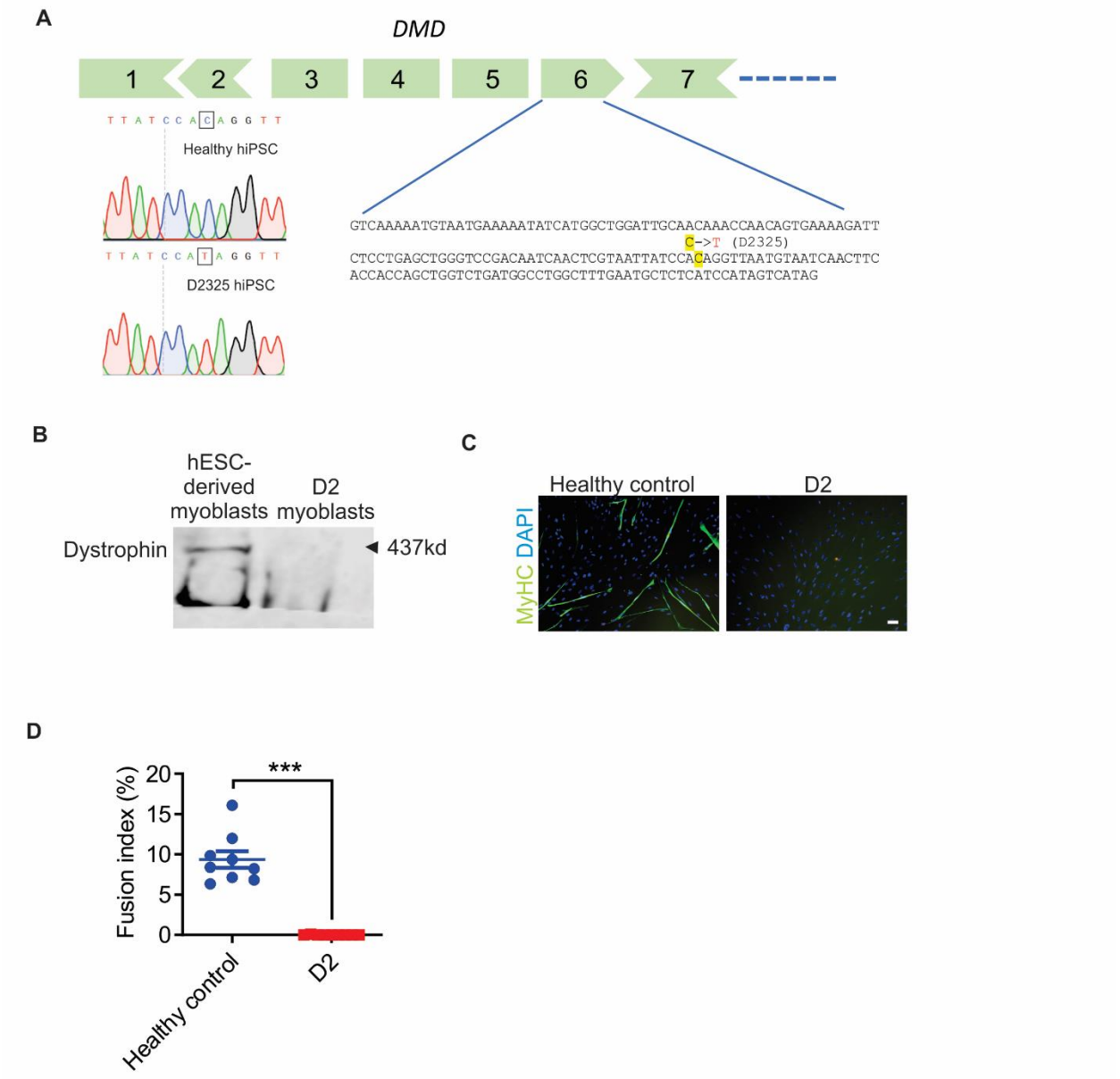
Supplemental Table 1

Target gene	Forward primer (5' to 3')	Reverse primer (5' to 3')
SMAD7	AGCCGACTCTGCGAACTAGA	ATTCGTTCCCCCTGTTTCA
SKI	ACTGGAAGGCGAGACCATCT	AGCACCGAGTTGAGAATCTGC
NOS3-2	GATCCCCCAGAACTCTTCCT	CAGGGCTGCAAACCACTC
HSP90B1	CTGGAAATGAGGAACTAACAGTCA	TCTTCTCTGGTCATTCCTACACC
PRKG1	TTCTGAATTTGAAAGTCTTCATGC	CAGCATTTCCTCAACAGTGG
LIPG	GGGAGCCCCGTACCTTTTG	CCTCACAGATGGTTTGACCTCA
NLRP12	AGACTGGGGCCTGTGGTT	TGTGAGGCCACAGCTATCC
U2AF2	CAGGCCTCACGACTACCAG	GGGACCACAGTGGACACAA
DNAH5	TGGATTGCATGTTTGATGCT	AACCCAGTGTACTAGAAATCCAAGA
RANBP3L	TTCCCAACCATCACGAAAAT	TTTTGTTGAATATGAAAAGCTTGC
CLEC7A	TGAGATAGGGTCTCACTTTGTTACC	GCTGAGGCGAGAGATAGCTG
TATDN2	GGAAGCGCTTAGGCATCTC	GTTTCCAAGCCCACAACG
ARHGAP42	CATTTAAATTTGTCCGCAAAGAA	GAAGTTCTGATGTTCTCGGTCA
MGEA5	GGAAACAGCGGAAGACCTAAG	GGTCCTGTCCTCGTTCTCTG
LRRC20	CCAACTGACAACACCAGTAACTAAA	TCACAAAAGGGCCTGAGC
EGFLAM	CCAGAAGTTTTCAGCCCTCA	CGTGGAGTTCCGCTTTGA
CLCA2	GCCAATGTGAAACAGGGATT	AGGAGTCTCAGCGTAACAGGA
LUZP2	CACAAAGAAAGTCCCCCAAG	ACCTCACATTCAGAGCAAGGA
GABRB1	TGGGTGTCTTTTTGGATCAAC	TGTAAGCACTGTCGTGATTCCT
