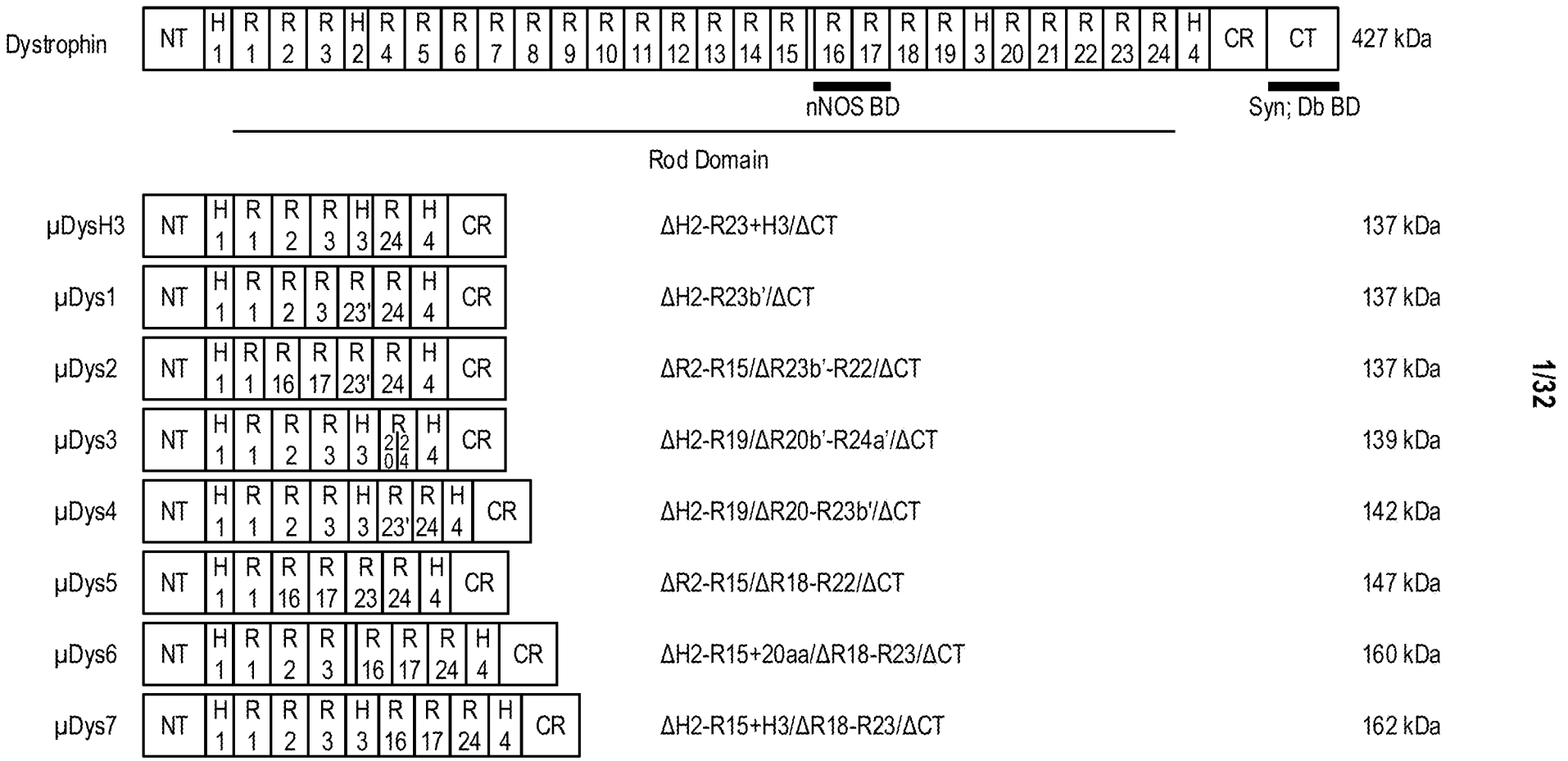

Dystrophin
NT
H1
R1
R2
R3
H2
R4
R5
R6
R7
R8
R9
R10
R11
R12
R13
R14
R15
R16
R17
R18
R19
H3
R20
R21
R22
R23
R24
H4
CR
CT
427 kDa
nNOS BD
Syn; Db BD
Rod Domain
μDysH3
NT H1 R1 R2 R3 H3 R24 H4 CR
ΔH2-R23+H3/ΔCT
137 kDa
μDys1
NT H1 R1 R2 R3 R23' R24 H4 CR
ΔH2-R23b'/ΔCT
137 kDa
μDys2
NT H1 R1 R16 R17 R23' R24 H4 CR
ΔR2-R15/ΔR23b'-R22/ΔCT
137 kDa
μDys3
NT H1 R1 R2 R3 H3 R20/24 H4 CR
ΔH2-R19/ΔR20b'-R24a'/ΔCT
139 kDa
μDys4
NT H1 R1 R2 R3 H3 R23' R24 H4 CR
ΔH2-R19/ΔR20-R23b'/ΔCT
142 kDa
μDys5
NT H1 R1 R16 R17 R23 R24 H4 CR
ΔR2-R15/ΔR18-R22/ΔCT
147 kDa
μDys6
NT H1 R1 R2 R3 R16 R17 R24 H4 CR
ΔH2-R15+20aa/ΔR18-R23/ΔCT
160 kDa
μDys7
NT H1 R1 R2 R3 H3 R16 R17 R24 H4 CR
ΔH2-R15+H3/ΔR18-R23/ΔCT
162 kDa

FIG. 1A

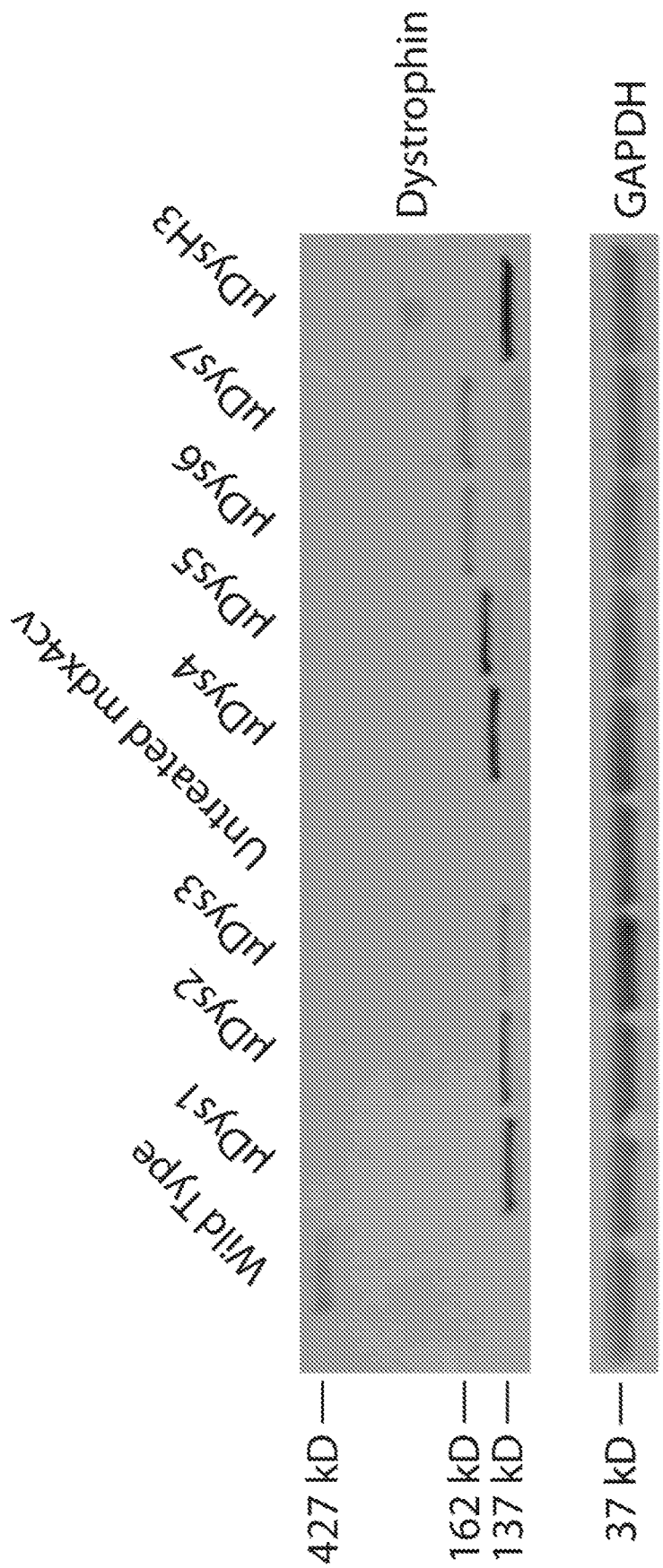

Dystrophin
GAPDH
427 kD
162 kD
137 kD
37 kD
Wild Type
hDys1
hDys2
hDys3
Untreated mdx4cv
hDys4
hDys5
hDys6
hDys7
hDysH3

FIG. 1B

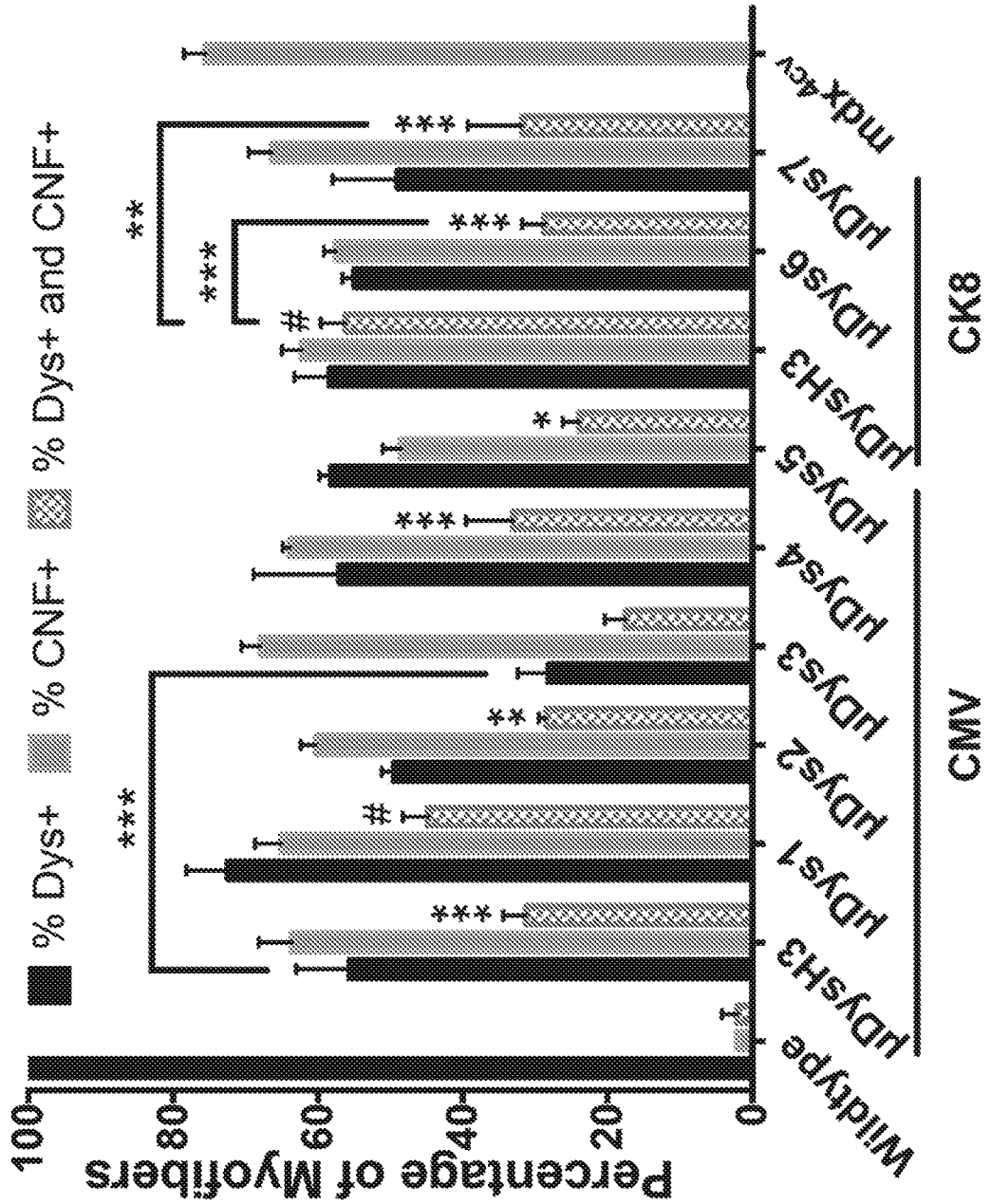

% Dys+
% CNF+
% Dys+ and CNF+
Percentage of Myofibers
100
80
60
40
20
0
Wildtype
μDysH3
μDys1
μDys2
μDys3
μDys4
μDys5
μDysH3
μDys6
μDys7
mdx4cv
CMV
CK8
***
**
***
***
***
#
*
***
**
#
***
***
**

FIG. 1C

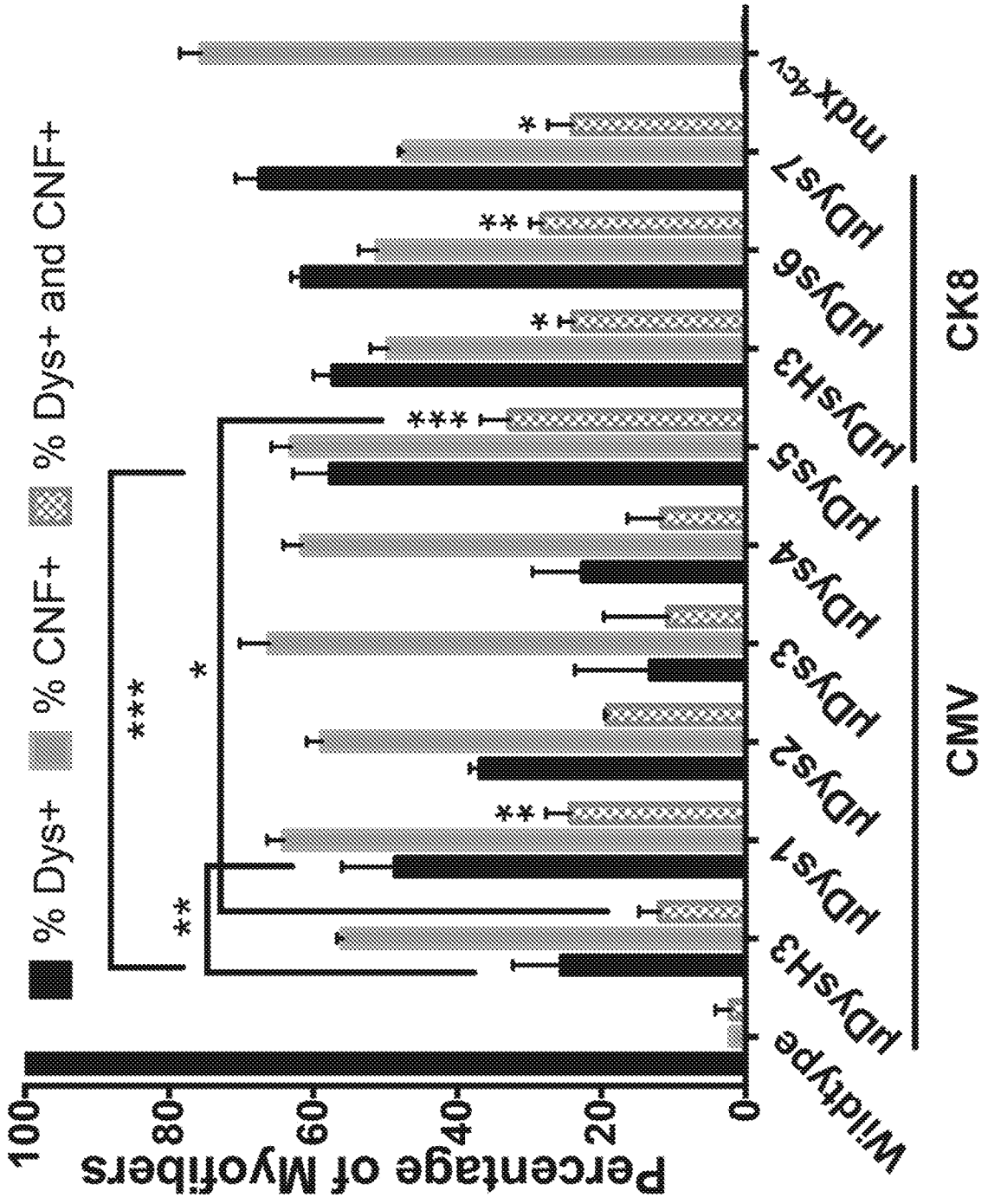

% Dys+
% CNF+
% Dys+ and CNF+
Percentage of Myofibers
100
80
60
40
20
0
***
**
*
Wildtype
hDysH3
hDys1
hDys2
hDys3
hDys4
hDys5
hDysH3
hDys6
hDys7
mdx4cv
CMV
CK8

