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CORRECTED PUBLICATION

- (54) **TREATMENT AND DETECTION OF INHERITED NEUROPATHIES AND ASSOCIATED DISORDERS**
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See (60) Related U.S. Application Data.
- (65) US 2022/0249624 A1 Aug. 11, 2022

Related U.S. Application Data

- (63) Continuation of application No. 17/517,227, filed on Nov. 2, 2021, which is a continuation of application No. PCT/US2020/031708, filed on May 6, 2020.
- (60) Provisional application No. 62/987,151, filed on Mar. 9, 2020, provisional application No. 62/844,370, filed on May 7, 2019.

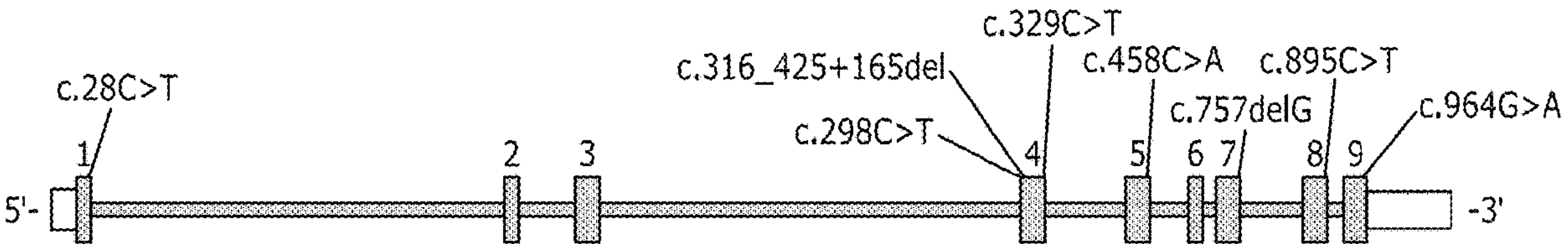
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- (52) **U.S. Cl.**
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(57) **ABSTRACT**

The present disclosure relates to methods of detecting and treating inherited neuropathy.
Specification includes a Sequence Listing.