GMNC	ACGGAGACTTGGGTCTCTTTC	TCCGGAAGAGGAAAATTTGA
CBL	TGACGTATGACGAAGTGAAAGC	CAGCTCAGCCGGAAGATATAA
GABRB3	GAAGGCTTTTCGGCATCTT	CCGGGATCGTTCACACTC
WNT2	TTTGGCAGGGTCCTACTCC	CCTGGTGATGGCAAATACAA
SDHAF3	AAGACCGTTGGTTCTGACGAGG	TCTTCTGGGAGGAAGGTGCCAA
ESR1	GCTTACTGACCAACCTGGCAGA	GGATCTCTAGCCAGGCACATTC
RPL12	GTGCACCGGAGGTGAAGT	TGGCAATGTCATCACCAACT
DGCR8	TGCAAAGATGAATCCGTTGA	AGTAACTTGCTCAAAGTCAAAACG
PIP5K1C	ACACAGTCGTCTGGACAGGA	CCACCTGCACTGTAATCTGC
DNAJC11	AAATGCACATATCCCAGTCCA	GGTTGAGAGGCTTCCAGAGAG
ANKRD36C	GGAGAGCAAAAGAGGCTTGA	GCTCACAGTGATTATCTTTAAGTTCTG
SPAG5	TTTGCTCAGCGTCACACAG	TCGGTTTCCTCTAAGTCCATTC
OR51T1	AGCGGAGACTCCACAAACC	AATGGTCAGACATAGATCAACAGC
TATDN2	GGAAGCGCTTAGGCATCTC	GTTTCCAAGCCCACAACG
GPC4	GGAGATGTCGTGAGCAAGGT	CTTCAACAGGGCATGGGTA
FCHO1	TTGTACACACAACCGCTATTGA	CACTCTGGGAGGGGTCACT
BPGM	CTAGGAGGCGCTGGCTCT	TCAAATGGGCTAATATTCAAGGA
ITIH4	CAGCACGTCCTGGAGTCA	CGAAGGGAGTGTCTCACTCAT
BBX	CACCTCTCTGCGAGCTAATGT	TCTTCATTCCAACACCCTTCA
ERV3	GACCCACTGGAAGCCTAGAA	CTAGGTCCTGTTGGCTGGTC
SRP54	TGCAGGGAGCATACAGAAAG	ATGCACCAAGGTGAACTGTG