FIG. 1D

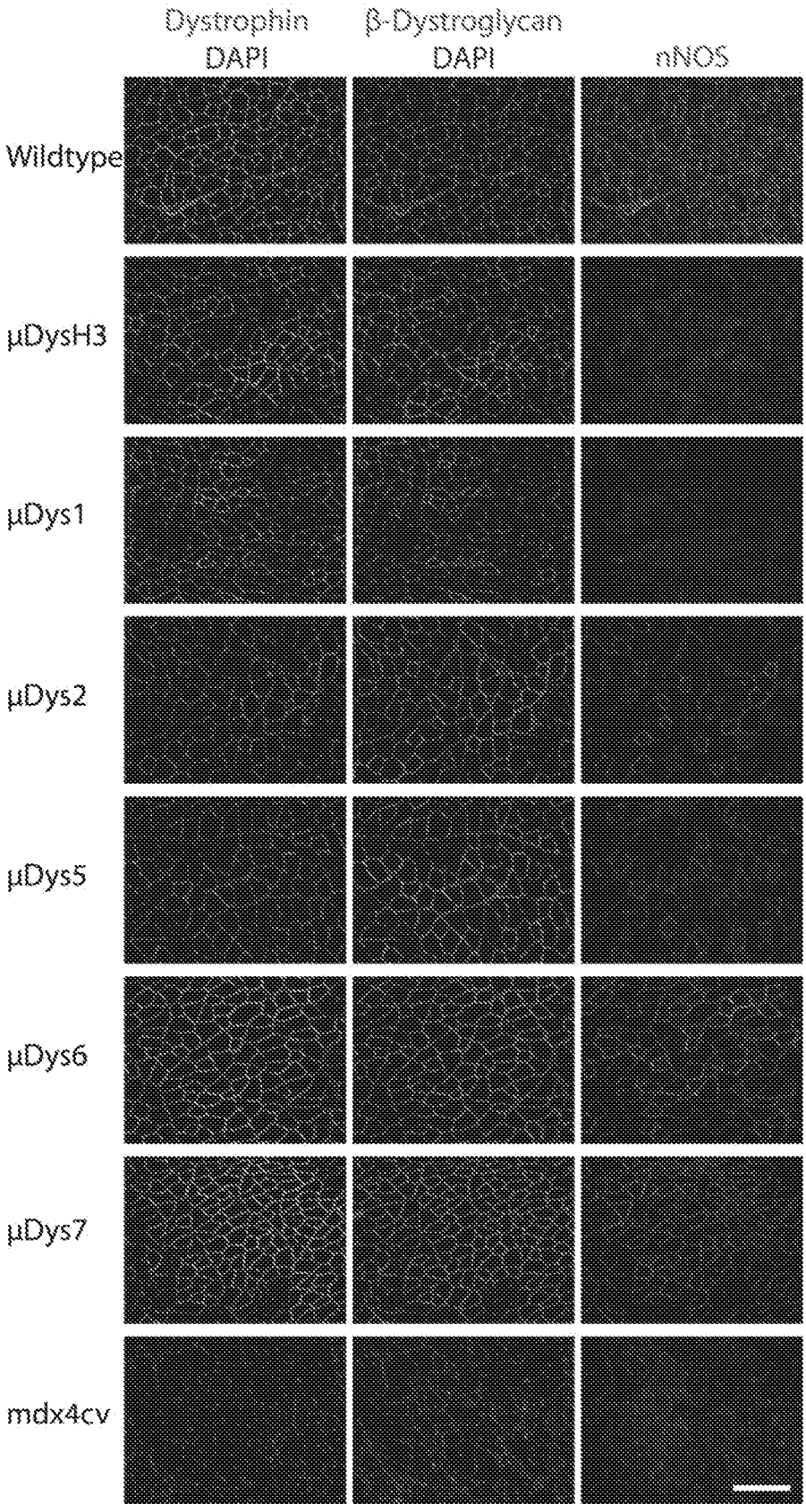

Dystrophin
DAPI
β-Dystroglycan
DAPI
nNOS
Wildtype
µDysH3
µDys1
µDys2
µDys5
µDys6
µDys7
mdx4cv

FIG. 2

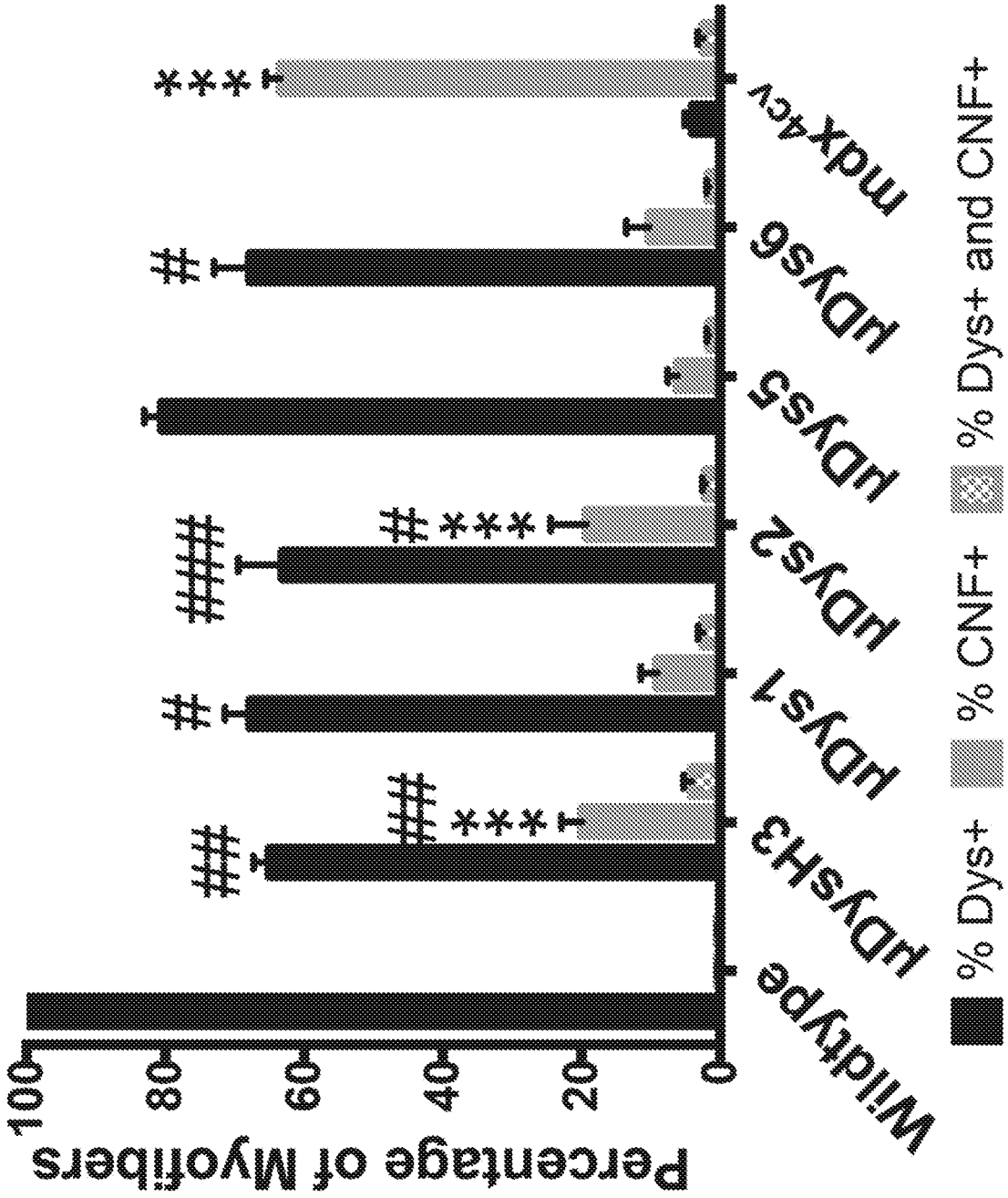

Percentage of Myofibers
100
80
60
40
20
0
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
mdx4cv
% Dys+
% CNF+
% Dys+ and CNF+
***
#
###

FIG. 3A

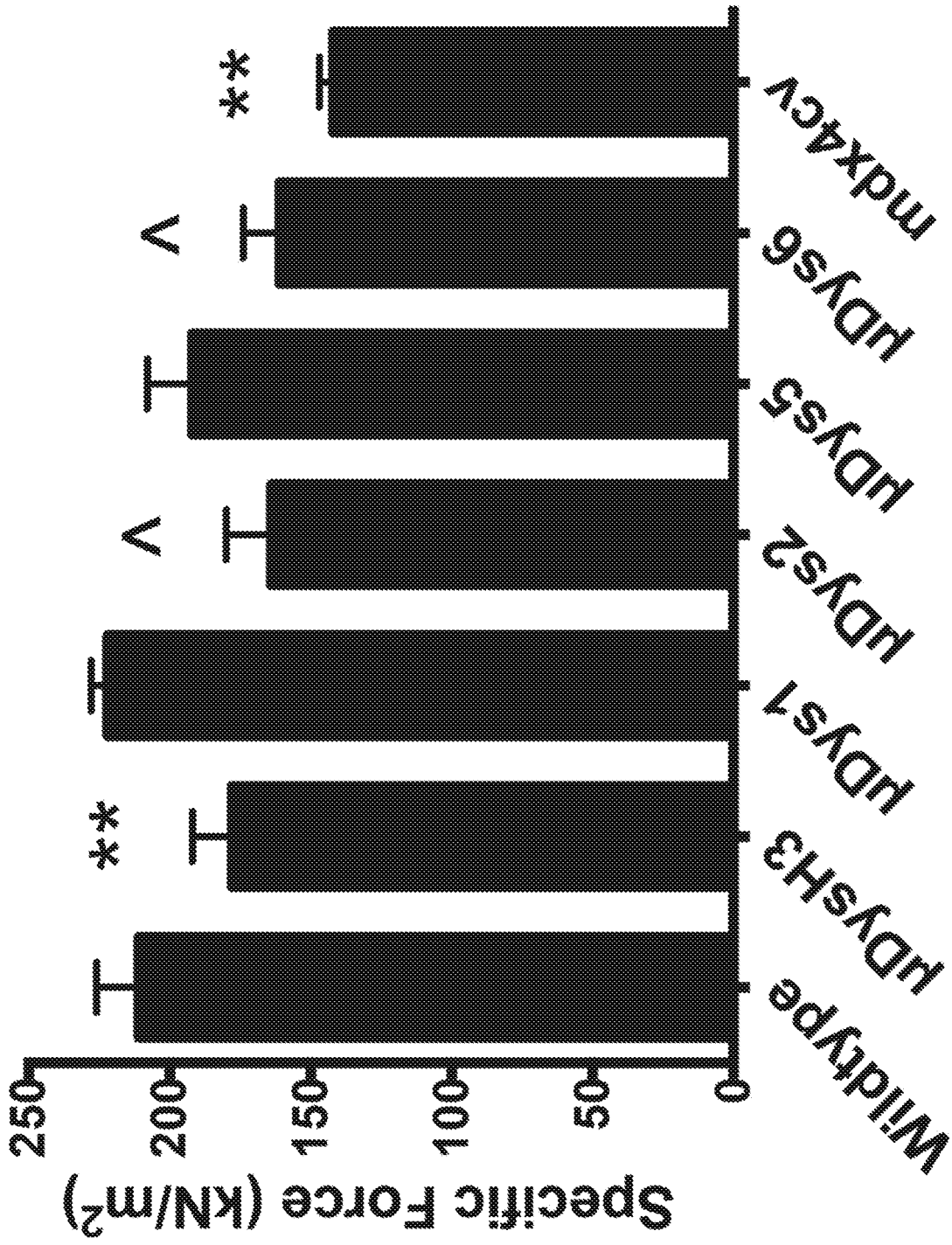

Specific Force (kN/m²)
250
200
150
100
50
0
**
**
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
mdx4cv

FIG. 3B

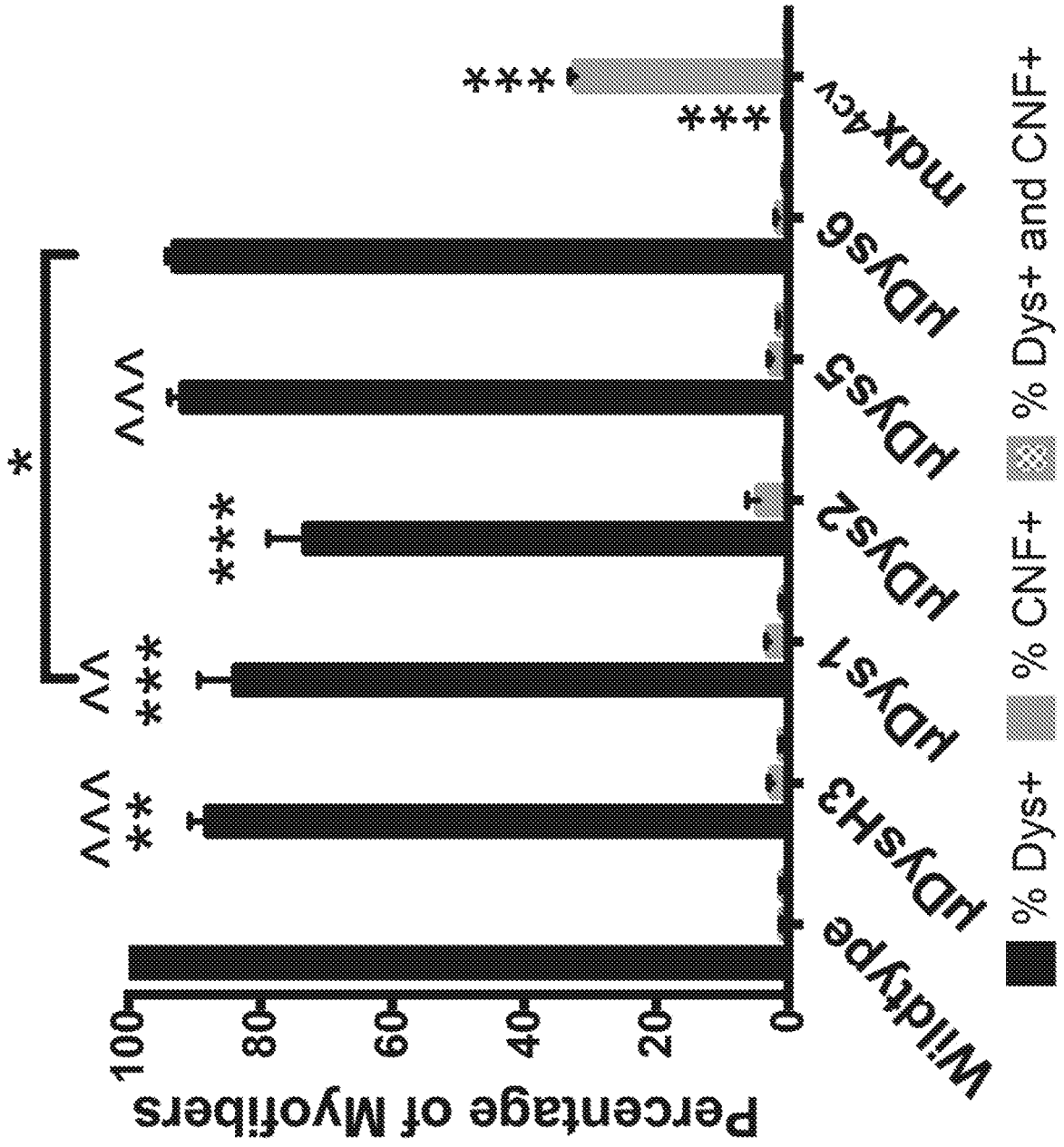

Percentage of Myofibers
100
80
60
40
20
0
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
mdx4cv
% Dys+
% CNF+
% Dys+ and CNF+
*
^^^
**
^^
***
****
^^^
^^^
***
***