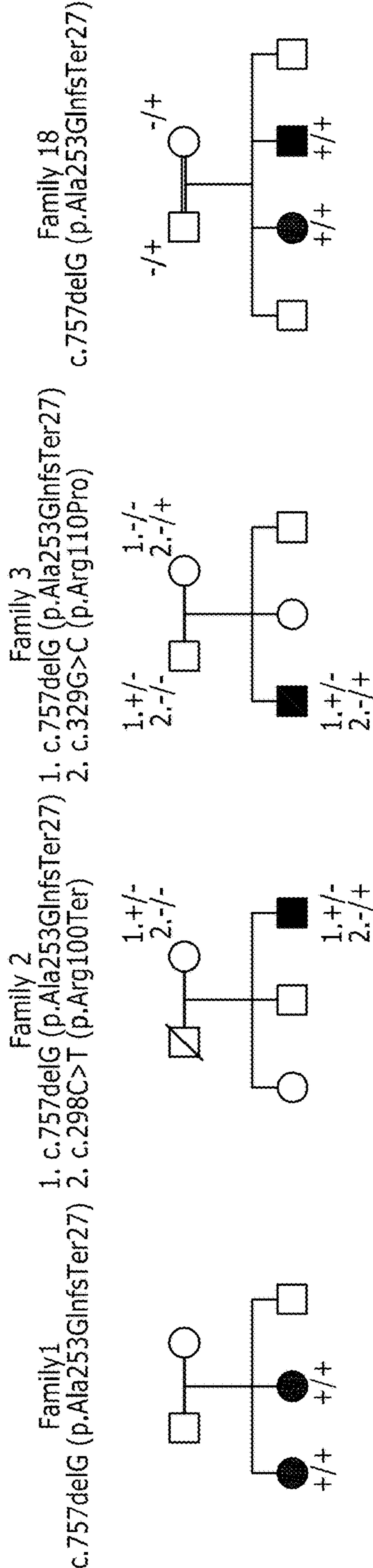


FIG. 1A

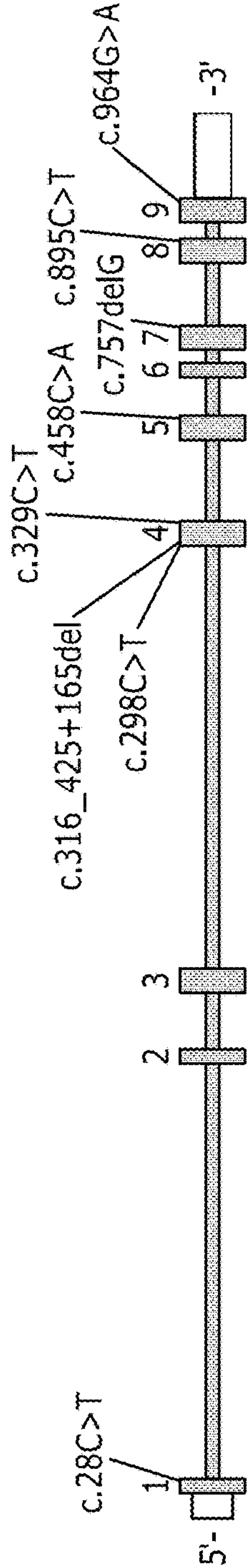


FIG. 1B