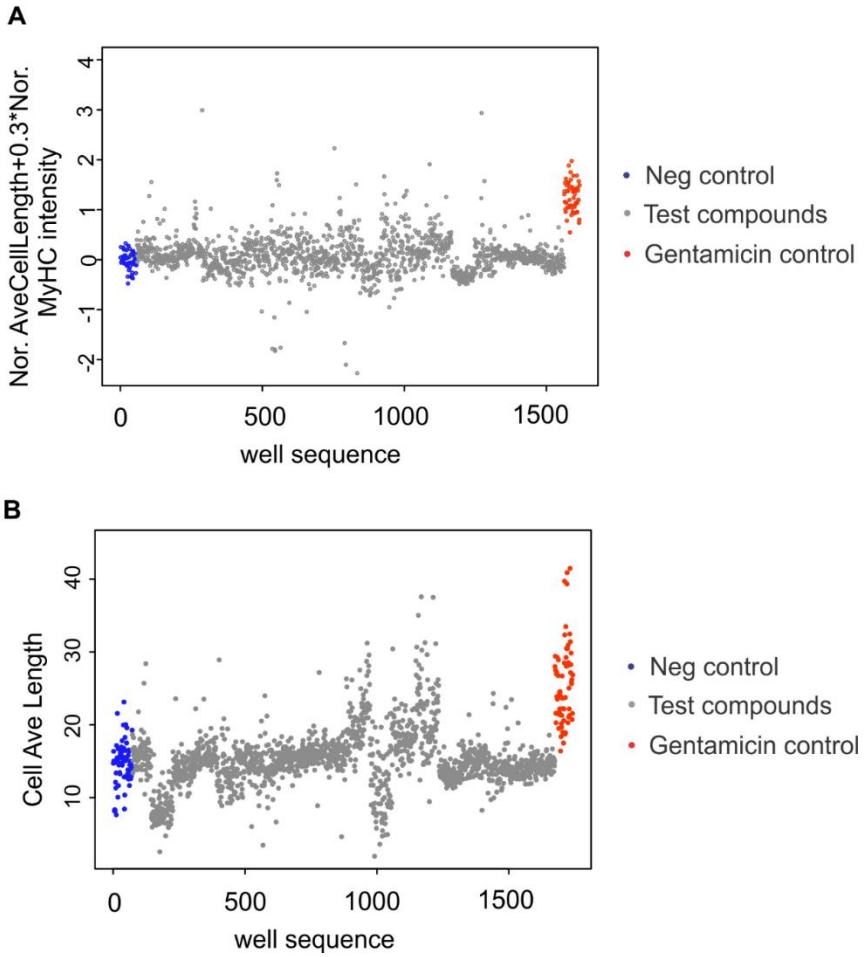
CDKL5	TCCATCGAGATATAAAACCAGAAA	CCTTCTGACAGATTACGAGCAA

Supplemental Figure 1



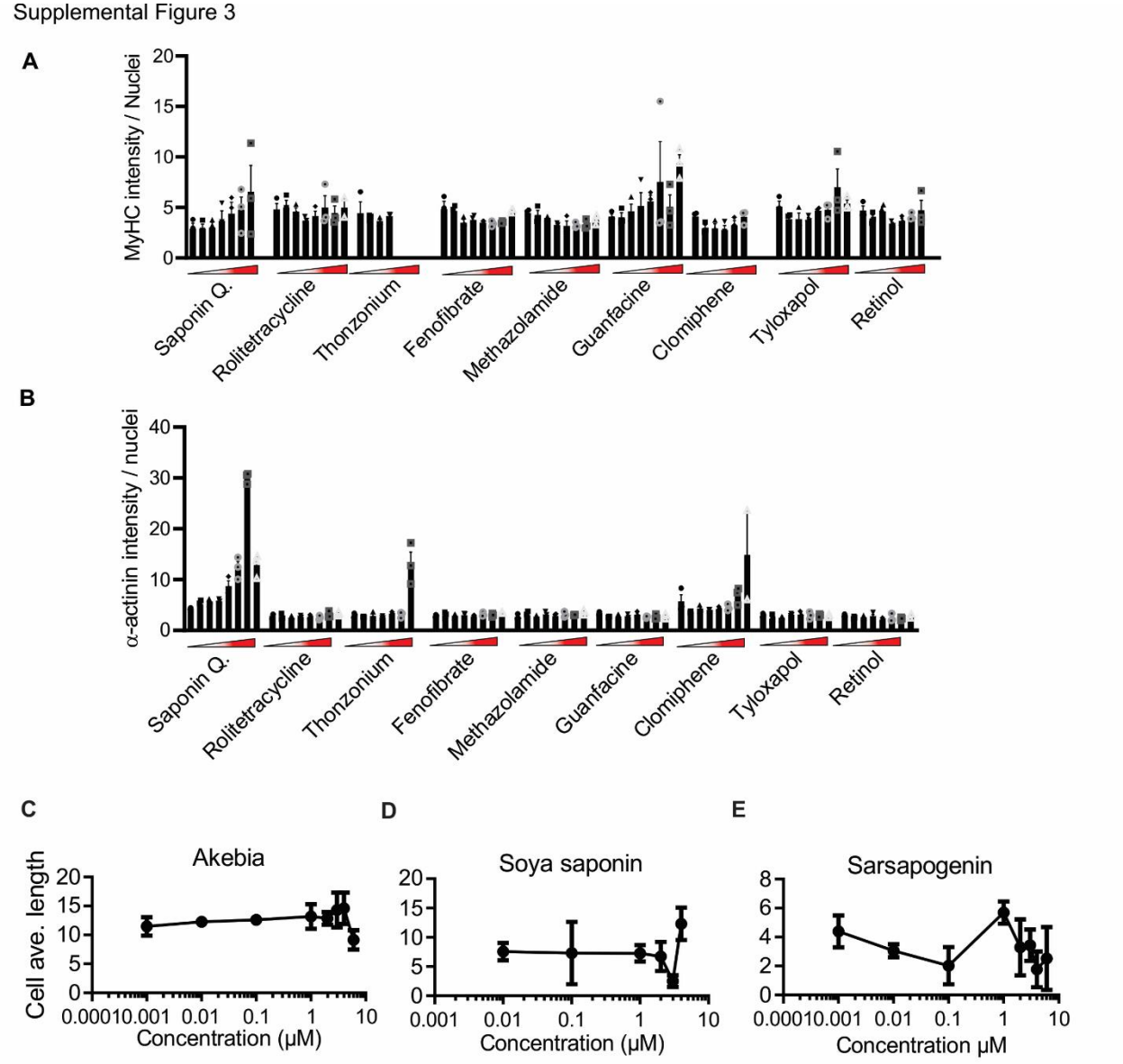
Supplemental Figure 1. Phenotype of DMD hiPSC-derived myoblasts. **(A)** Illustration of the point mutation in dystrophin gene of D2325 patient. **(B)** Western blot of hESC-derived myoblasts and D2 myoblasts cultured for 9 days in differentiation medium showing D2 myoblasts does not express dystrophin protein. **(C)** Representative image of MyHC antibody-labeled myotubes compared with myoblasts derived from healthy hiPSC or D2 myoblasts, scale bar = 50 μm. **(D)** Quantification of fusion index, n = 9 for each group, ***P ≤ 0.001. (Data = Mean ±SEM, each point represents an experimental repeat, Student's t-test).