FIG. 3C

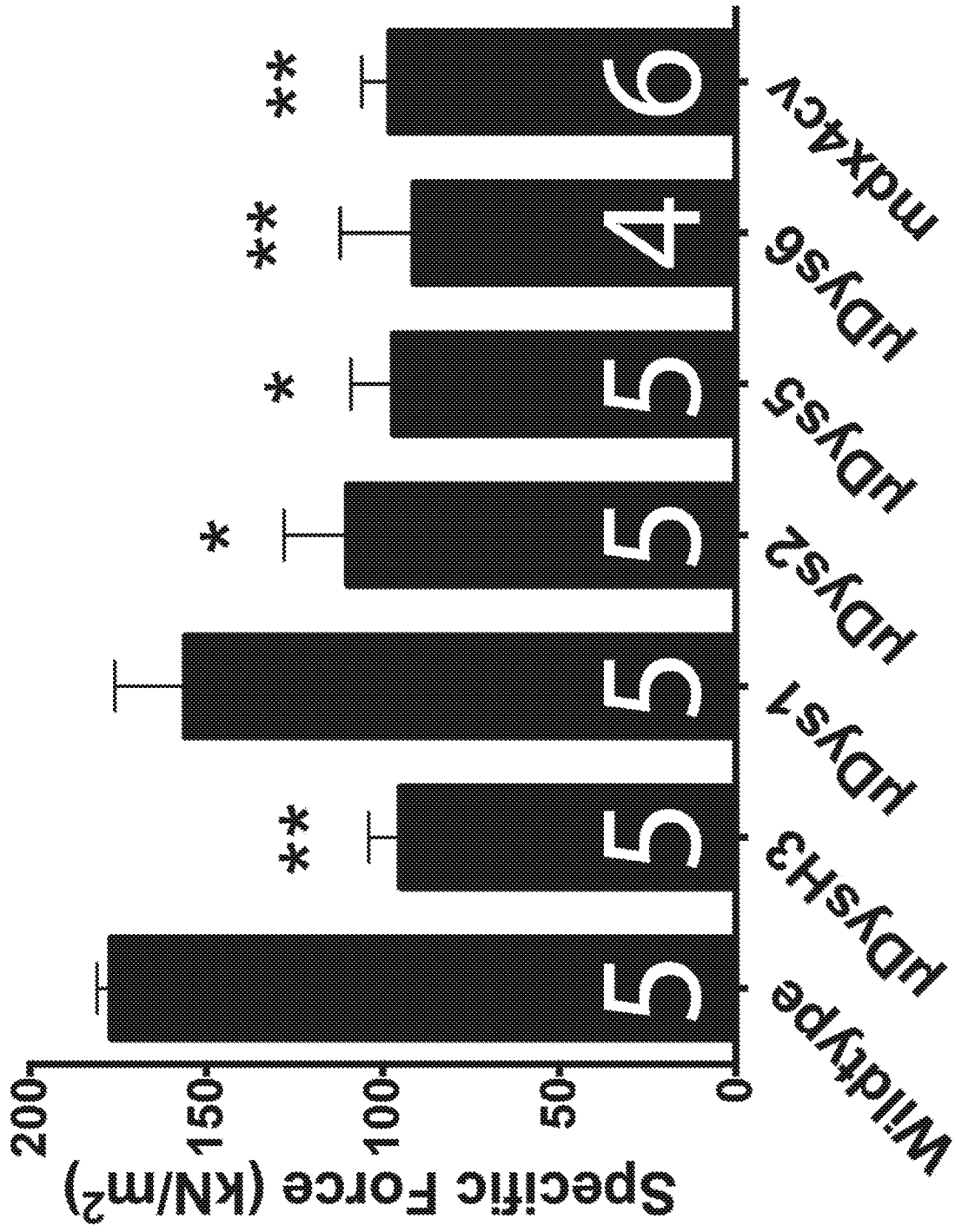

Specific Force (kN/m²)
200
150
100
50
0
5
5
5
5
5
5
5
4
6
**
*
*
**
**
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
mdx4cv

FIG. 3D

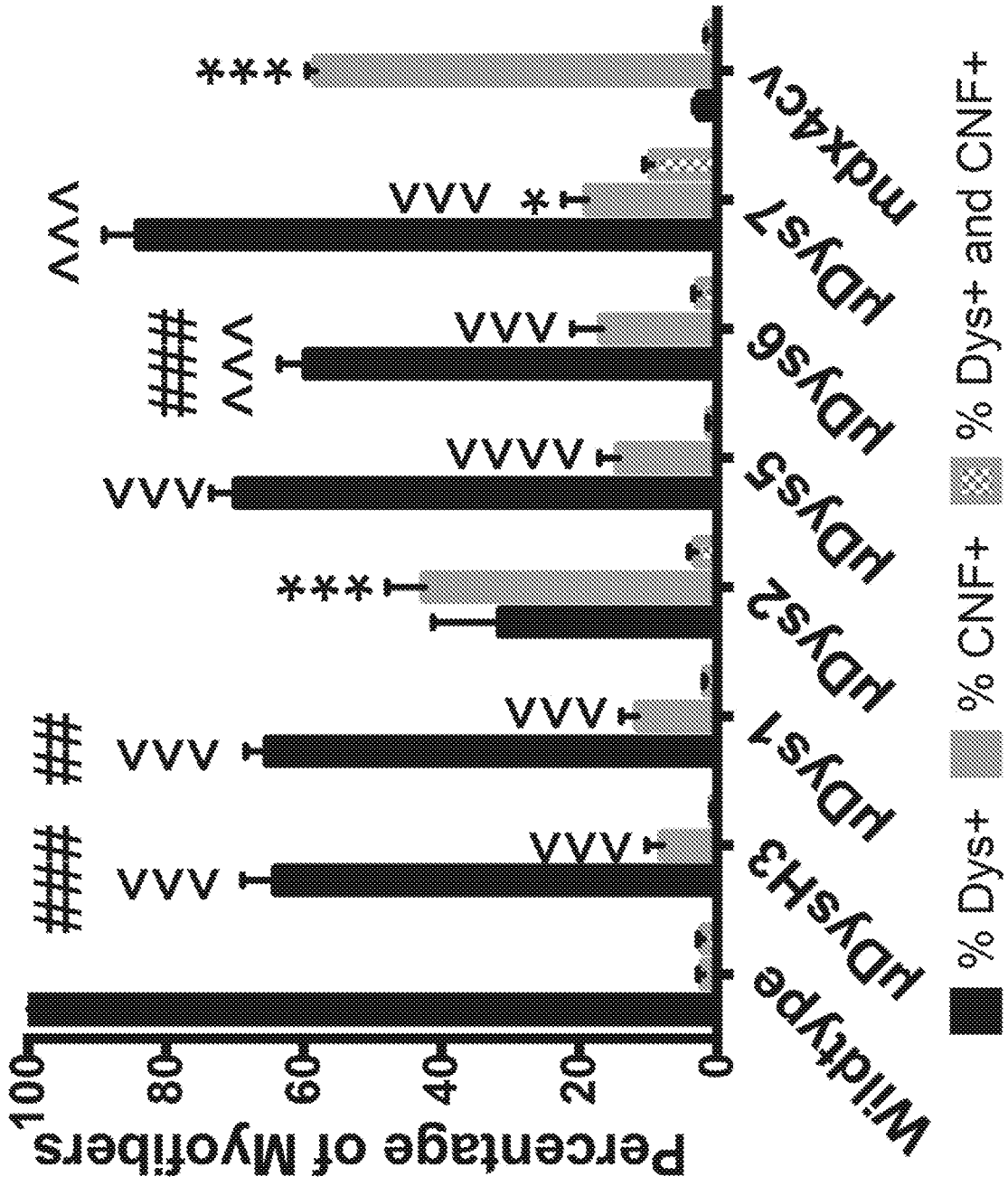

Percentage of Myofibers
100
80
60
40
20
0
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
hDys7
mdx4cv
% Dys+
% CNF+
% Dys+ and CNF+
***
*
^^^
###

FIG. 4A

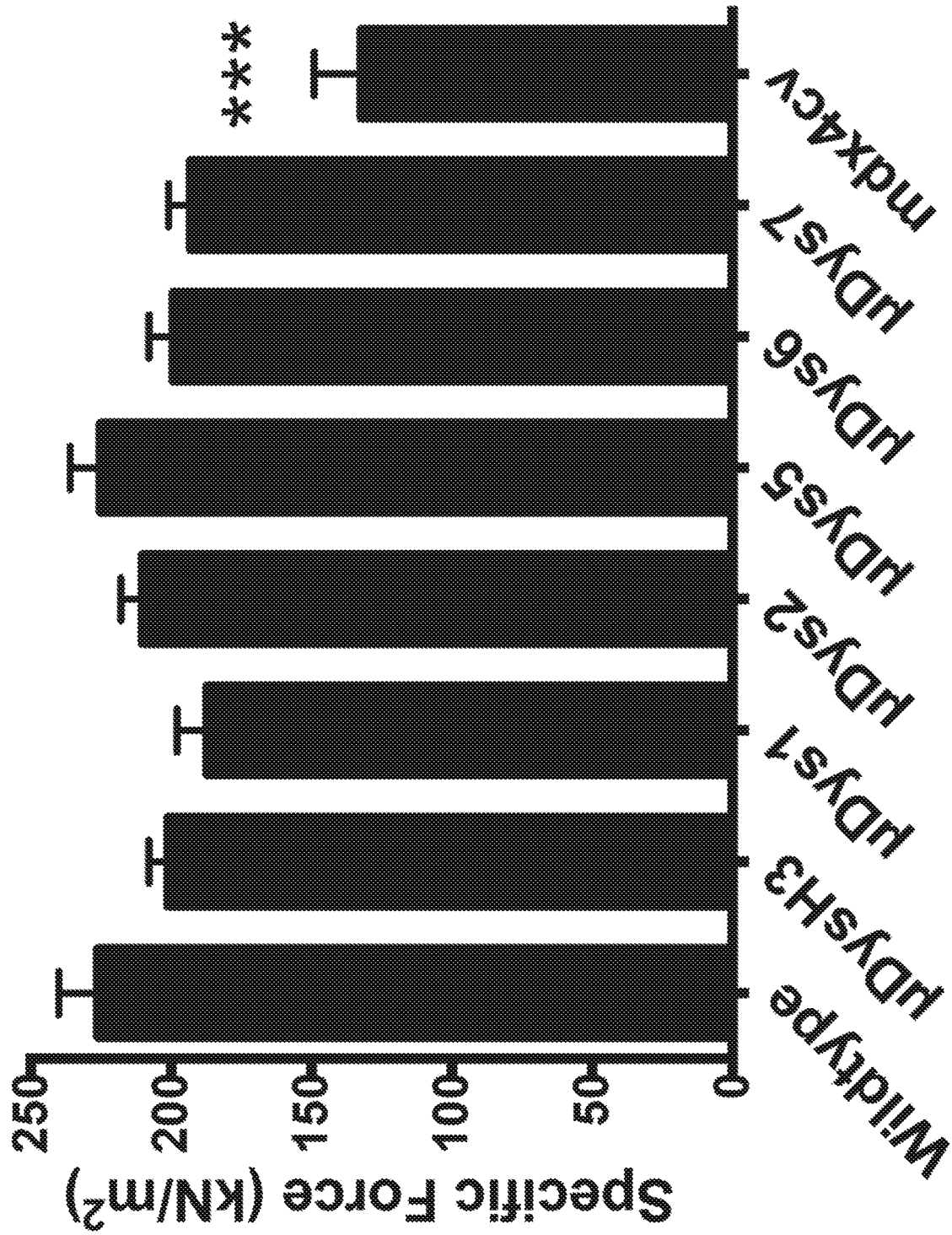

Specific Force (kN/m²)
250
200
150
100
50
0
****
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
hDys7
mdx4cv

FIG. 4B

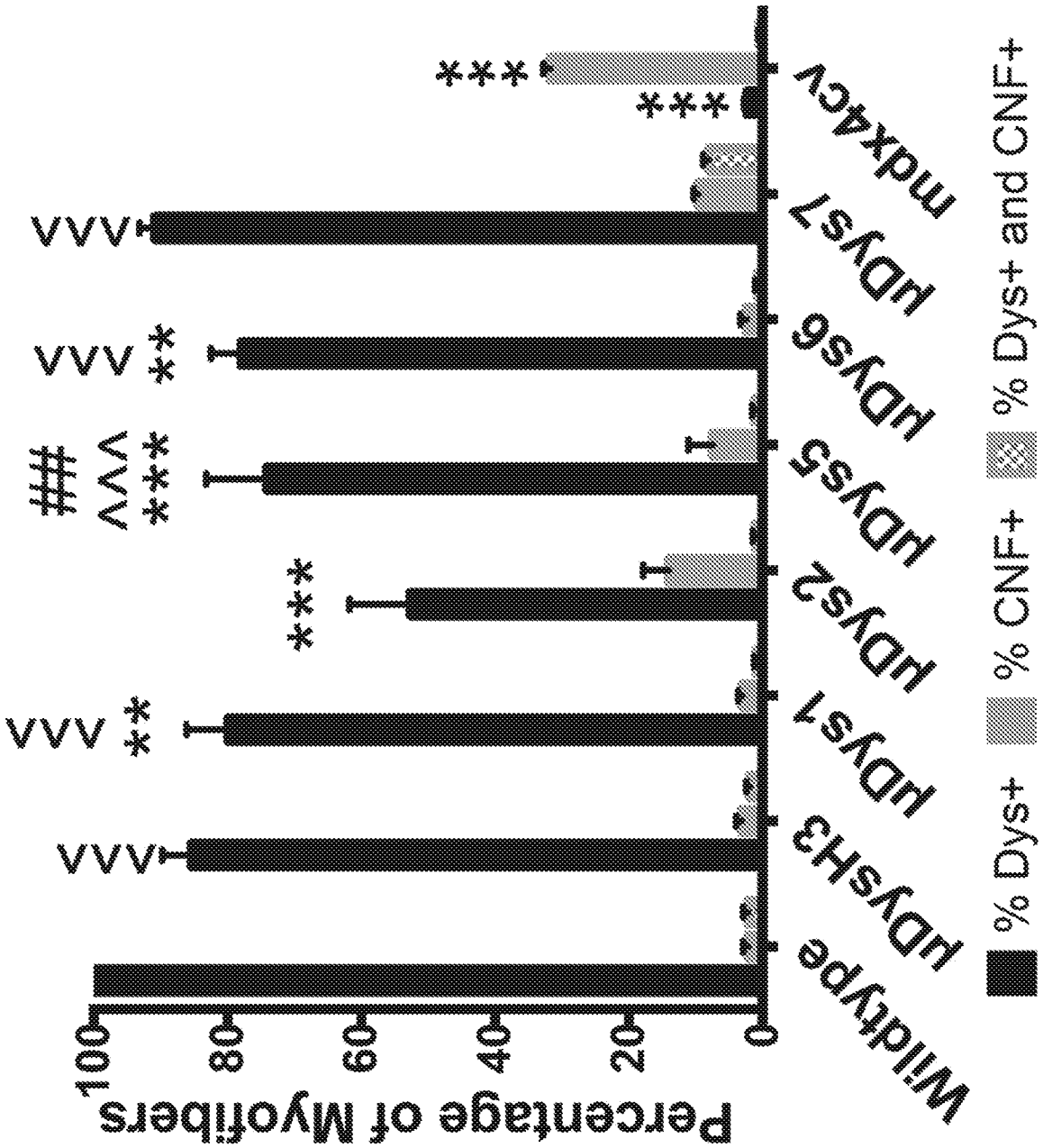

Percentage of Myofibers
100
80
60
40
20
0
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
hDys7
mdx4cv
% Dys+
% CNF+
% Dys+ and CNF+
***
***
^^^
^^^ **
^^^ ****
###
^^^ **
^^^

