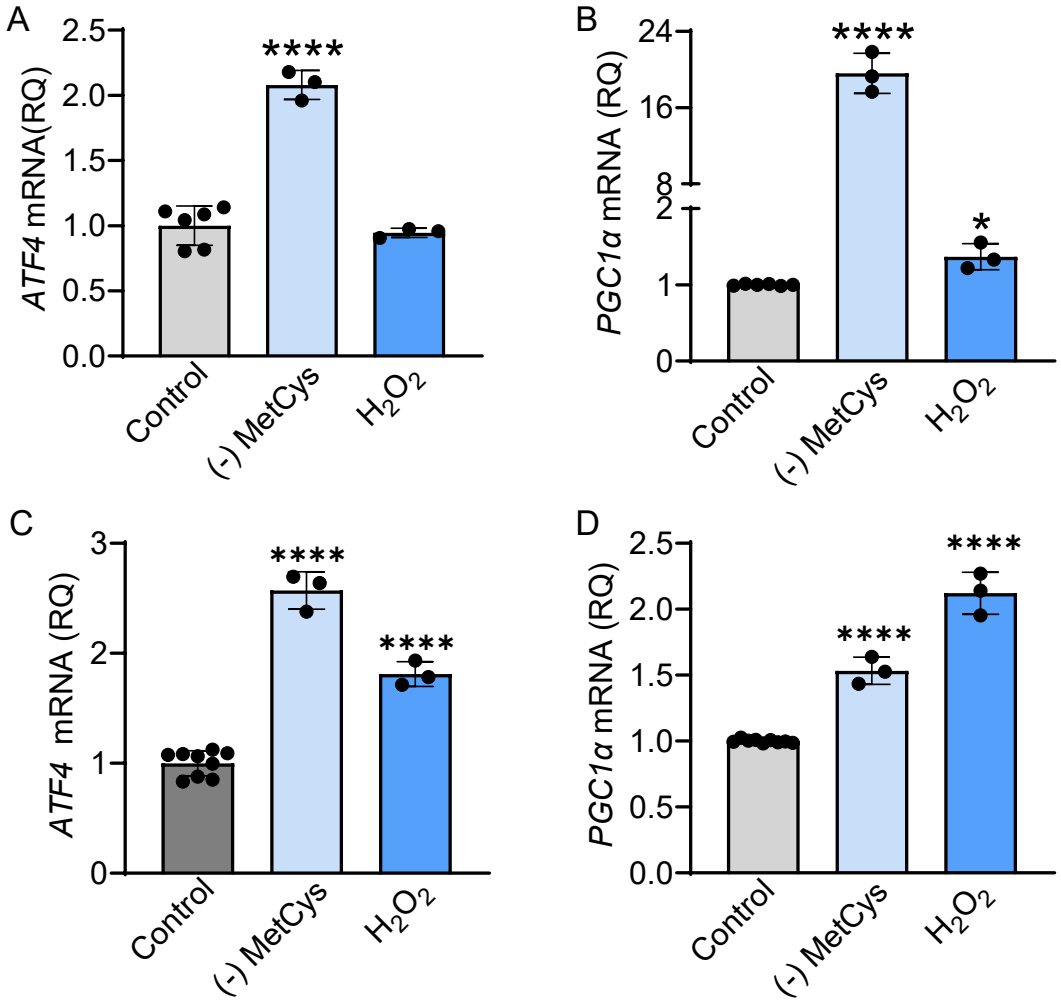


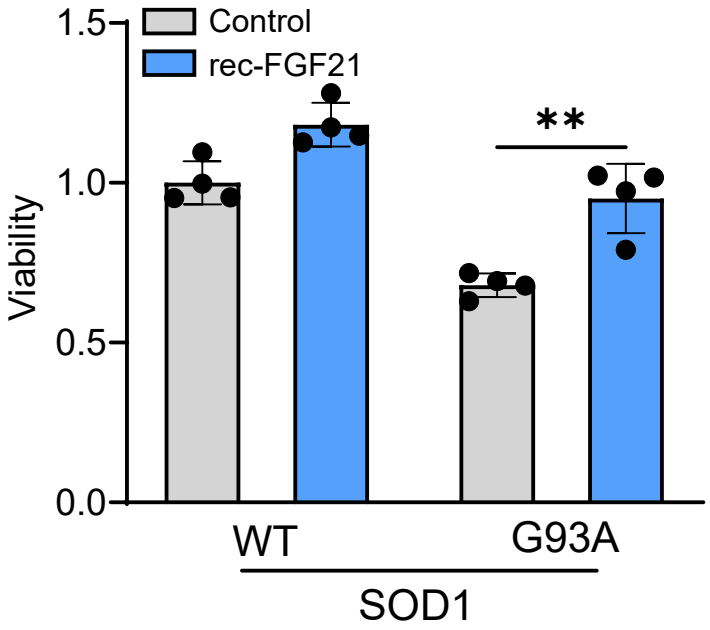
Supplementary Figure 1. Spearman rank test correlation between *HDAC4* and *FGF21* mRNA expression levels (assessed by qPCR) in 9 post-mortem ALS muscle samples.