Supplemental Figure 2



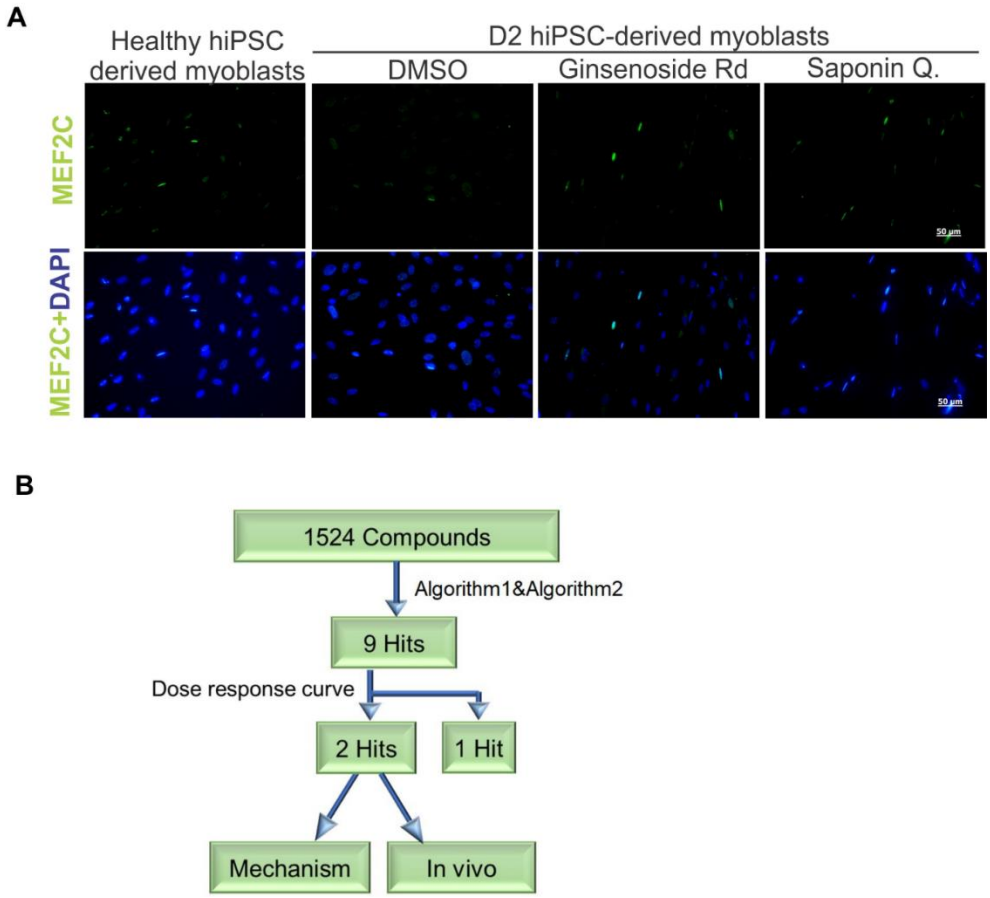
Supplemental Figure 2. Scatter plots show result of two algorithms of D2 myoblasts treated with the JHCCL compound library. Algorithm 1 **(A)** and algorithm 2 (**B**) plot of all tested compounds along with DMSO (blue) and gentamicin (red) treated D2 cells**,** n(Test cmp)=1324, n(Negative control)=50, n(Gentamicn)=50. (each point represents result from one well of cells from 96-well plates)