FIG. 4C

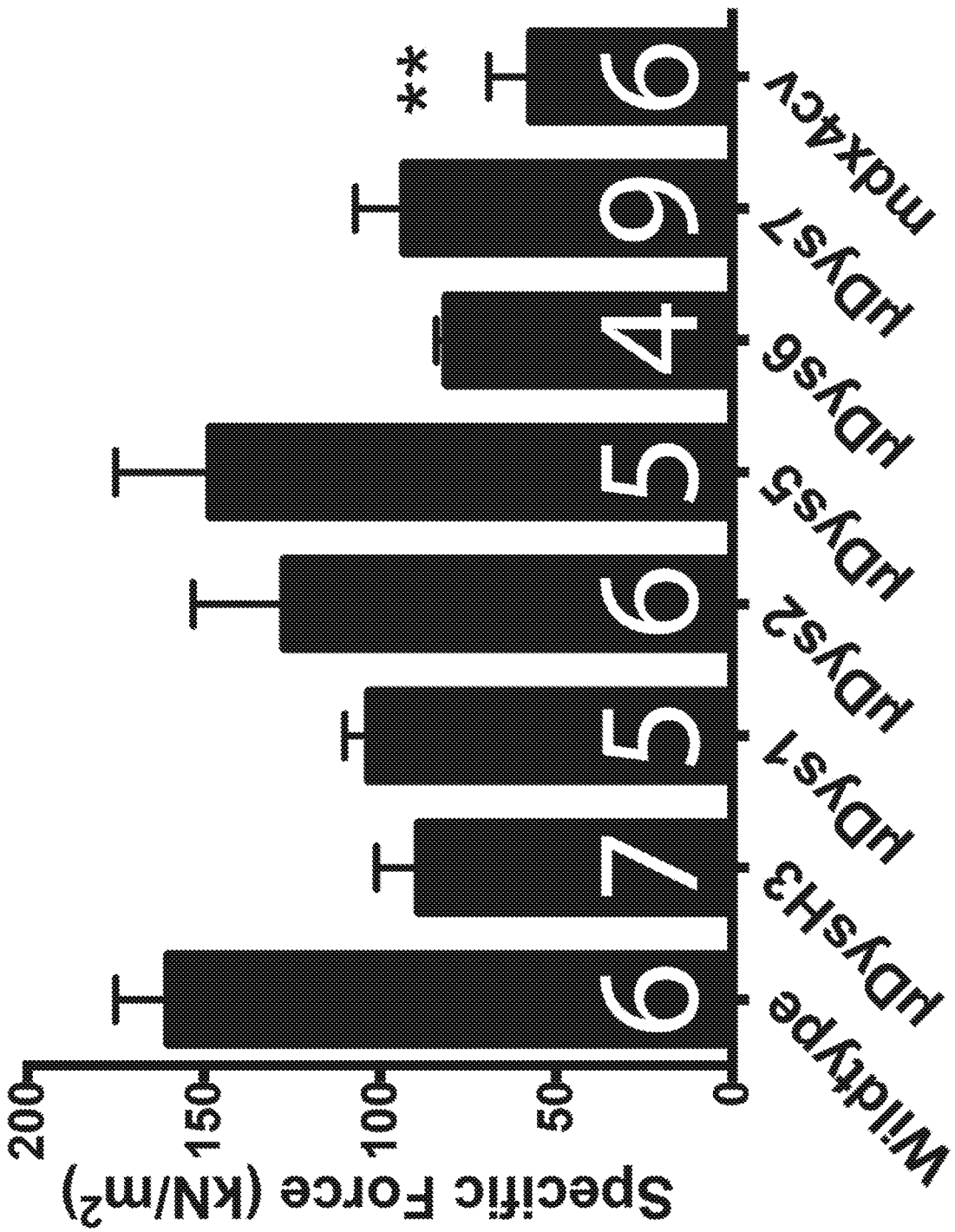

Specific Force (kN/m²)
200
150
100
50
0
Wildtype
hDysH3
hDys1
hDys2
hDys5
hDys6
hDys7
mdx4cv
**

FIG. 4D

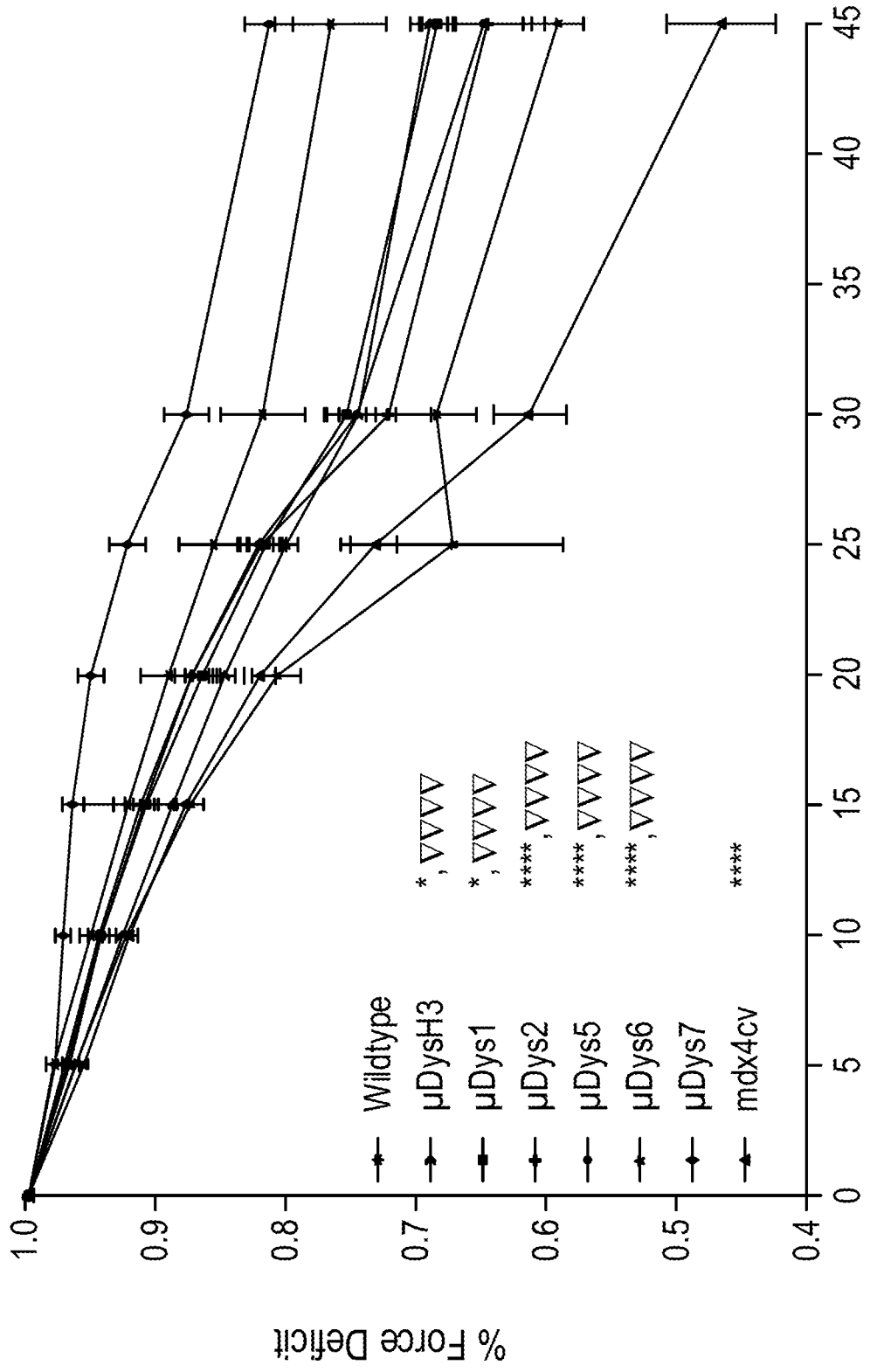

% Force Deficit
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20
25
30
35
40
45
% Beyond Optimal Fiber Length (Lo)
Wildtype
µDysH3
µDys1
µDys2
µDys5
µDys6
µDys7
mdx4cv
*, ∇∇∇∇
*, ∇∇∇∇
****, ∇∇∇∇
****, ∇∇∇∇
****, ∇∇∇∇
****

FIG. 5A

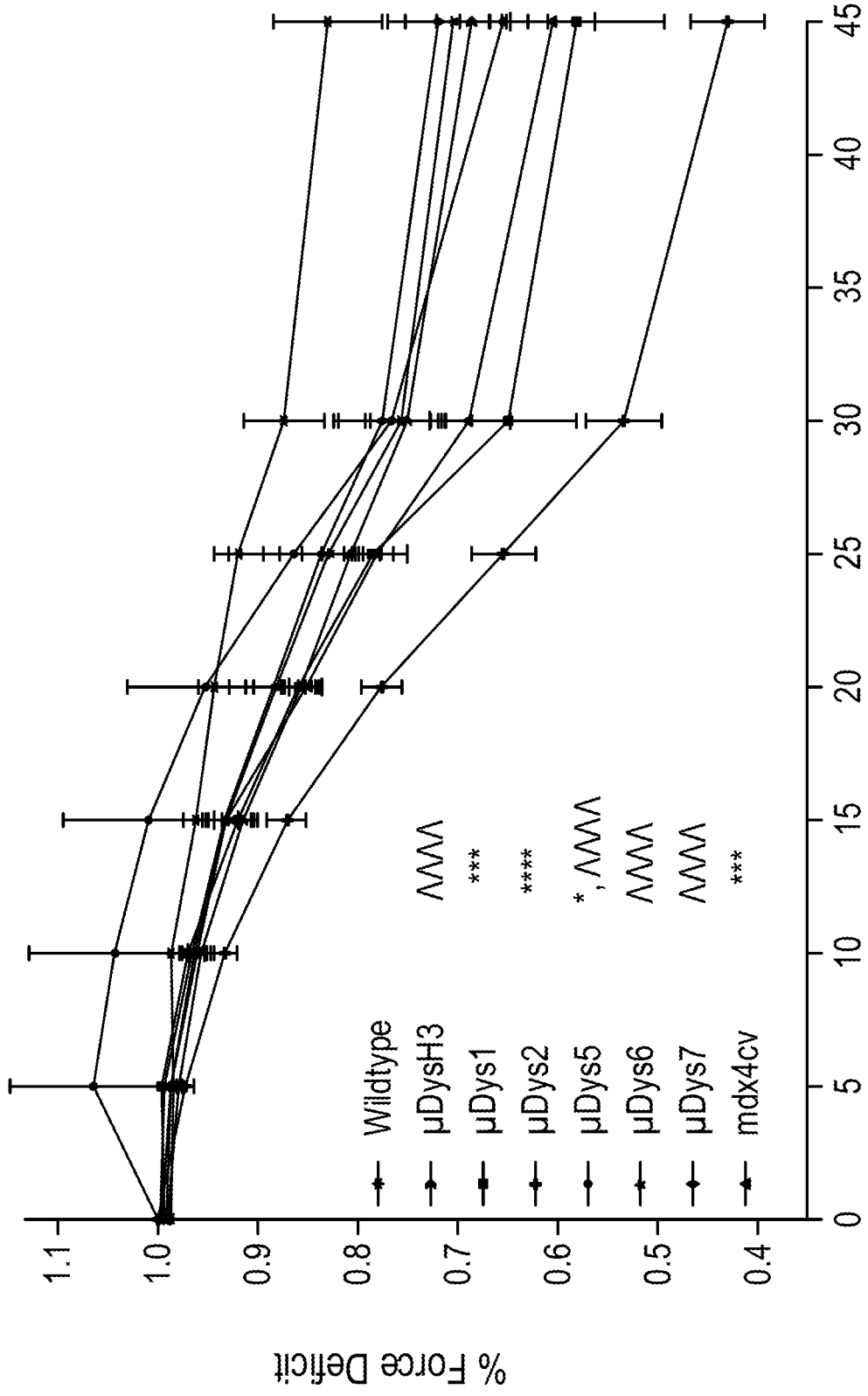

% Force Deficit
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20
25
30
35
40
45
% Beyond Optimal Fiber Length (Lo)
Wildtype
µDysH3
µDys1
µDys2
µDys5
µDys6
µDys7
mdx4cv
VVVV
***
****
*, VVVV
VVVV
VVVV
***