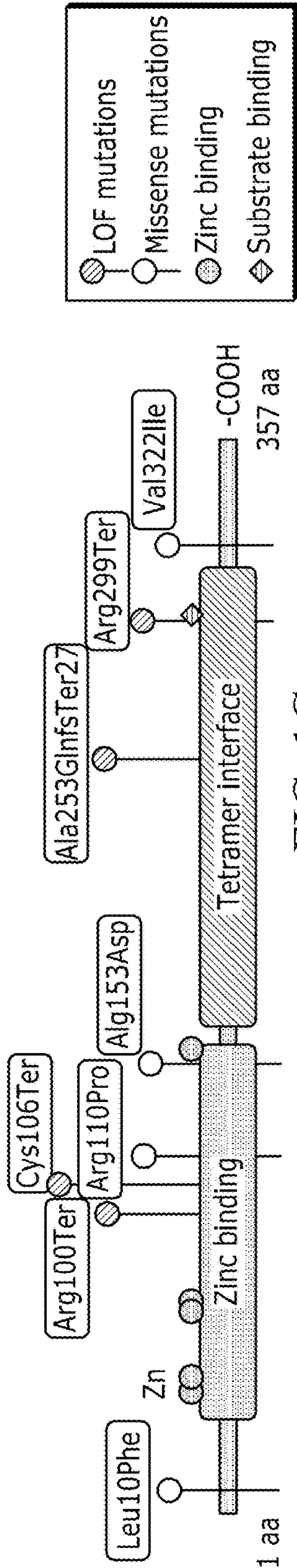
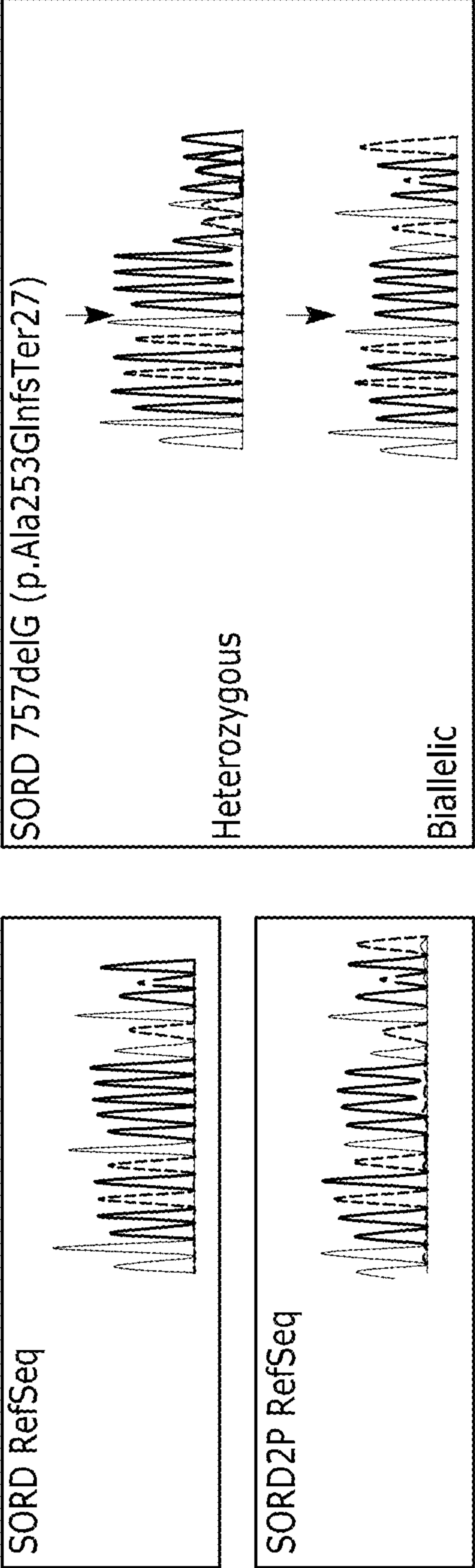
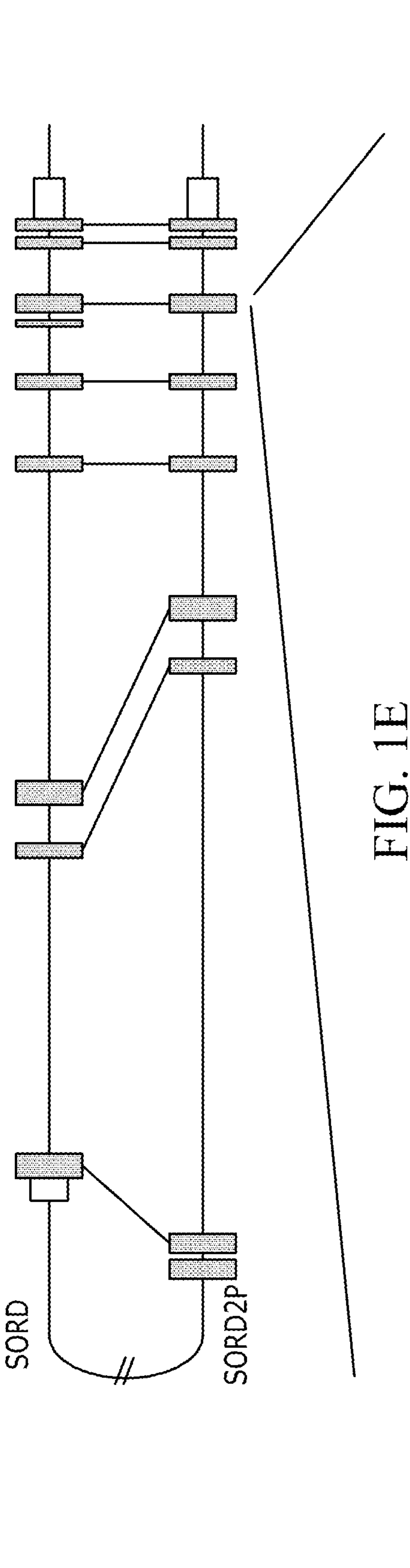