Supplemental Figure 3



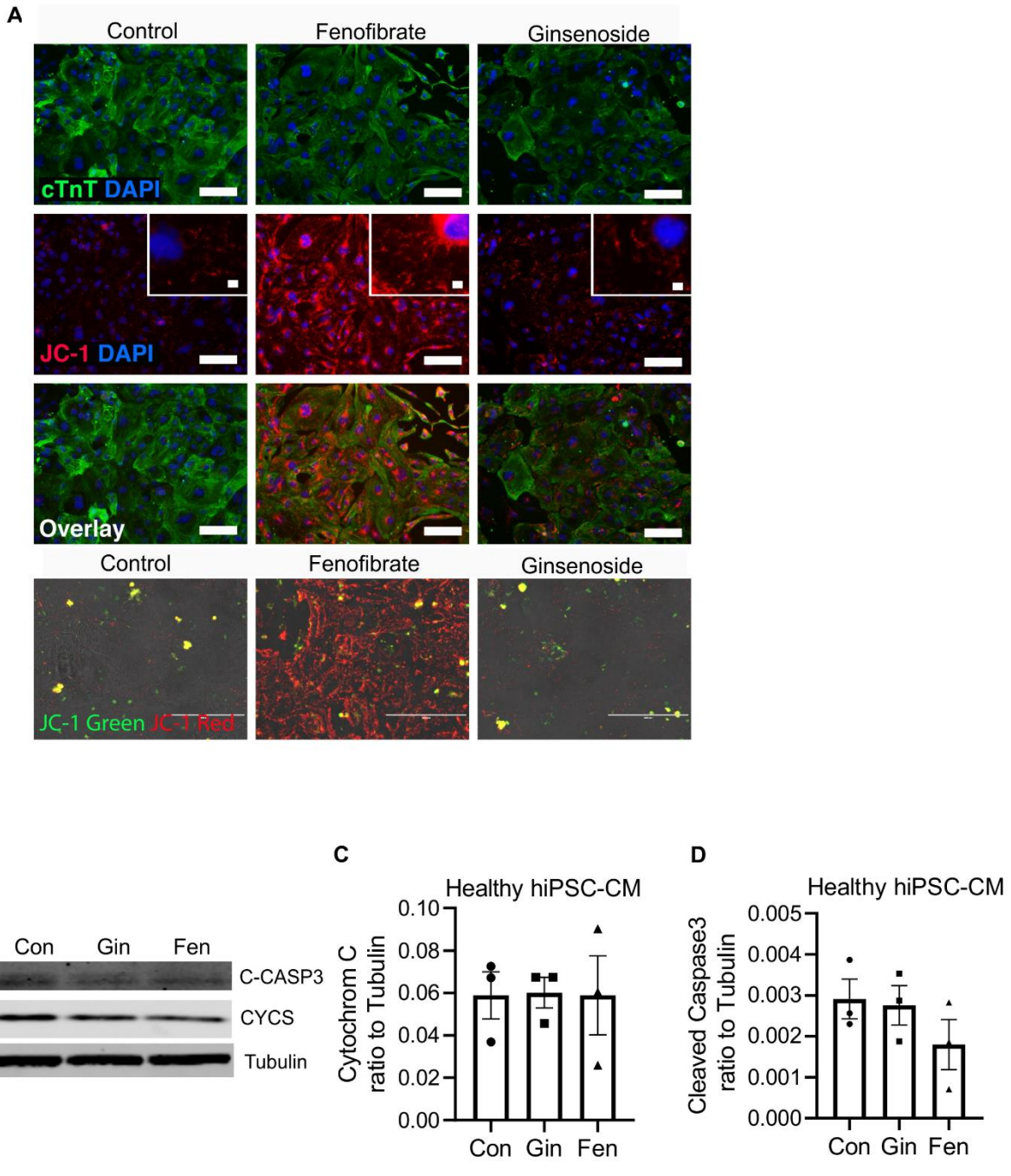
Supplemental Figure 3. Dose-response of 9 hit compounds, analogs of Saponin Q and fenofibrate. **(A)** 9 primary hit compounds dose-response measured by MyHC antibody immunofluorescent intensity/nuclei. Concentrations of compounds were 0.001, 0.01, 0.1, 1, 2, 3, 4, 6 μM, except for saponin Q. which was 0.001, 0.01, 0.1, 0.2, 0.4, 0.6, 1 μM, n = 3 for all groups. **(B)** 9 primary hit compounds dose-response measured by α-actinin antibody immunofluorescent intensity/nuclei. Concentrations were same as above, n = 3 for all groups. **(C-E)** Dose-response measured by cell average length of 3 analogs of saponin Q, n=3. (Data = Mean ±SEM, A,B: each dot represents an experimental repeat)

Supplemental Figure 4



Supplemental Figure 4. **Selecting final Ginsenoside Rd based on MEF2C staining.** **(A)** Representative immunocytochemistry images of MEF2C antibody labeled healthy hiPSC derived myoblasts or D2 cells that were treated with DMSO, ginsenoside Rd or saponin Q, scale bar = 50 μm, performed in triplicate **(B)** Flow chart of the tiered compounds screen (The separate 1 hit refers to clomiphene that was not pursued in this study)