FIG. 5B

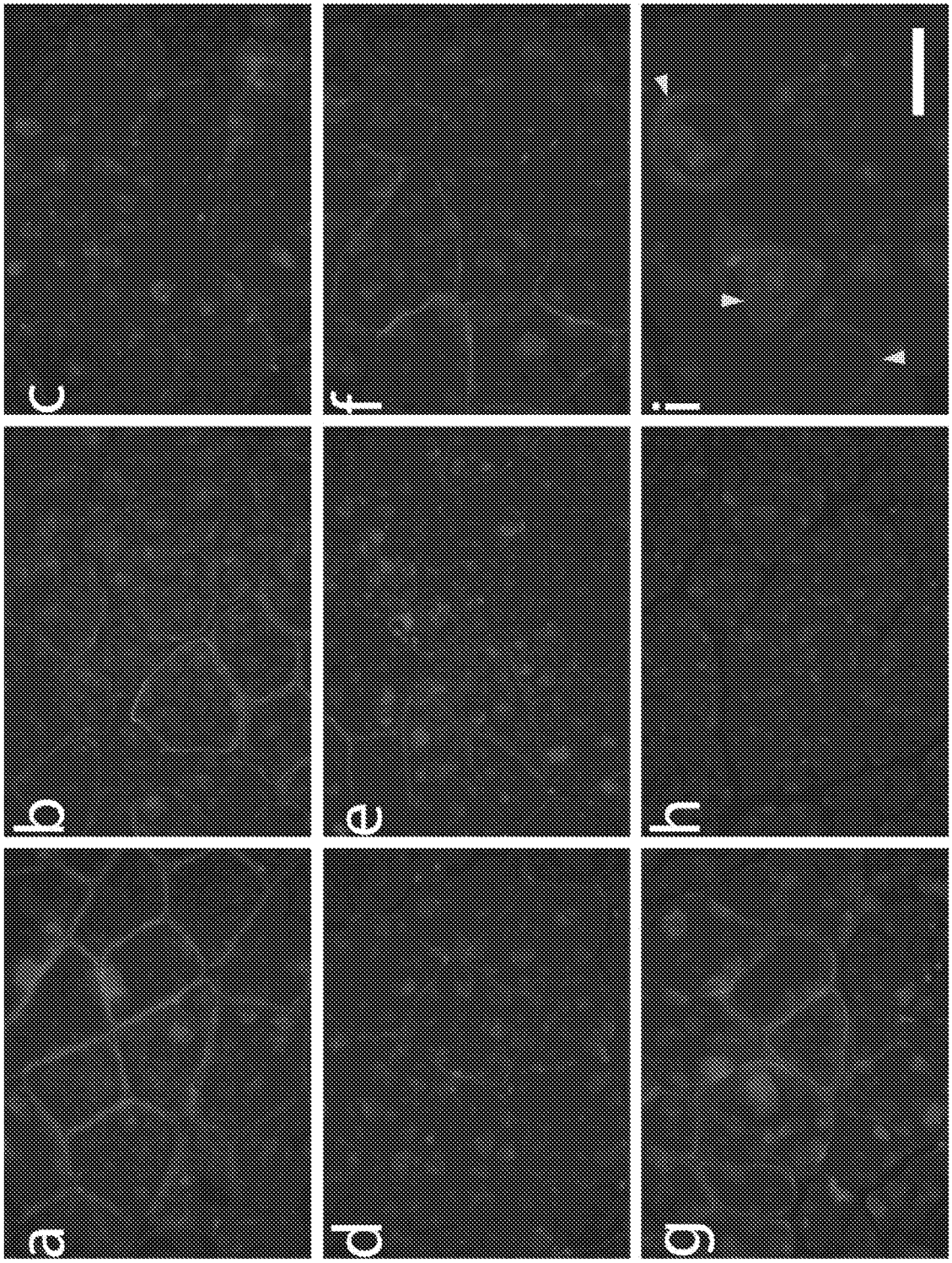


FIG. 6

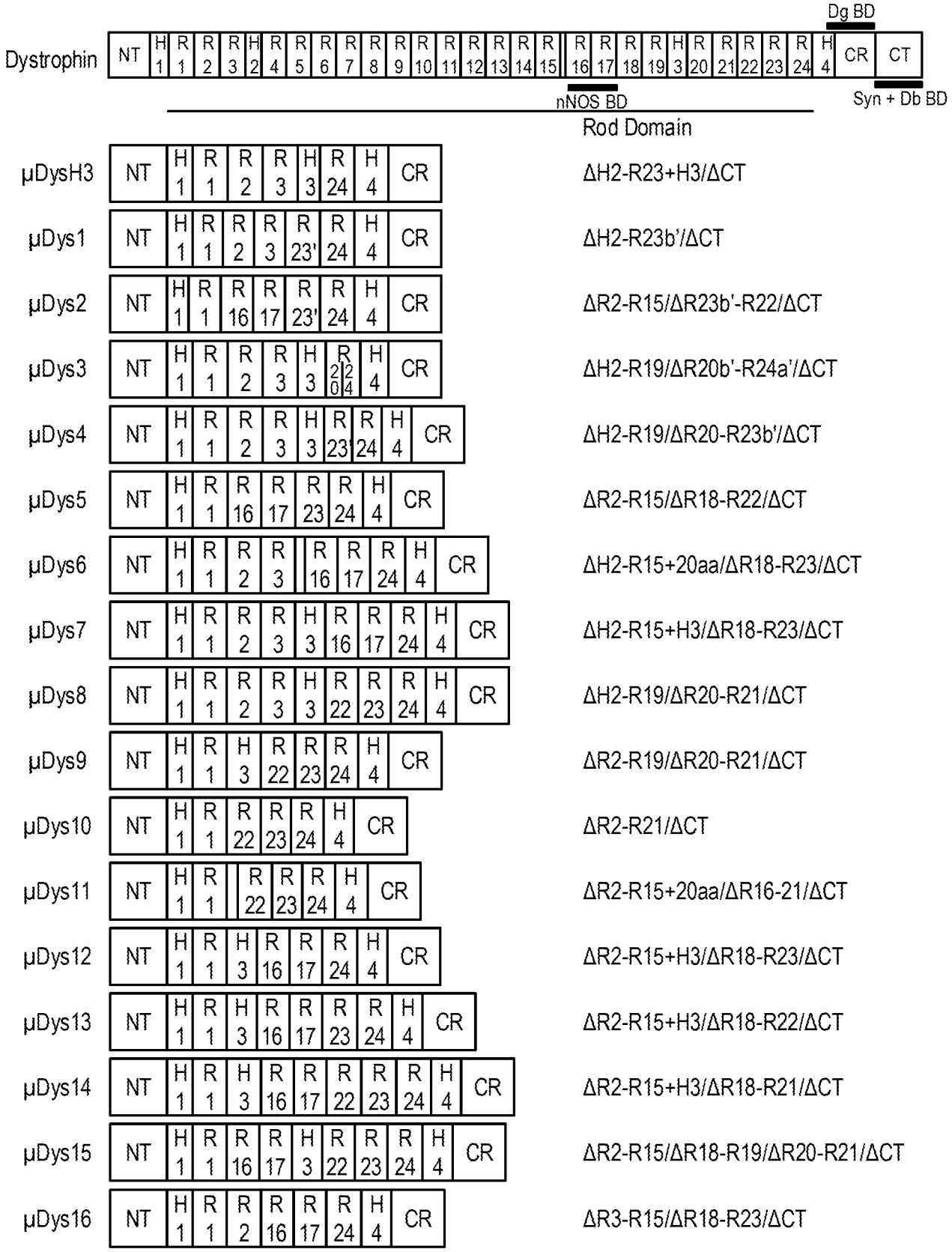

Dystrophin
NT
H1 R1 R2 R3 H2 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 H3 R20 R21 R22 R23 R24 H4 CR CT
Dg BD
nNOS BD
Syn + Db BD
Rod Domain
μDysH3 NT H1 R1 R2 R3 H3 R24 H4 CR ΔH2-R23+H3/ΔCT
μDys1 NT H1 R1 R2 R3 R23' R24 H4 CR ΔH2-R23b'/ΔCT
μDys2 NT H1 R1 R16 R17 R23' R24 H4 CR ΔR2-R15/ΔR23b'-R22/ΔCT
μDys3 NT H1 R1 R2 R3 H3 R20 R24 H4 CR ΔH2-R19/ΔR20b'-R24a'/ΔCT
μDys4 NT H1 R1 R2 R3 H3 R23' R24 H4 CR ΔH2-R19/ΔR20-R23b'/ΔCT
μDys5 NT H1 R1 R16 R17 R23 R24 H4 CR ΔR2-R15/ΔR18-R22/ΔCT
μDys6 NT H1 R1 R2 R3 R16 R17 R24 H4 CR ΔH2-R15+20aa/ΔR18-R23/ΔCT
μDys7 NT H1 R1 R2 R3 H3 R16 R17 R24 H4 CR ΔH2-R15+H3/ΔR18-R23/ΔCT
μDys8 NT H1 R1 R2 R3 H3 R22 R23 R24 H4 CR ΔH2-R19/ΔR20-R21/ΔCT
μDys9 NT H1 R1 H3 R22 R23 R24 H4 CR ΔR2-R19/ΔR20-R21/ΔCT
μDys10 NT H1 R1 R22 R23 R24 H4 CR ΔR2-R21/ΔCT
μDys11 NT H1 R1 R22 R23 R24 H4 CR ΔR2-R15+20aa/ΔR16-21/ΔCT
μDys12 NT H1 R1 H3 R16 R17 R24 H4 CR ΔR2-R15+H3/ΔR18-R23/ΔCT
μDys13 NT H1 R1 H3 R16 R17 R23 R24 H4 CR ΔR2-R15+H3/ΔR18-R22/ΔCT
μDys14 NT H1 R1 H3 R16 R17 R22 R23 R24 H4 CR ΔR2-R15+H3/ΔR18-R21/ΔCT
μDys15 NT H1 R1 R16 R17 H3 R22 R23 R24 H4 CR ΔR2-R15/ΔR18-R19/ΔR20-R21/ΔCT
μDys16 NT H1 R1 R2 R16 R17 R24 H4 CR ΔR3-R15/ΔR18-R23/ΔCT

FIG. 7

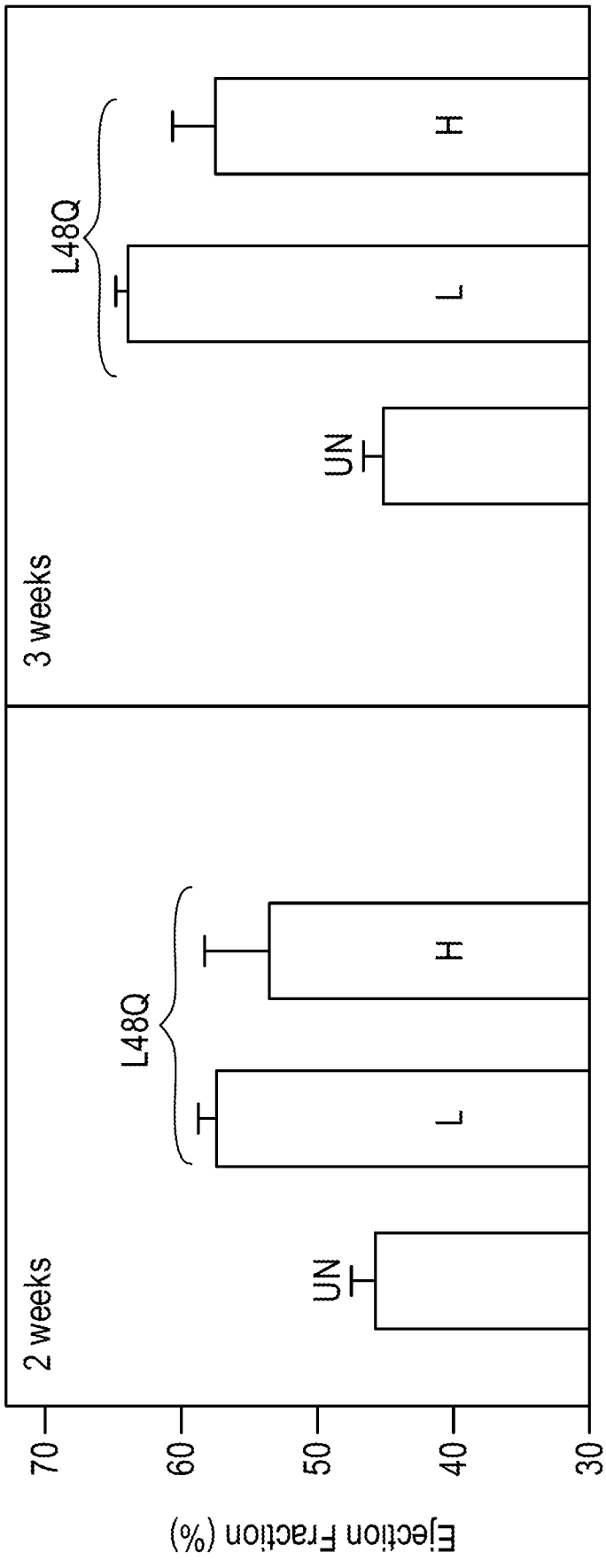

Ejection Fraction (%)
70
60
50
40
30
2 weeks
UN
L48Q
L
H
3 weeks
UN
L48Q
L
H

FIG. 8

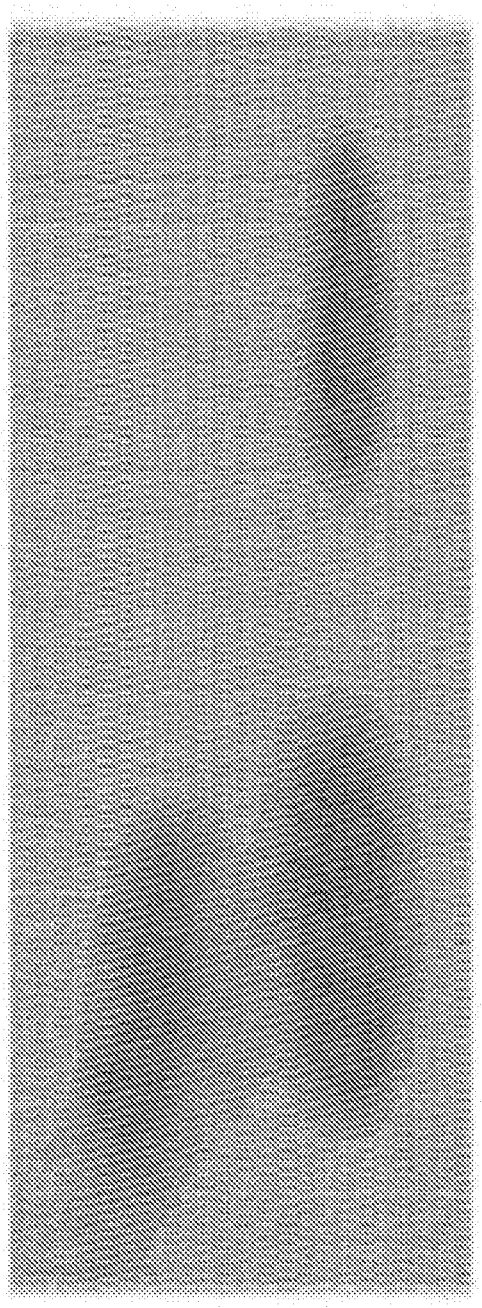


FIG. 9

FIG. 10A

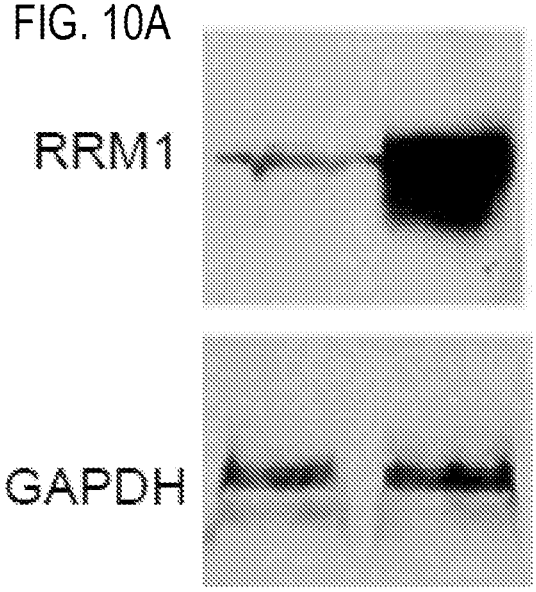


FIG. 10B

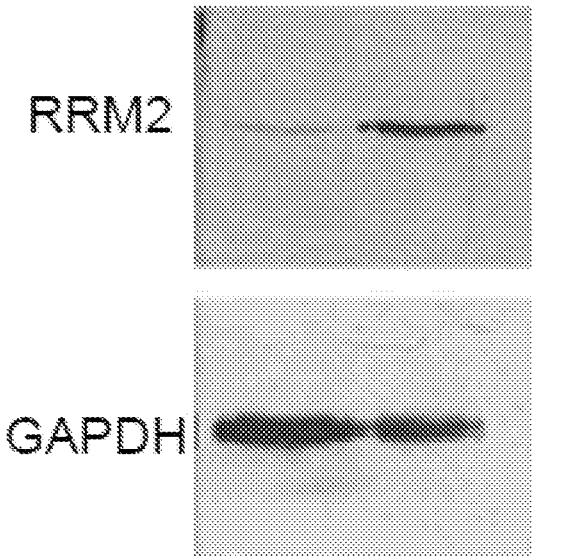
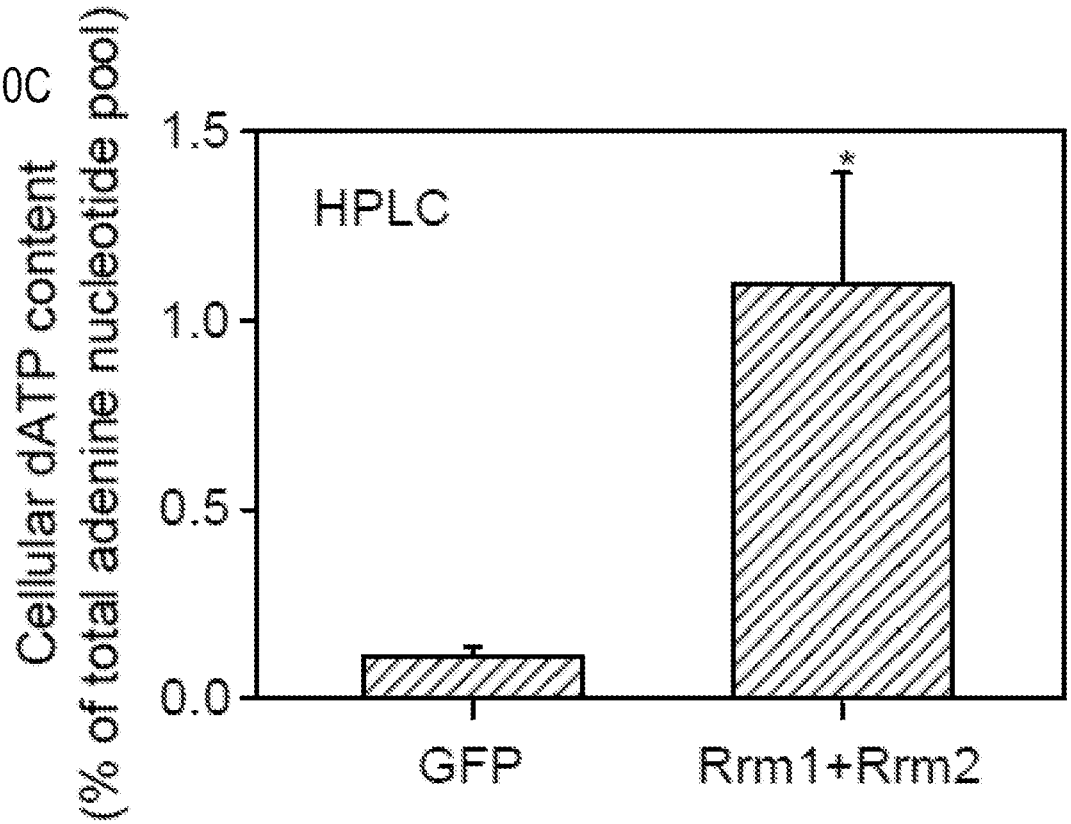