FIG. 1C

Humans	P	N	N	L	S	L	V	*	K	M	G	R	Y	N	L	*	E	E	G	A	L	I	E	*	K	P	L	V	T	H	R	SEQ ID NO:537 and 542-544
Rhesus	P	K	N	L	S	L	V	*	K	S	G	R	Y	N	L	*	E	E	G	A	L	I	E	*	K	P	L	V	T	H	R	SEQ ID NO:538 and 545-547
Mouse	G	E	N	L	S	L	V	*	K	I	G	R	Y	N	L	*	E	E	G	A	L	I	E	*	K	P	L	V	T	H	R	SEQ ID NO:539 and 548-550
Dog	A	E	N	L	T	L	V	*	K	I	G	R	Y	N	L	*	E	E	G	A	L	I	E	*	K	P	L	V	T	H	R	SEQ ID NO:540 and 551-553
Drosophila	K	D	N	L	T	A	V	*	K	Q	G	R	Y	N	L	*	E	E	G	A	L	L	E	*	K	R	L	V	T	H	H	SEQ ID NO:541 and 554-556

FIG. 1D



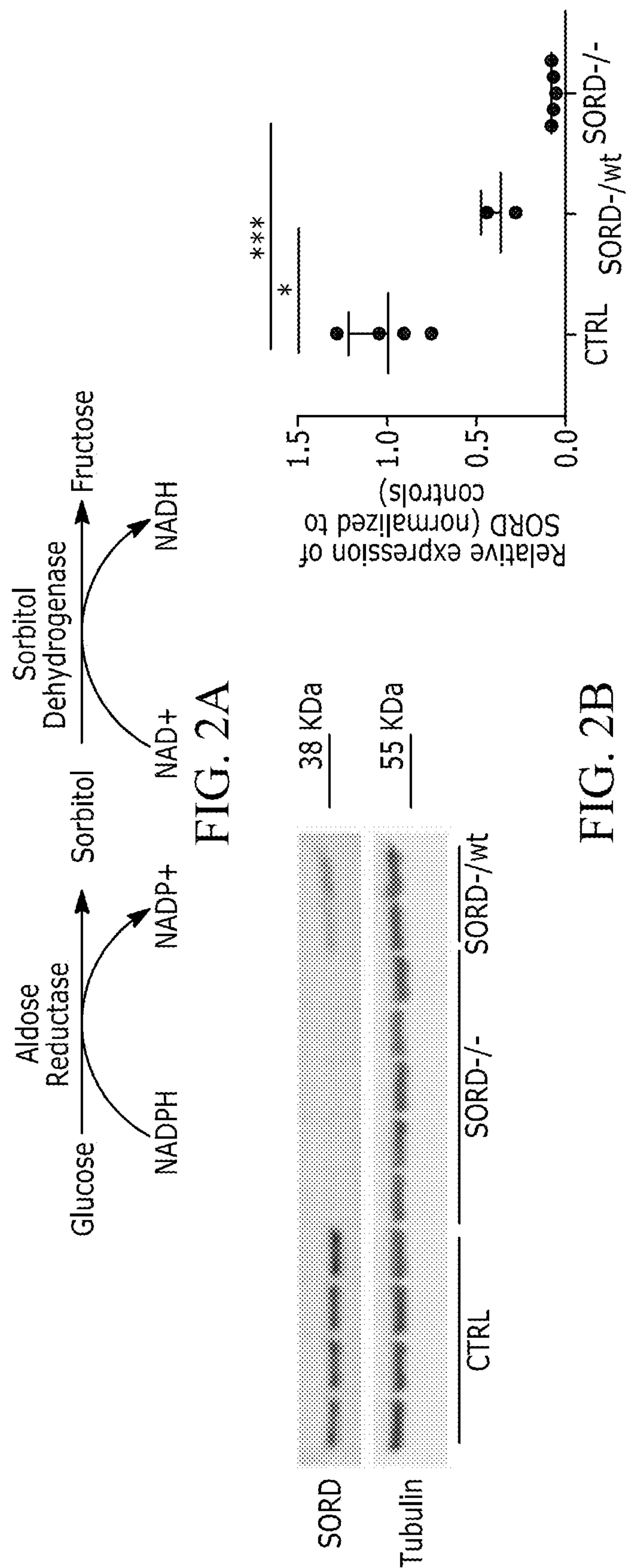


FIG. 2B