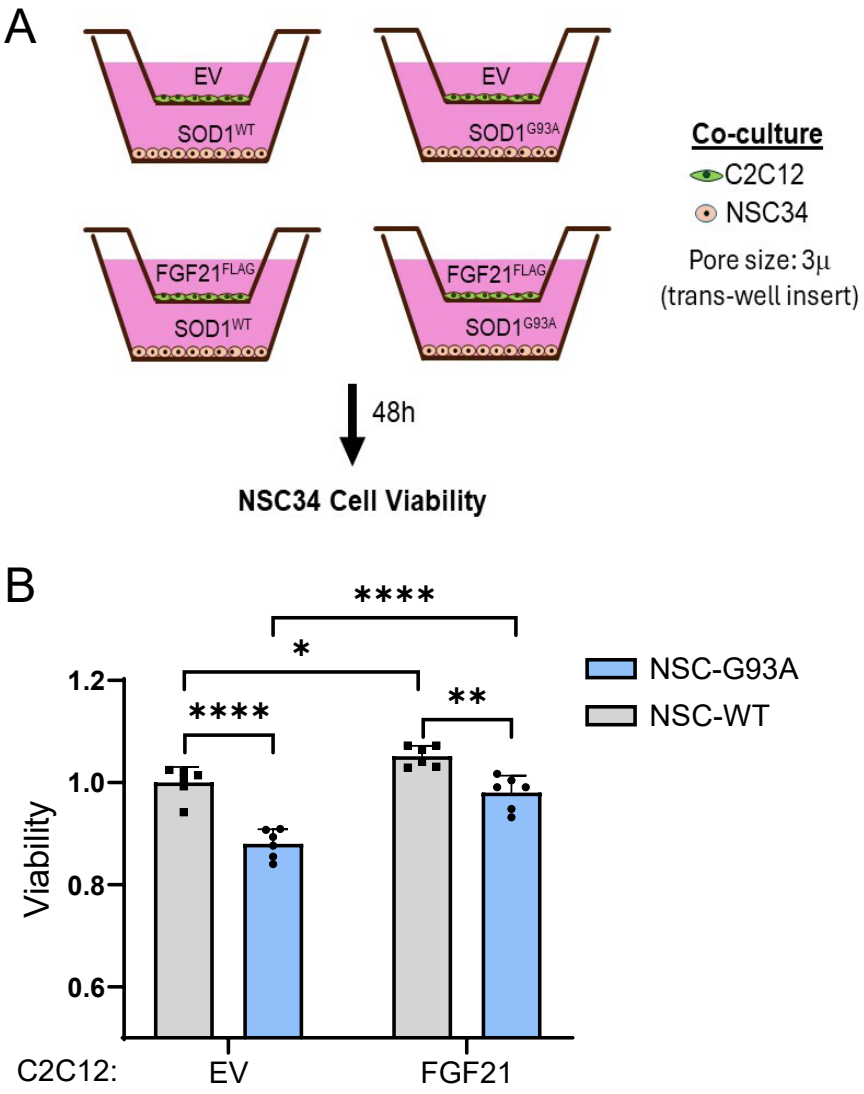
Supplementary Figure 2. FGF21 mRNA is increased in muscle and liver tissue in the SOD1^{G93A} mouse. RNA was extracted from wild-type (WT) and SOD1^{G93A} mouse tissue at post-natal day 60 and assessed by qPCR for FGF21 mRNA. All values represent fold-change compared to WT muscle which was set at 1. Data points represent individual mice and bars represent the mean ± SD. *$P < 0.05$, ****$P < 0.0001$; one-way ANOVA followed by Tukey's multiple comparisons test.



Supplementary Figure 3. Oxidative stressors induce *ATF4* and *PGC-1α* in NSC-34 motor neuron-like cells and C2C12 myoblasts. (A) and (B) *ATF4* and *PGC-1α* mRNA levels in NSC-34 cells were quantified after treatment with 100 μM H2O2 or methionine-cysteine (MetCys)-depleted media for 24 h. (C) and (D) *ATF4* and *PGC-1α* mRNA levels were quantified in C2C12 myoblasts after exposure to the same conditions as in (A) and (B). Data points are independent biological samples and bars represent the mean ± SD.*P = 0.048, ****P < 0.0001; one-way ANOVA followed by Tukey's multiple comparisons test.