FIG. 10C



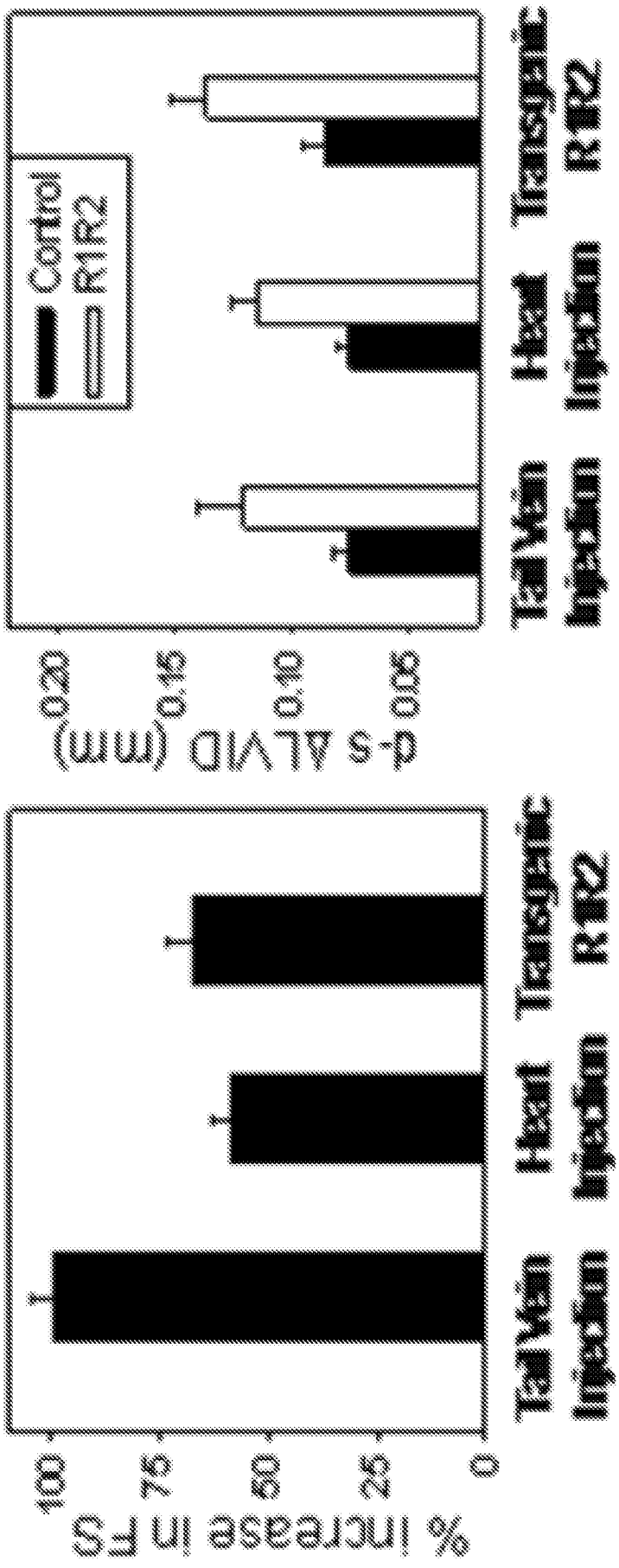

Control
R1R2
Tail Vein Injection
Heart Injection
Transgenic R1R2
d-s ΔLVID (mm)
0.20
0.15
0.10
0.05
% Increase in FS
100
75
50
25
0

FIG. 11

FIG. 12A

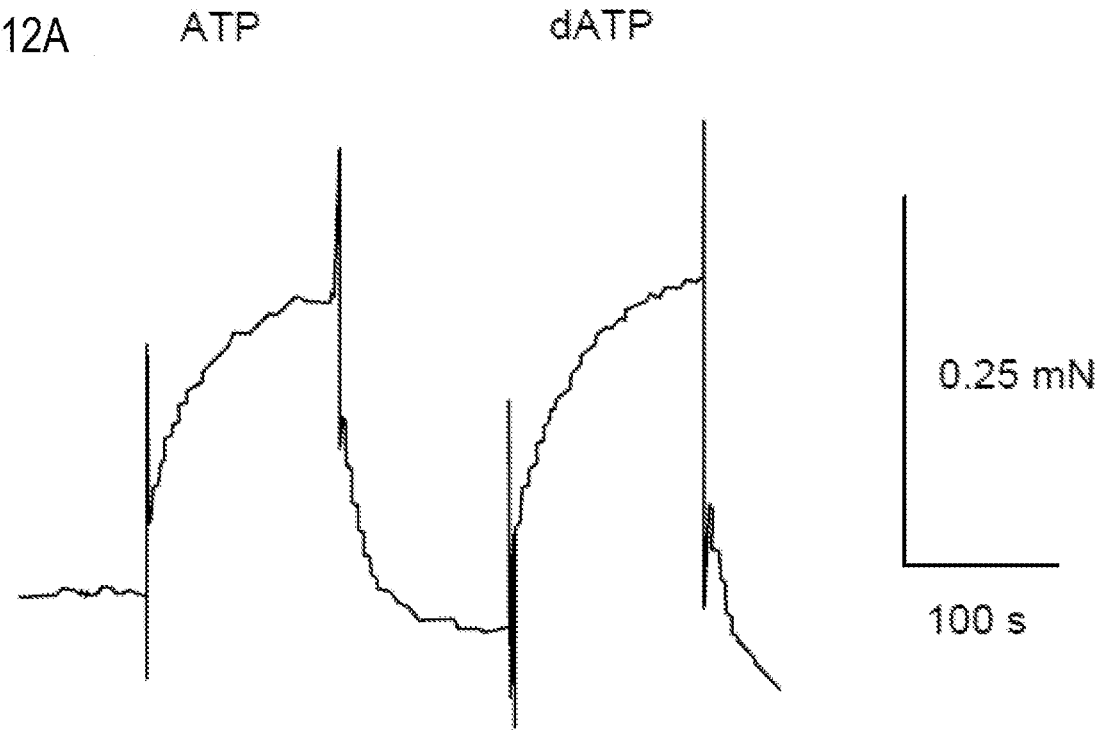


FIG. 12B

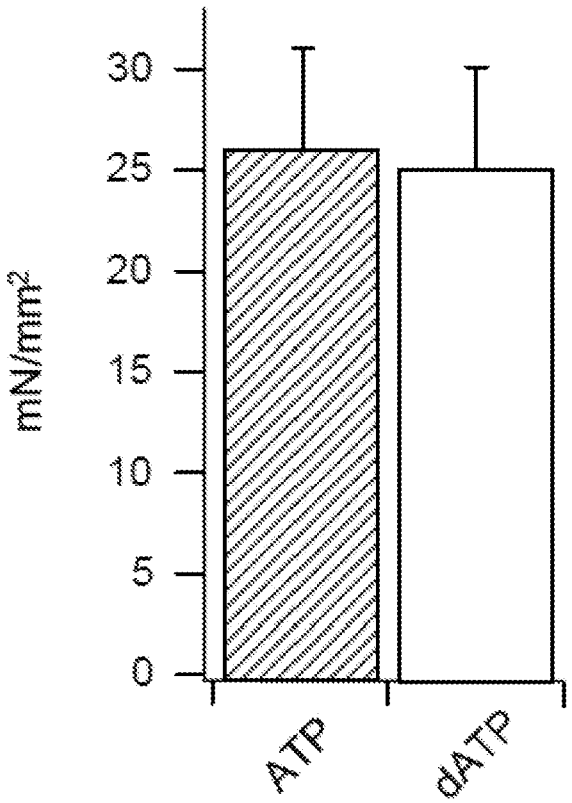


FIG. 13A

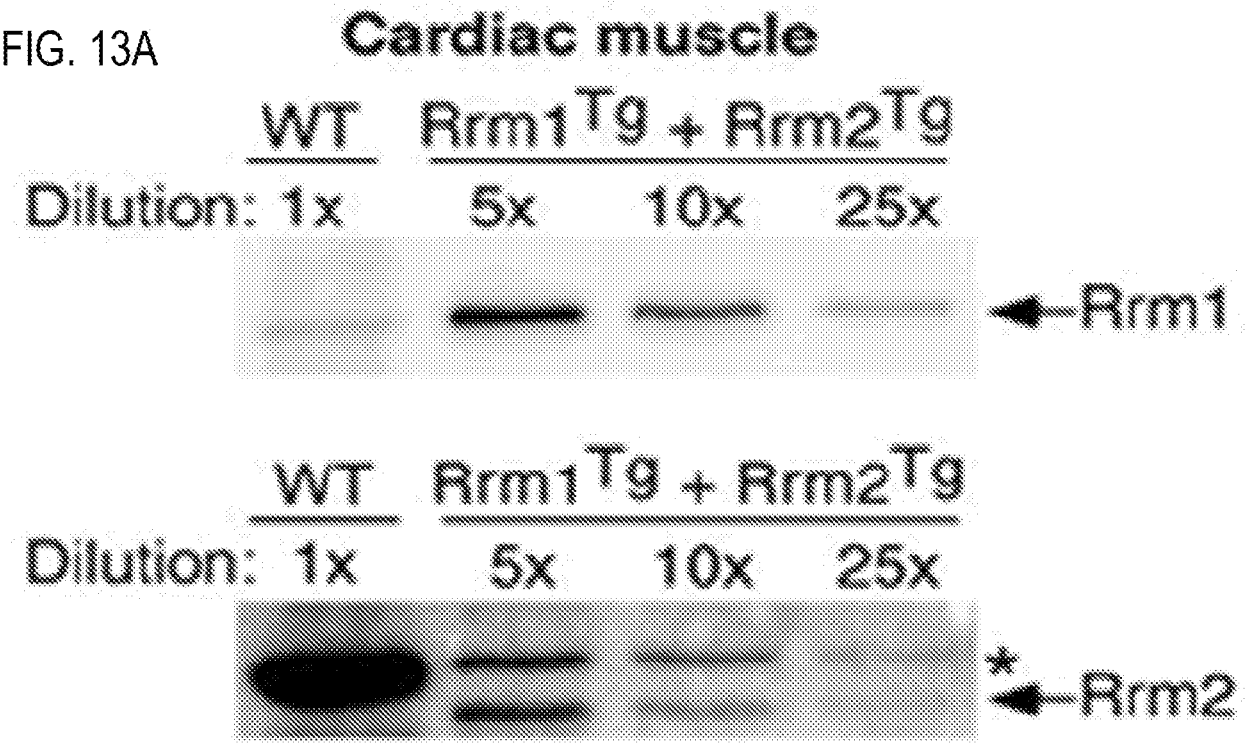
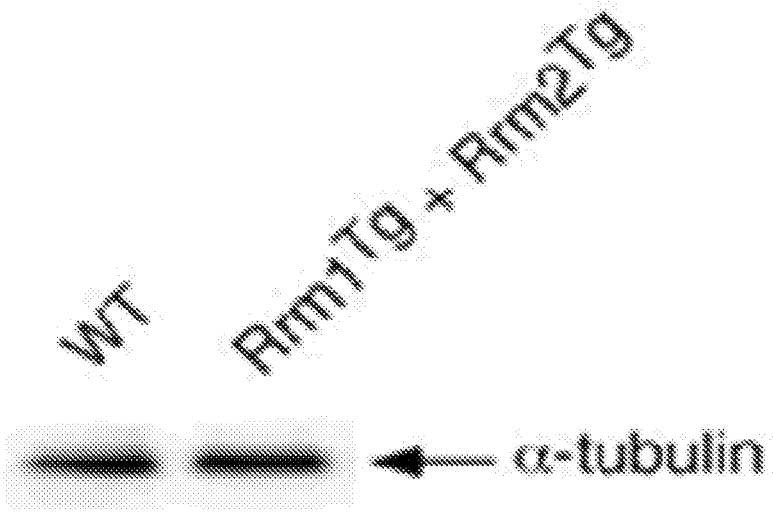


FIG. 13B



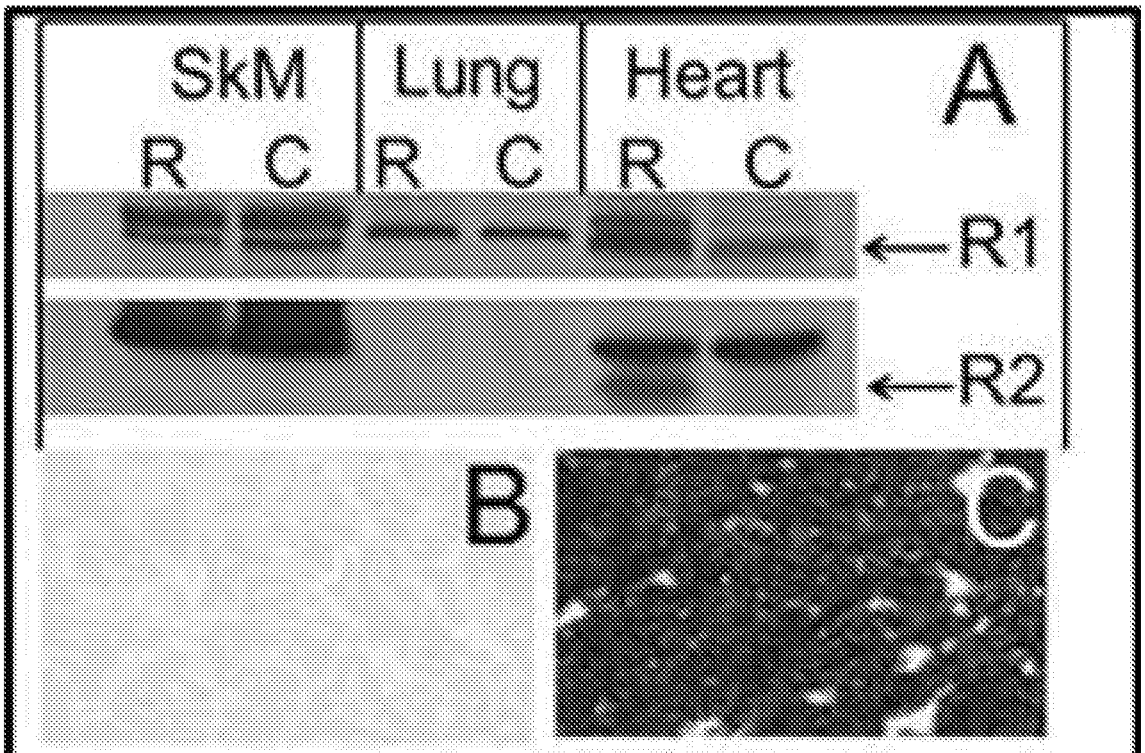


Fig. 12.. Western blots **(A)** for R1 & R2. AAV6-R1R2^{cTnT455} injected (R) & control (C) mice. SkM=skeletal muscle. Untreated (B) vs. AAV6-alkphos (C) after 20 months.