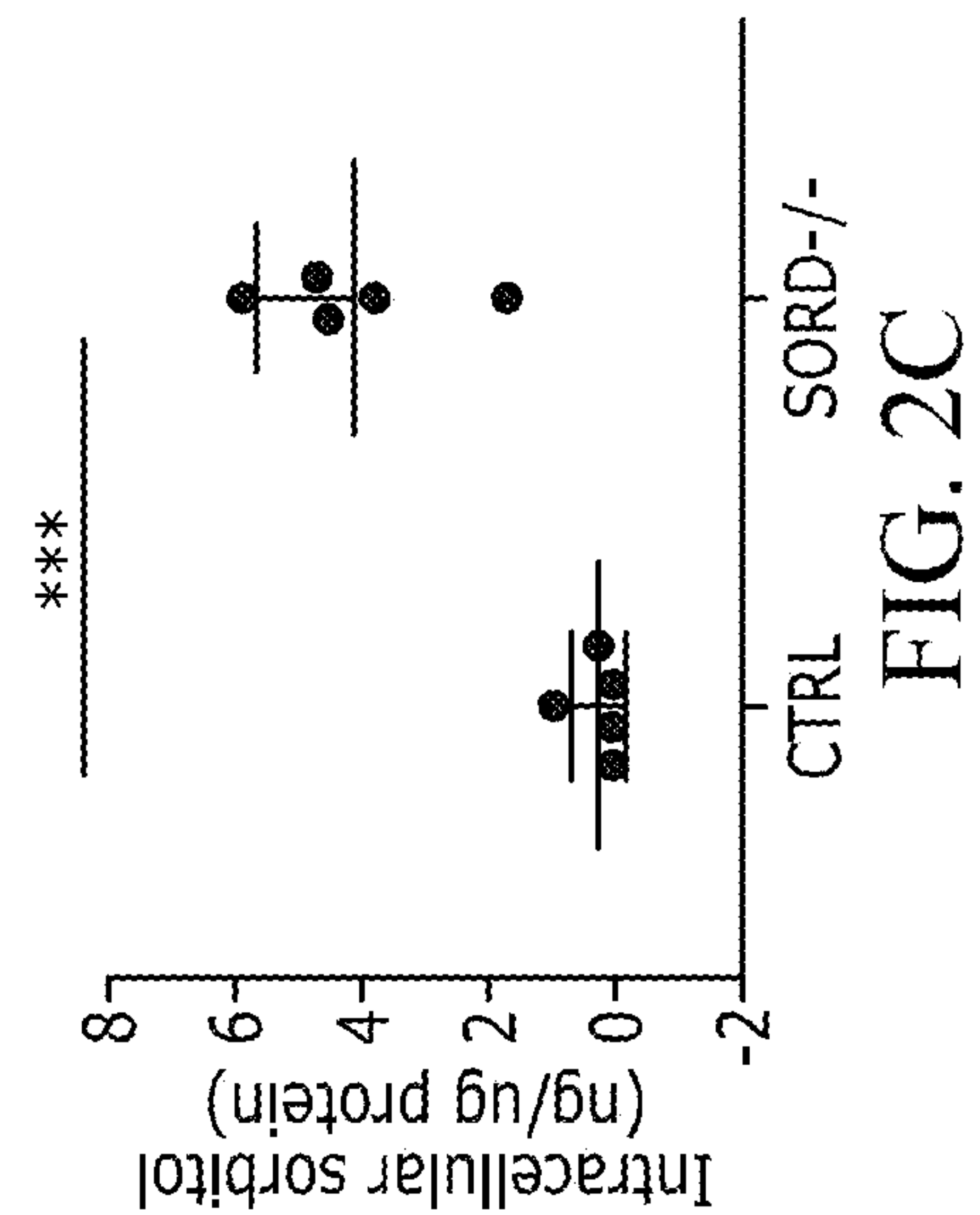


FIG. 2C

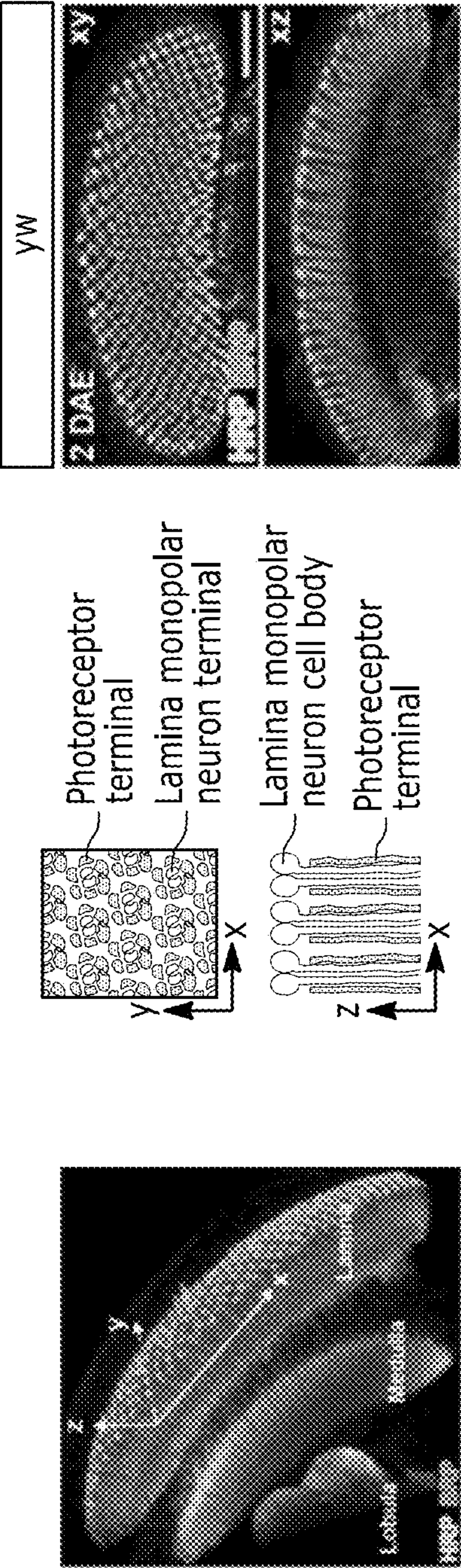


FIG. 3B

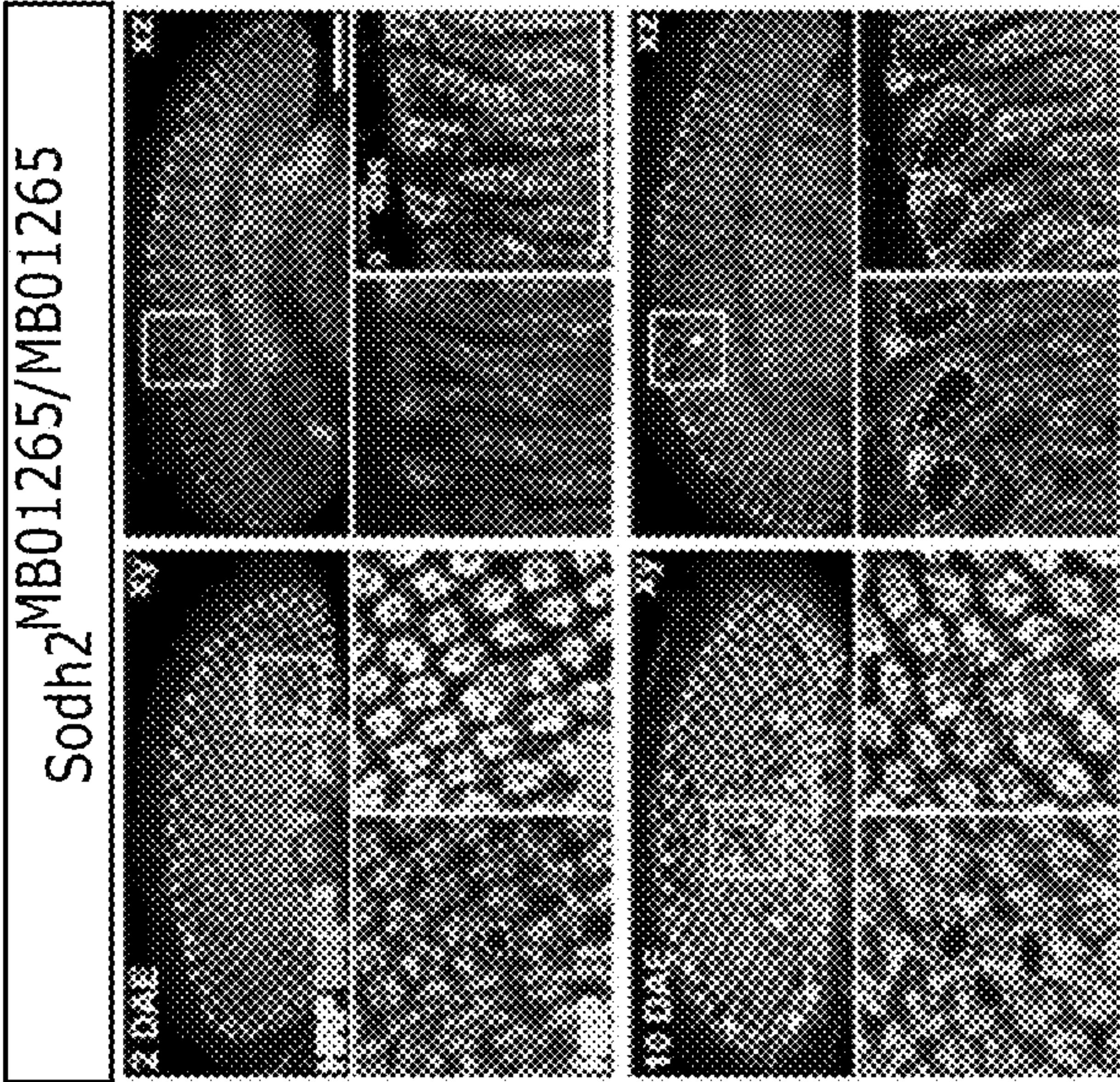
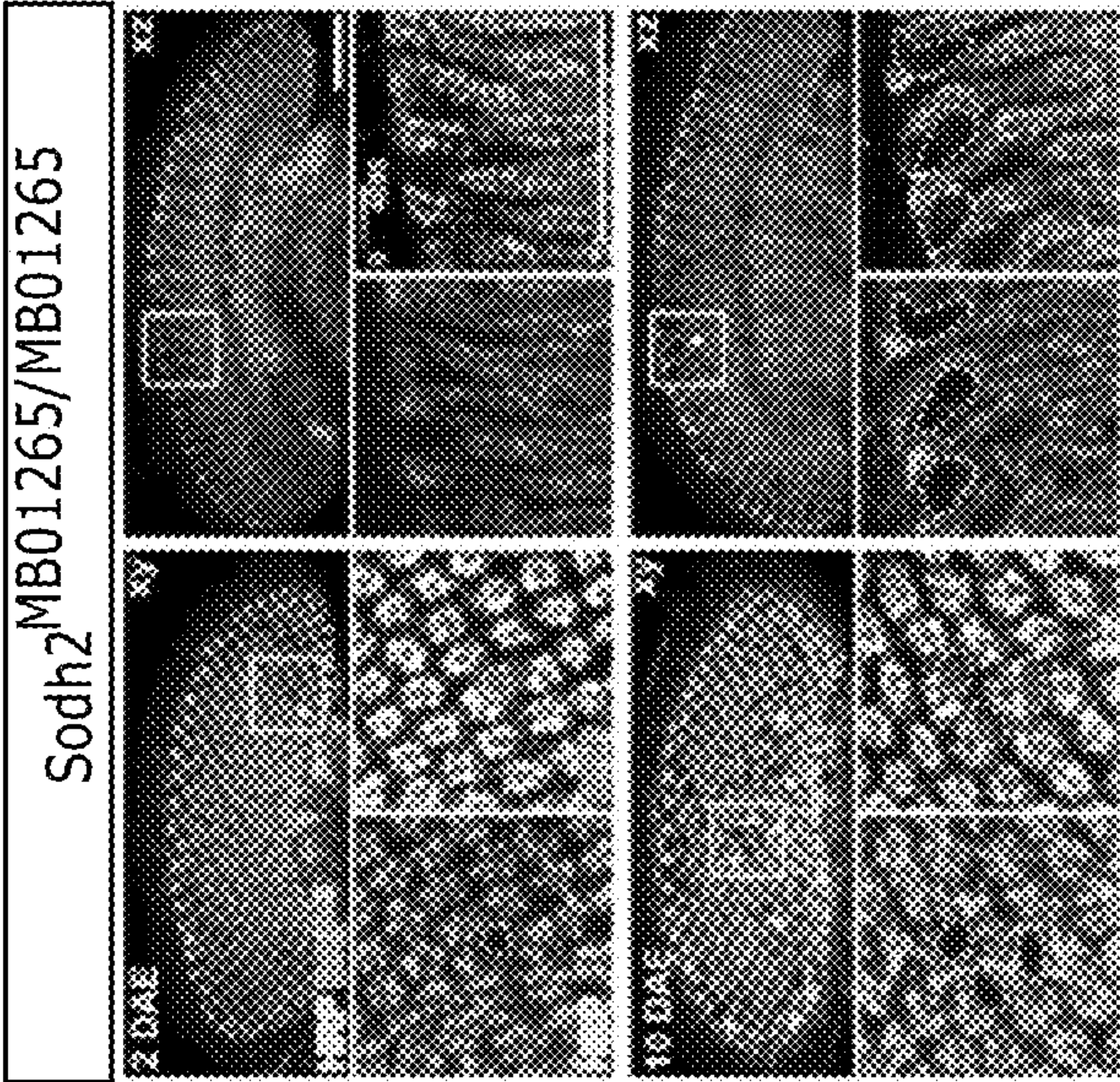