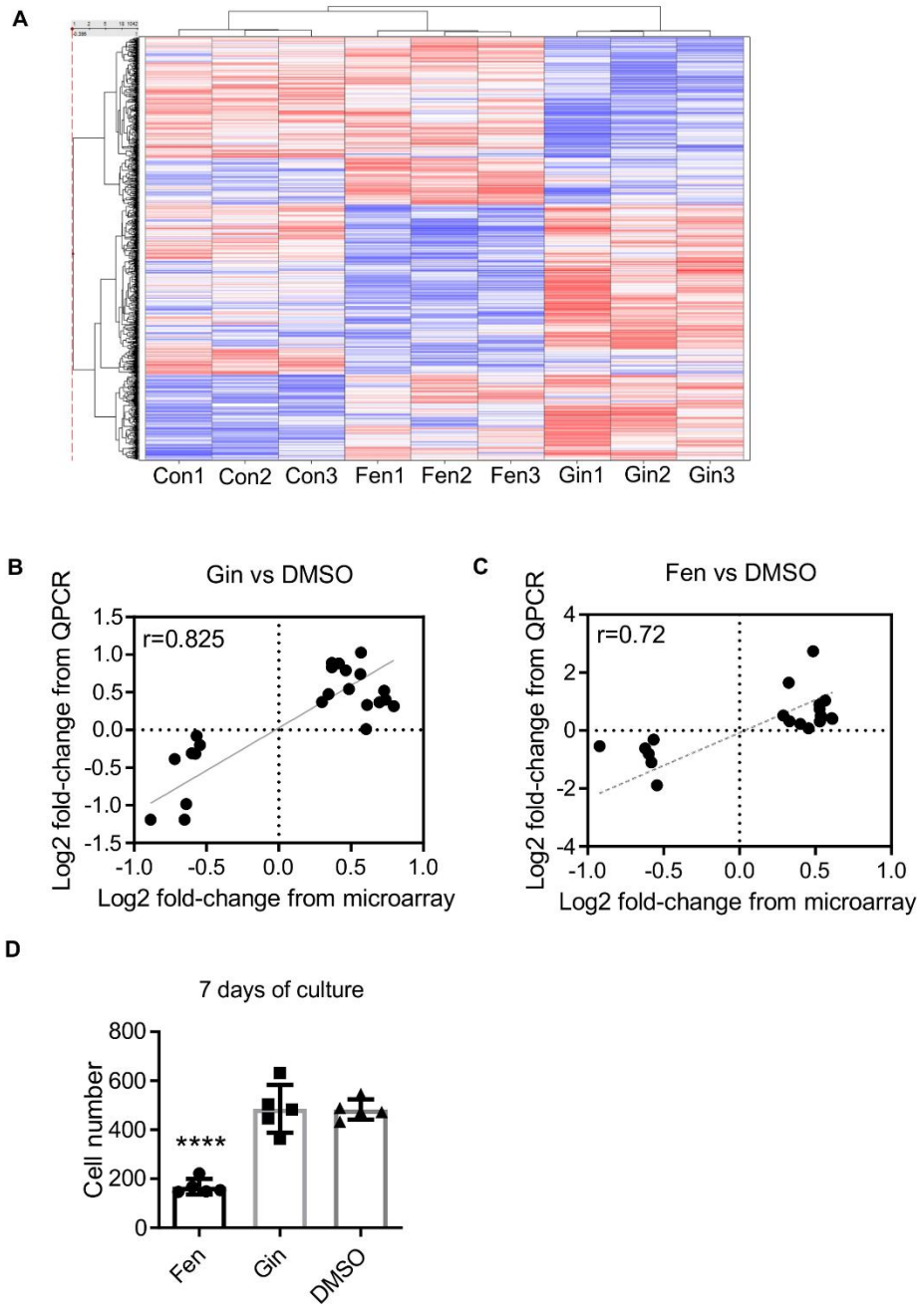
Supplemental Figure 5



Supplemental Figure 5. JC-1 dye stained hiPSC- CMs and apoptosis related protein expression in DMD and healthy hiPSC-CMs after fenofibrate (5 μM) and ginsenoside (5 μM) treatment. (A) Representative images (fixed and live) of JC1 dye stained DMD hiPSC-CMs after 7 days treatment of fenofibrate (5 μM) and ginsenoside (5 μM), performed in triplicate. (**B-D**) Quantification of western blot of cytochrome C and

cleaved Caspase3 in DMD hiPSC-derived cardiomyocytes treated with ginsenoside Rd (5 µM), fenofibrate (5 µM), or DMSO, n = 3 for all groups. (Data = Mean ±SEM, each dot represents an experimental repeat)