FIG. 14

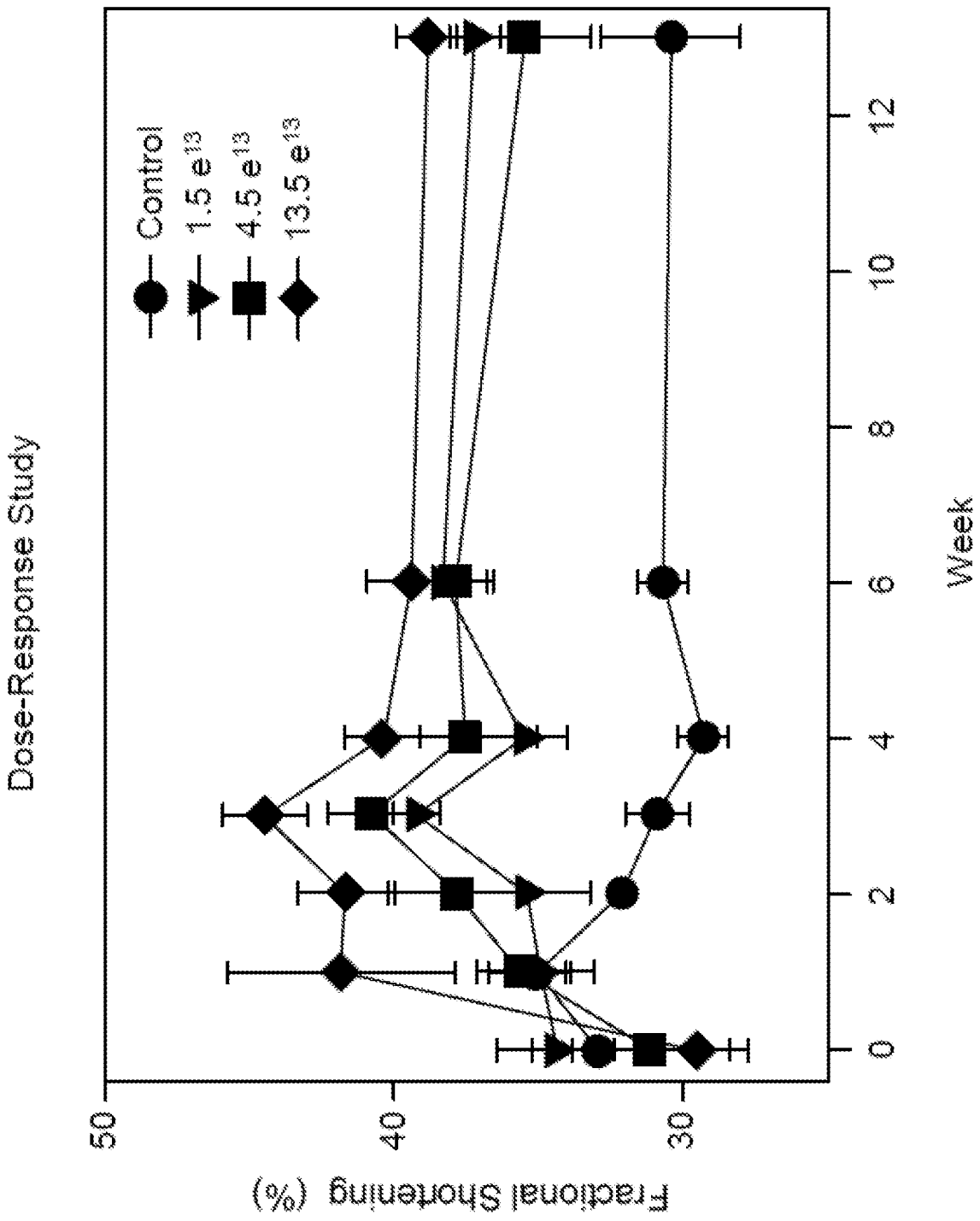

Dose-Response Study
Control
1.5 e13
4.5 e13
13.5 e13
Fractional Shortening (%)
50
40
30
0
2
4
6
8
10
12
Week

FIG. 15

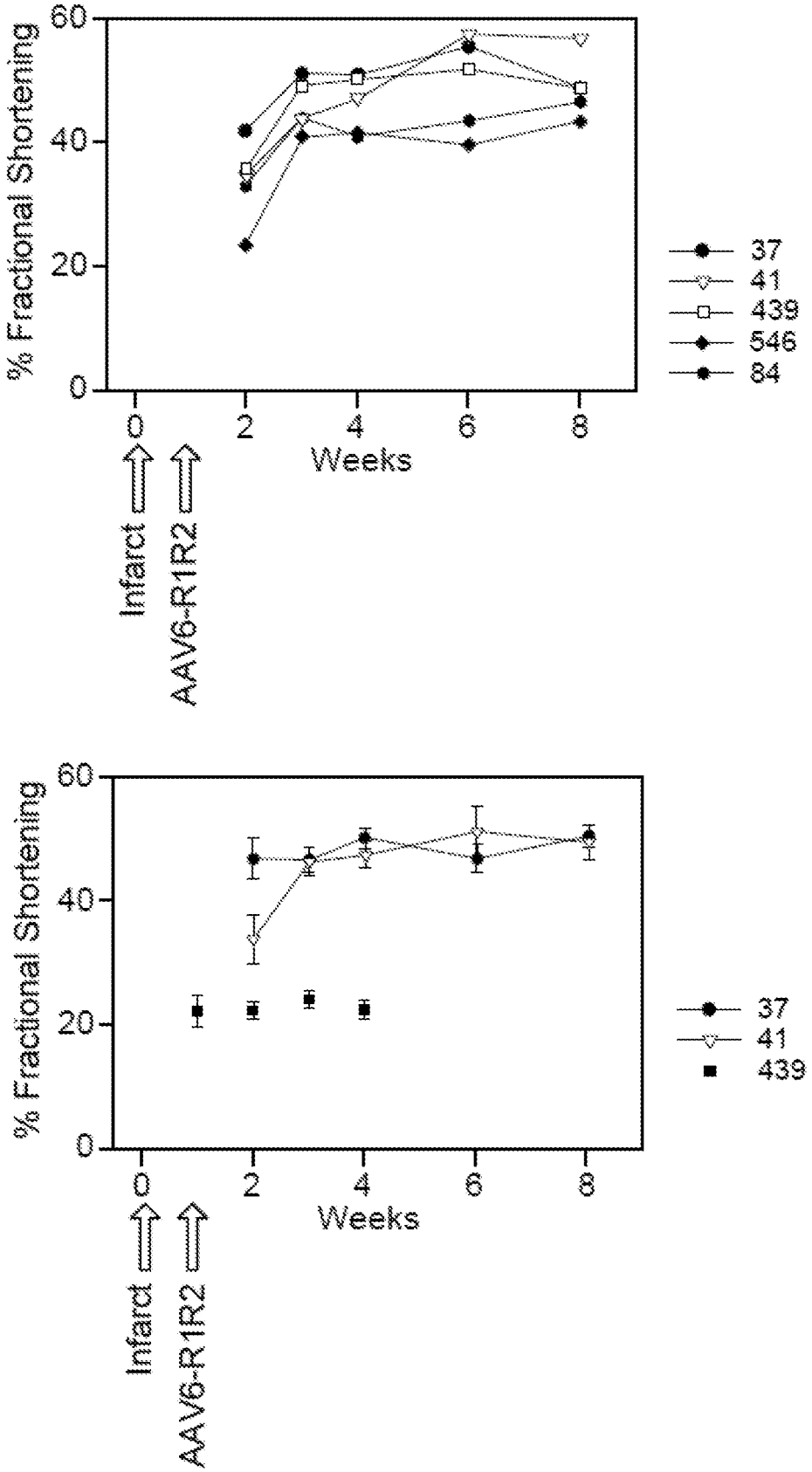

% Fractional Shortening
60
40
20
0
0
2
4
6
8
Weeks
Infarct
AAV6-R1R2
37
41
439
546
84
% Fractional Shortening
60
40
20
0
0
2
4
6
8
Weeks
Infarct
AAV6-R1R2
37
41
439

FIG. 16

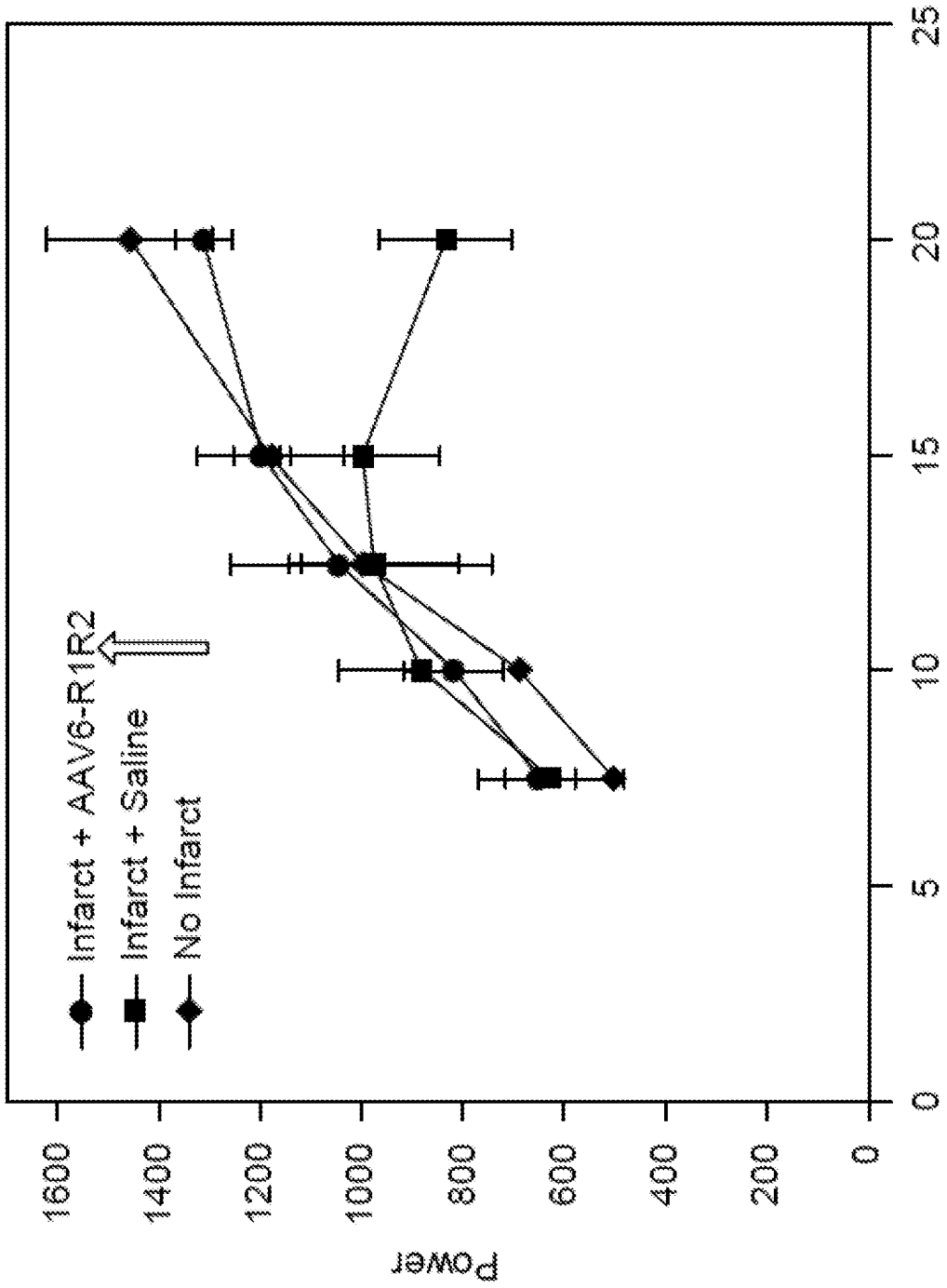

Infarct + AAV6-R1R2
Infarct + Saline
No Infarct
Power
Preload (cm H_2O)
0
200
400
600
800
1000
1200
1400
1600
0
5
10
15
20
25

FIG. 17

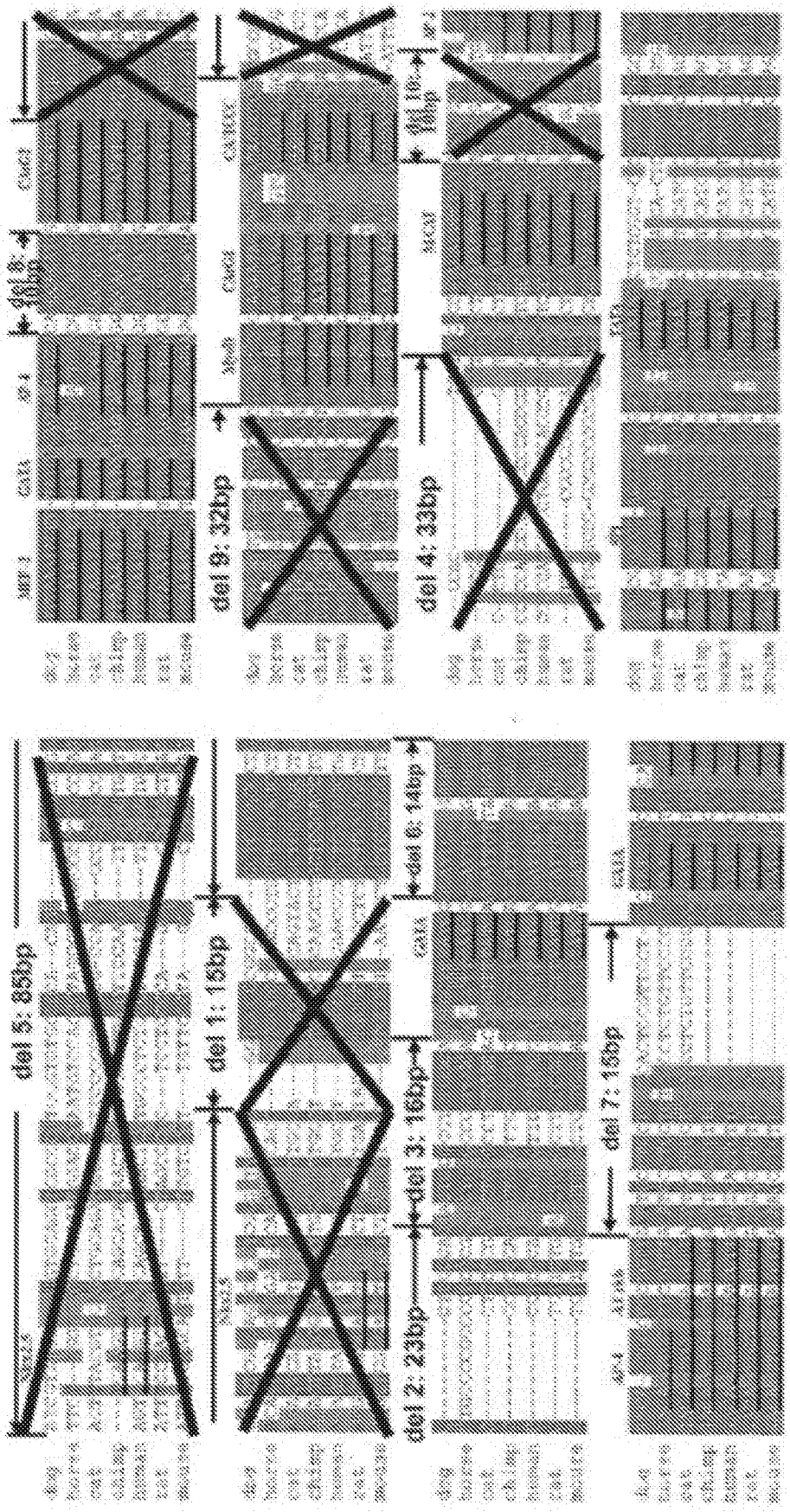

del 5: 85bp
del 1: 15bp
del 2: 23bp
del 3: 16bp
del 6: 14bp
del 7: 15bp
del 8: 32bp
del 4: 33bp