Supplementary Figure 4. Recombinant FGF21 treatment reverses cytotoxicity of NSC-34 motor neuron-like cells expressing SOD1^{G93A}. NSC-34 cells expressing either WT SOD1 or SOD1^{G93A} were treated with recombinant FGF21 (100 ng/ml). Cell viability was measured 24 hours later as described in the methods. Bars represent the mean ± SD of 4 independent biological samples. **P = 0.003; unpaired two-tailed t-test.



Supplementary Figure 5. C2C12 cells expressing FGF21 rescue SOD1^{G93A}-mediated toxicity in NSC-34 motor neuron like cells in co-culture. (A) Schematic of co-culture system used. (B) Cell viability of NSC-34 cells expressing either WT-SOD1 or SOD1^{G93A} (lower well) was assessed in the presence or absence of FGF21-expressing C2C12 cells (upper well). Data points represent biological replicates and bars are the mean ± SD. **P* = 0.025, ***P* = 0.002, *****P* < 0.0001; one-way ANOVA followed by Tukey's multiple comparisons test.

Supplementary Table 1: Demographic and clinical data for iPSC-derived motor neurons.

Cell Line	Sex	Age (y)	Clinical Diagnosis	Primary tissue	Mutation
CS0002iCTR	M	51	Normal	PBMC	N/A
CS83iCTR	F	21	Normal	Fibroblast	N/A
CS188iCTR	M	80	Normal	PBMC	N/A
CS14iCTR	F	35	Normal	Fibroblast	N/A
CS00iCTR	M	6	Normal	Fibroblast	N/A
FA0000011	F	49	Normal	Fibroblast	N/A
NN0003920	M	64	Normal	Fibroblast	N/A
CS0118iALS-SOD1-I114T	F	73	ALS	Fibroblast	SOD1 I113T
CS28iALS	M	47	ALS	Fibroblast	C9ORF72 (HRE ~800)
CS29iALS	M	47	ALS	Fibroblast	C9ORF72 (HRE ~800)
CS52iALS	M	49	ALS	Fibroblast	C9ORF72 (HRE ~800)
CS30iALS	F	51	ALS	Fibroblast	C9ORF72 (HRE ~70)
NN0004306	F	51	ALS	Fibroblast F10330	C9ORF72 (HRE 2.7kb)
NN0004307	M	57	ALS	Fibroblast F09152	C9ORF72 (HRE 6-8kb)

ALS = amyotrophic lateral sclerosis; F = female; HRE = hexanucleotide repeat expansion; M = male; ORF = open reading frame; PBMC = peripheral blood mononuclear cells; SOD1 = superoxide dismutase 1; y = years

Supplementary Table 2. Demographic and clinical data of tissue samples.

	Biopsy		Autopsy	
	Normal	**ALS**	**Normal**	**ALS**
Number	24	36	22	23
Mean age (years) [a]	52 ± 15	57 ± 13	67 ± 12	64 ± 11
Age range (years)	24 - 77	27- 86	34 - 83	40 - 81
Gender (M:F)	11:13	21:15	18:4	18:5
Duration [b] **(m)**		15 ± 9		51 ± 32
Diagnosis		Spinal onset (33) Bulbar onset (3)		Spinal onset (20) Bulbar onset (3)
Muscle sampled				
Biceps brachii	5	2		2
Deltoid	3	11	4	3
Vastus lateralis	15	8	3	5
Tibialis anterior	1	15		Triceps (1)

[a] Mean age (± SD) at time of sample collection.
[b] Mean duration (± SD) from onset of symptoms to sample collection. Duration was unknown for three ALS patients in the biopsy pool.

Supplementary Table 3: Demographic and clinical data of plasma samples

	Normal	ALS
Number	23	28
Mean age (y) [a]	61 ± 9	59 ± 10
Age range (y)	45 - 84	35- 82
Gender (M:F)	12:11	18:10
Duration [b] (m)		26 ± 20
Onset		Spinal onset (22) Bulbar onset (6)

F = female; M = male; m = months; y = years

[a] Mean age (± SD) at time of sample collection.

[b] Mean duration (± SD) from onset of symptoms to sample collection.

Supplementary Table 4: ALS study patients

Plasma FGF21 (FC)[a]	**< 1.5**	**≥ 1.5**
Number	7	9
Age (y)[b]	65 ± 9	57 ± 9[d]
Age range (y)	58 - 82	42 – 70[d]
Gender (M:F)	4:3	7:2
Duration[c] (m)	18 ± 10	26 ± 23[d]
Onset	Bulbar (4) Spinal (3)	Spinal (9)

F = female; FC = fold-change; M = male; m = months; y = years
[a]Fold-change over normal control group
[b]Mean age (± SD) at time of sample collection.
[c] Mean duration (± SD) from onset of symptoms to sample collection.
[d]No significant difference between the 2 groups