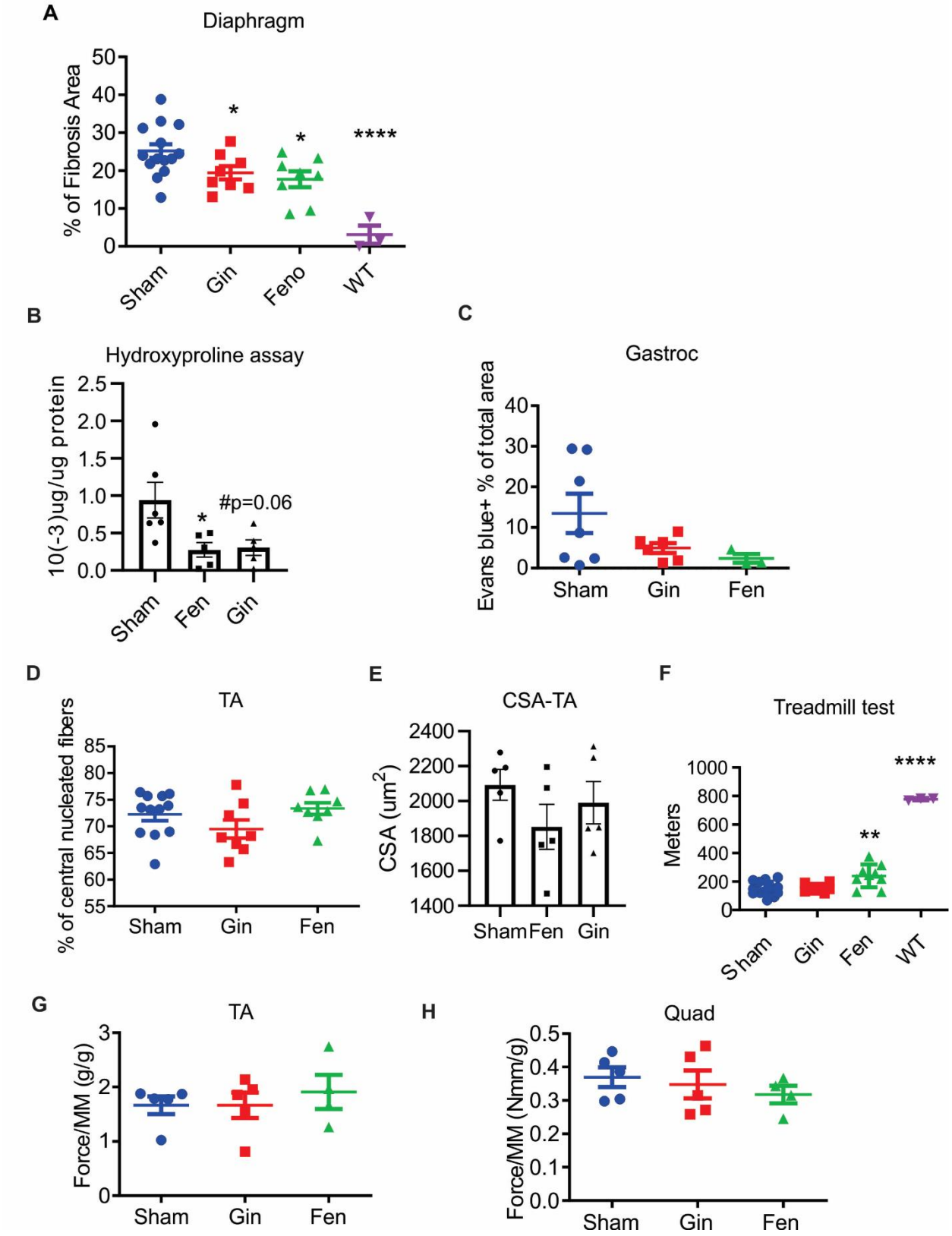
Supplemental Figure 6



Supplemental Figure 6 Fig. Gene expression profiling by microarray. (A) Heat map of gene expression level in D2 myoblasts treated by DMSO (control), fenofibrate (fen) and ginsenoside Rd (gin) showing how treatment with each compound results in distinct gene expression changes, n = 3. **(B-C)** Correlation between log2 fold change from

microarray and from qPCR for ginsenoside treatment (B) (5 µM, 24h) vs. DMSO (control) treatment; fenofibrate treatment **(C)** (8 µM, 24h) vs. DMSO (control) treatment (n = 3 for all groups) **(D)** fibroblast cell number after 7 days of culture and treatment of fenofibrate and ginsenoside compared to DMSO control, n=5 for all groups, ****P≤0.0001. (Data = Mean ± SEM, student's t-test, B,C: each point represent one gene, D: each point represent an experimental repeat)