FIG. 18

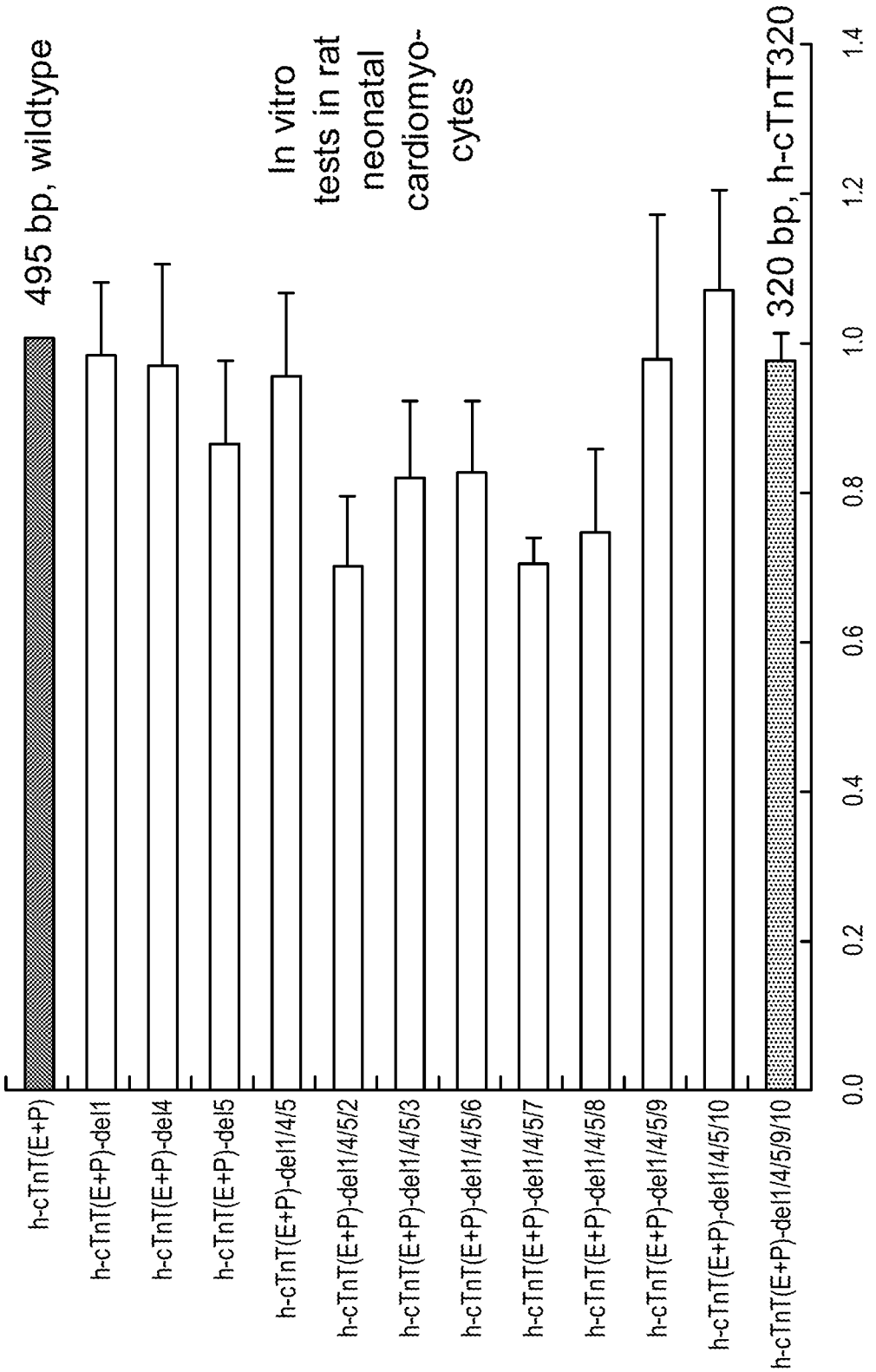

495 bp, wildtype
320 bp, h-cTnT320
In vitro tests in rat neonatal cardiomyo-cytes
h-cTnT(E+P)
h-cTnT(E+P)-del1
h-cTnT(E+P)-del4
h-cTnT(E+P)-del5
h-cTnT(E+P)-del1/4/5
h-cTnT(E+P)-del1/4/5/2
h-cTnT(E+P)-del1/4/5/3
h-cTnT(E+P)-del1/4/5/6
h-cTnT(E+P)-del1/4/5/7
h-cTnT(E+P)-del1/4/5/8
h-cTnT(E+P)-del1/4/5/9
h-cTnT(E+P)-del1/4/5/10
h-cTnT(E+P)-del1/4/5/9/10
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4

FIG. 19

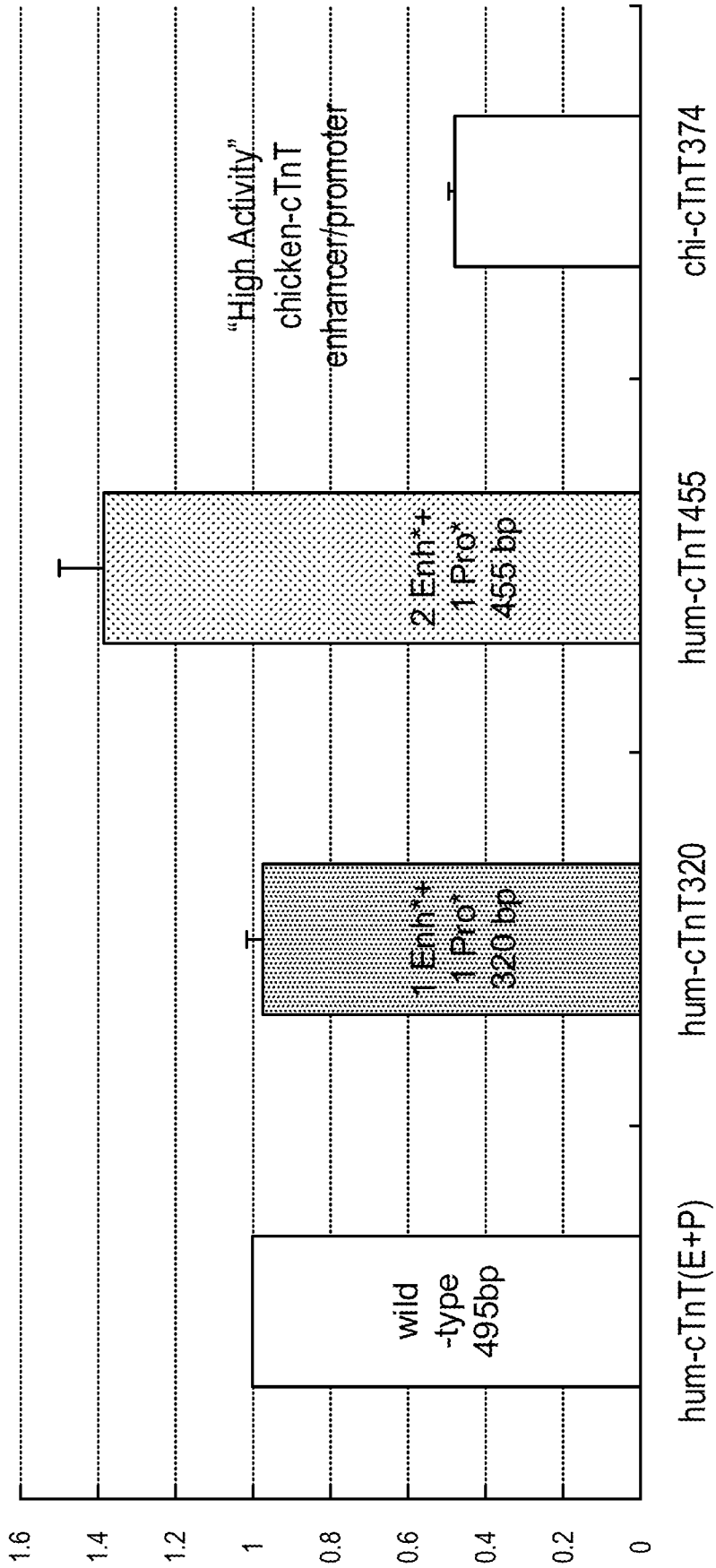

1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
"High Activity"
chicken-cTnT
enhancer/promoter
wild
-type
495bp
1 Enh*+
1 Pro*
320 bp
2 Enh*+
1 Pro*
455 bp
hum-cTnT(E+P)
hum-cTnT320
hum-cTnT455
chi-cTnT374

FIG. 20

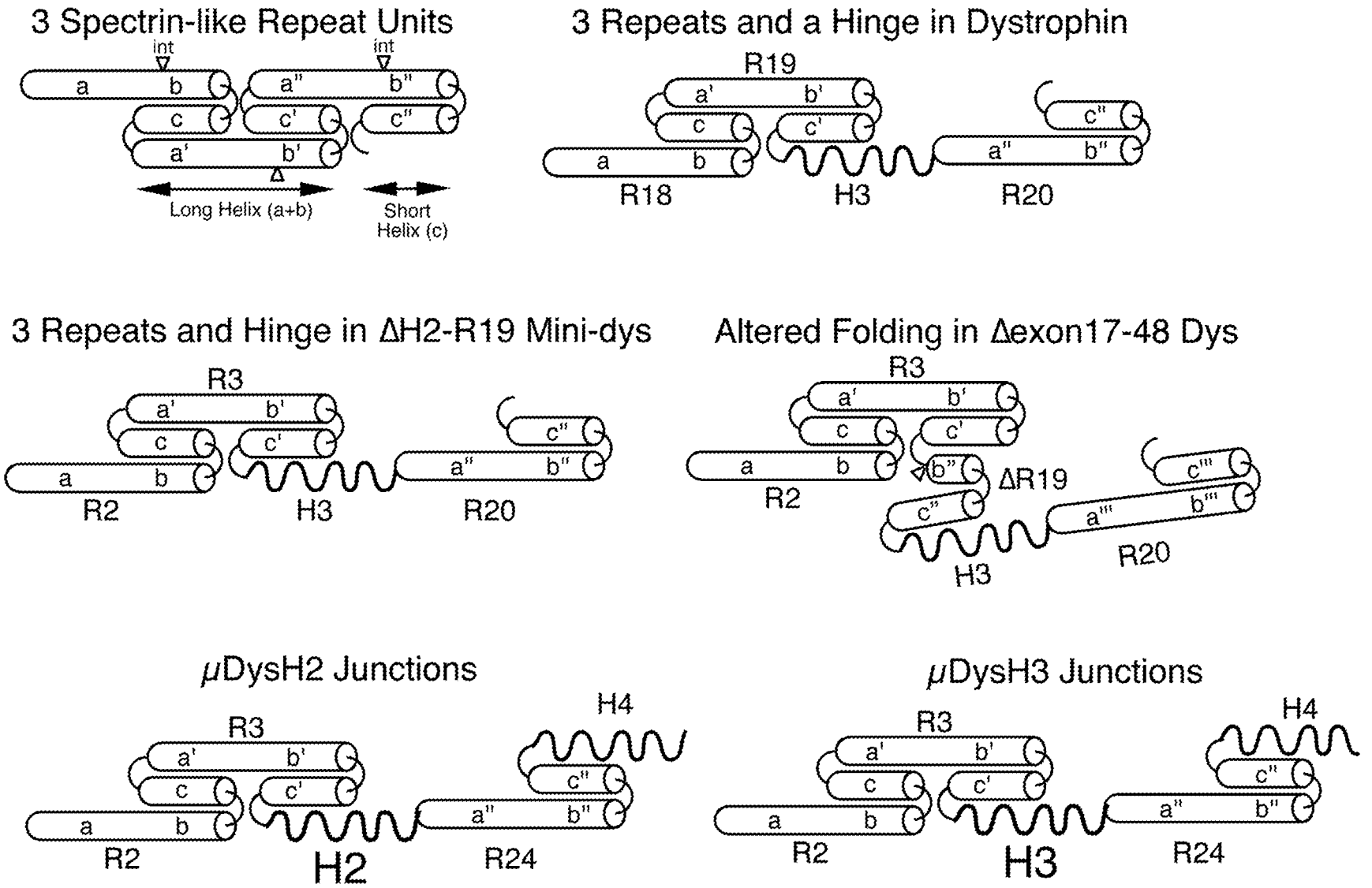

3 Spectrin-like Repeat Units
int
int
a
b
a"
b"
c
c'
c"
a'
b'
Long Helix (a+b)
Short Helix (c)
3 Repeats and a Hinge in Dystrophin
R19
a'
b'
c
c'
c"
a
b
a"
b"
R18
H3
R20
3 Repeats and Hinge in ΔH2-R19 Mini-dys
R3
a'
b'
c
c'
c"
a
b
a"
b"
R2
H3
R20
Altered Folding in Δexon17-48 Dys
R3
a'
b'
c
c'
a
b
b"
ΔR19
c'''
c"
a'''
b'''
R2
H3
R20
μDysH2 Junctions
H4
R3
a'
b'
c
c'
c"
a
b
a"
b"
R2
H2
R24
μDysH3 Junctions
H4
R3
a'
b'
c
c'
c"
a
b
a"
b"
R2
H3
R24

FIG. 21

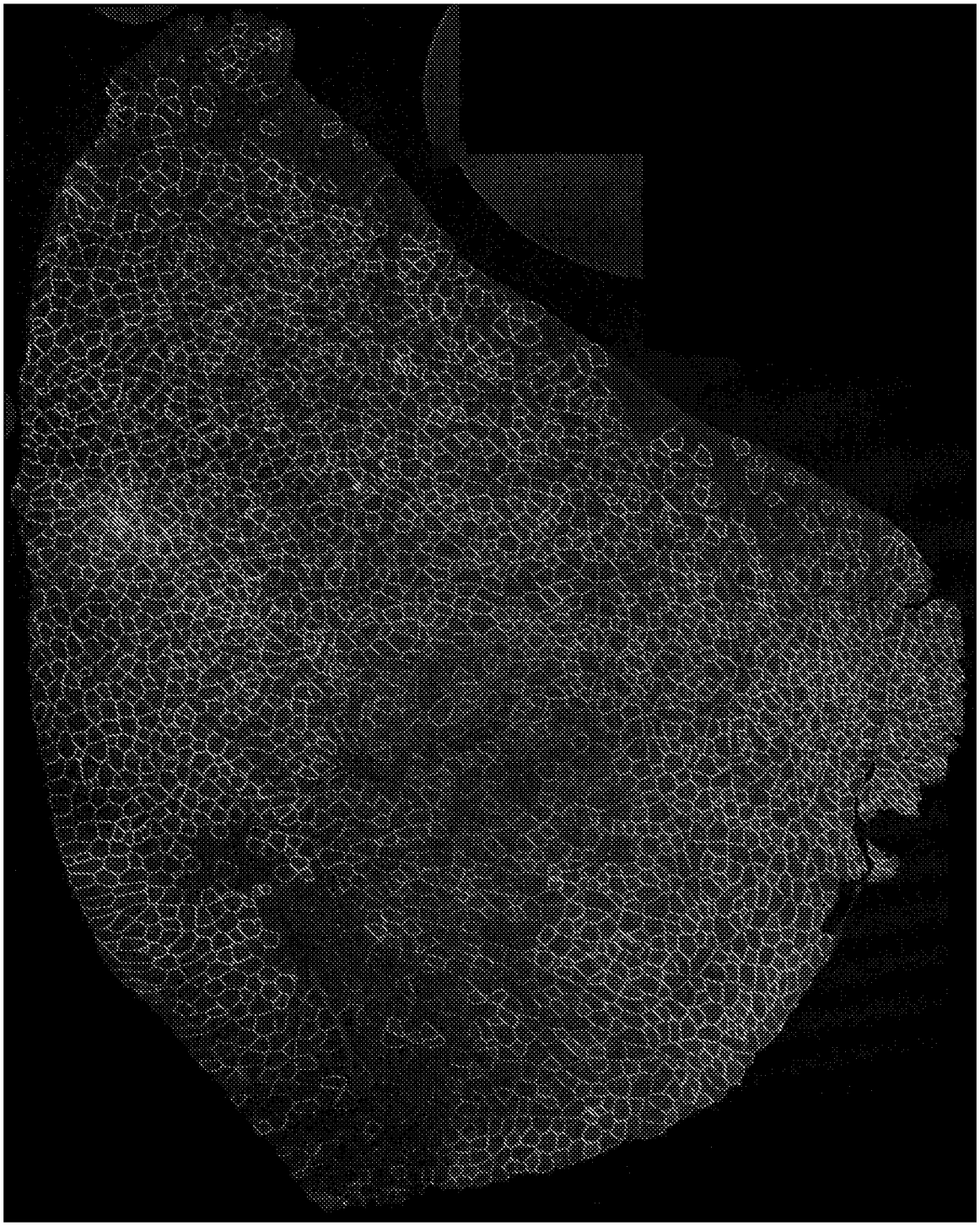


FIG. 22