Supplemental Figure 7



Supplemental Figure 7. Histological and physiological findings of 10-week old *mdx* mice treated with Ginsenoside Rd (gin) (10 mg/kg) or fenofibrate (fen) (0.1% w/w). (**A**) Quantification of Masson Trichrome-labeled fibrotic area (blue) in diaphragm muscle of mice including wildtype mice, n(sham)=14, n(gin)=8, n(fen)=8, n(WT)=3, *P ≤ 0.05, ****P ≤ 0.0001, scale bar = 200 μm. **(B)** Hydroxyproline assay of diaphragm tissue of *mdx* mice treated with ginsenoside Rd and fenofibrate, n (sham)=5, n (gin)=5, N(fen)=6, *P ≤ 0.05. **(C)** Quantification of Evans blue dye-stained area signifying necrotic fibers (n(sham)=7, n(gin)=6, n(feno)=3) in gastrocnemius muscle and **(D)** Percentage of central nucleated fibers in tibialis anterior (TA) muscle (n(sham) = 12, n(gin) = 8, n(feno) = 8) from *mdx* mice treated by ginsenoside Rd, fenofibrate along with the sham control **(E)** Mean cross-section area of TA muscle from three treatment groups, n=5. (**F**) Maximum treadmill distance, n(sham) = 16, n(gin) = 8, n(fen) = 9, n(WT)=3, **P ≤ 0.01, ****P ≤ 0.0001. **(G)** Specific force (muscle force normalized to muscle mass (MM), g/g) of TA muscle **(H)** Specific force (muscle torque normalized to muscle mass (MM), N·mm/g) generated by quadriceps (Quad) muscle from *mdx* mice treated by ginsenoside Rd or fenofibrate along with the sham control, n = 5 for all 3 groups, *P≤0.05, ***P ≤ 0.001. (Data = Mean ± SEM, each point represents one mouse, one-way ANOVA with Dunnett's multiple comparison test with sham control).

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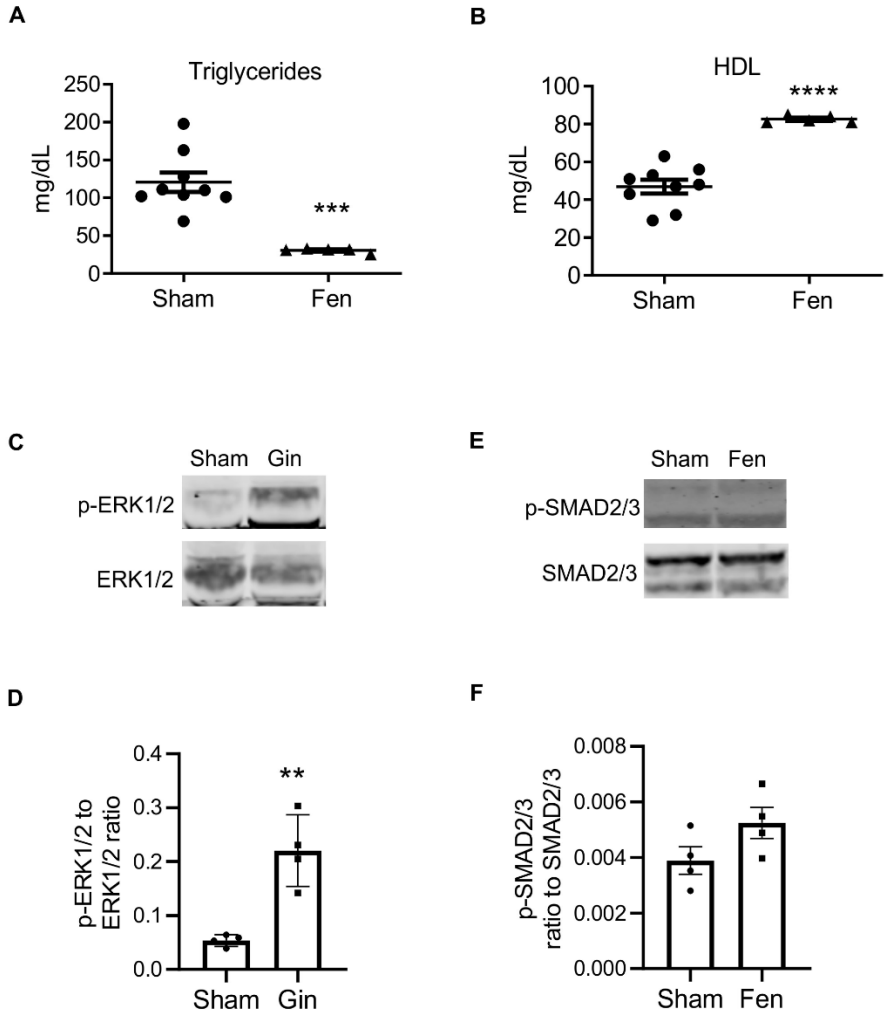
Supplemental Figure 8



Supplemental Figure 8. FLT3 and TGF- β signaling in quadriceps and endurance test from ginsenoside Rd or fenofibrate treated *mdx* mice. **(A-B)** Triglycerides and HDL content in serum from mice treated with fenofibrate (Fen)and sham control, n(sham) = 9, n(fenofibrate) = 5, ***P ≤ 0.001, ****P ≤ 0.00*1. **(C-D)** Quantification of western blot of phosphorylated ERK 1/2 (p-ERK 1/2) in quadriceps muscle of *mdx* mice treated with ginsenoside Rd (Gin) or sham, n = 4 for both groups, **P ≤ 0.01. **(E-F)** Quantification of western blot of phosphorylated SMAD2/3 (p-SMAD2/3) in quadriceps muscle of *mdx* mice treated with fenofibrate or sham n = 4, **P ≤ 0.01 (Data = Mean ± SEM, A-B: each point represent one mouse, student t test, D,F: each point represents an experimental repeat, one-way ANOVA with Dunnett's multiple comparison test with sham control.)