FIG. 3C



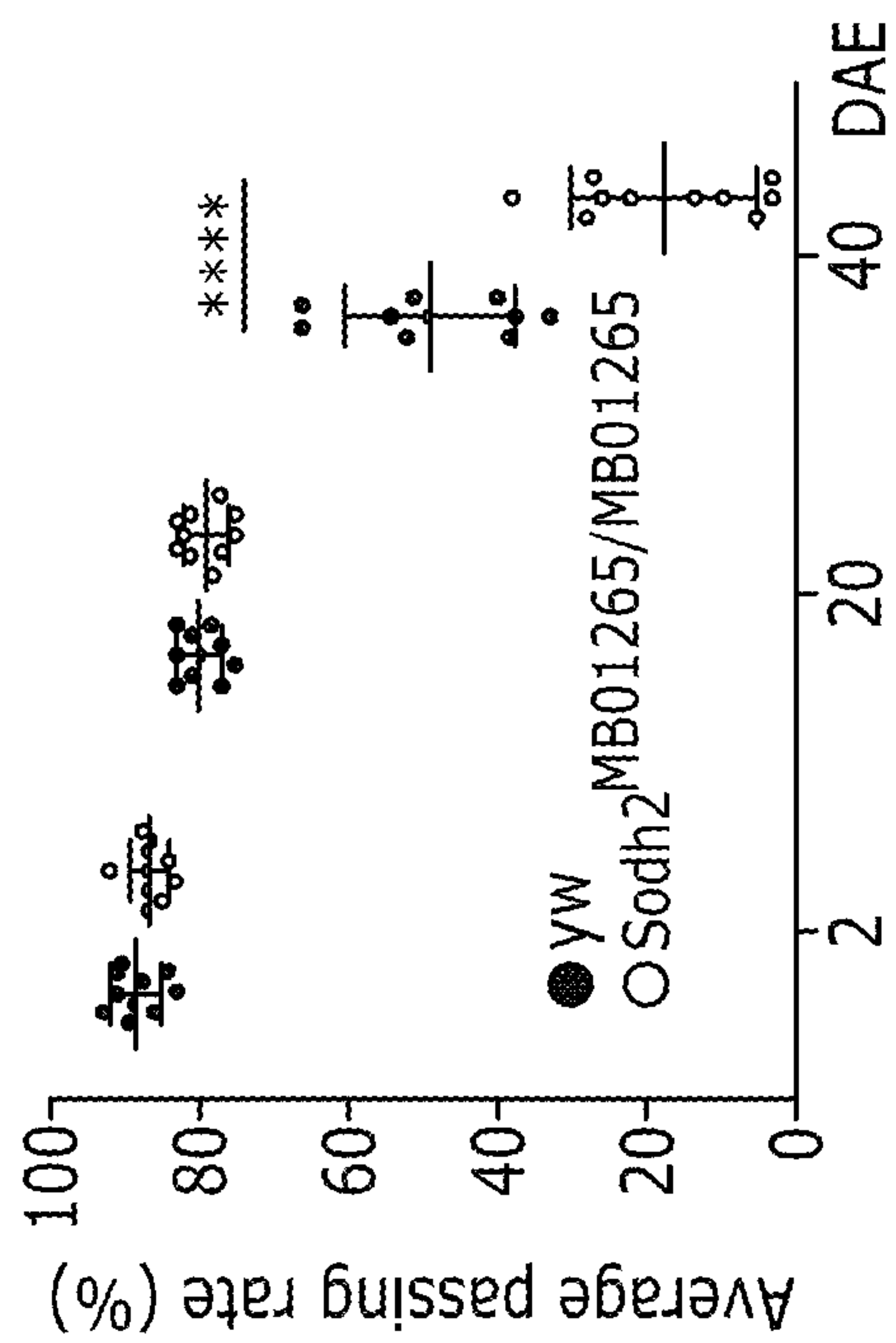
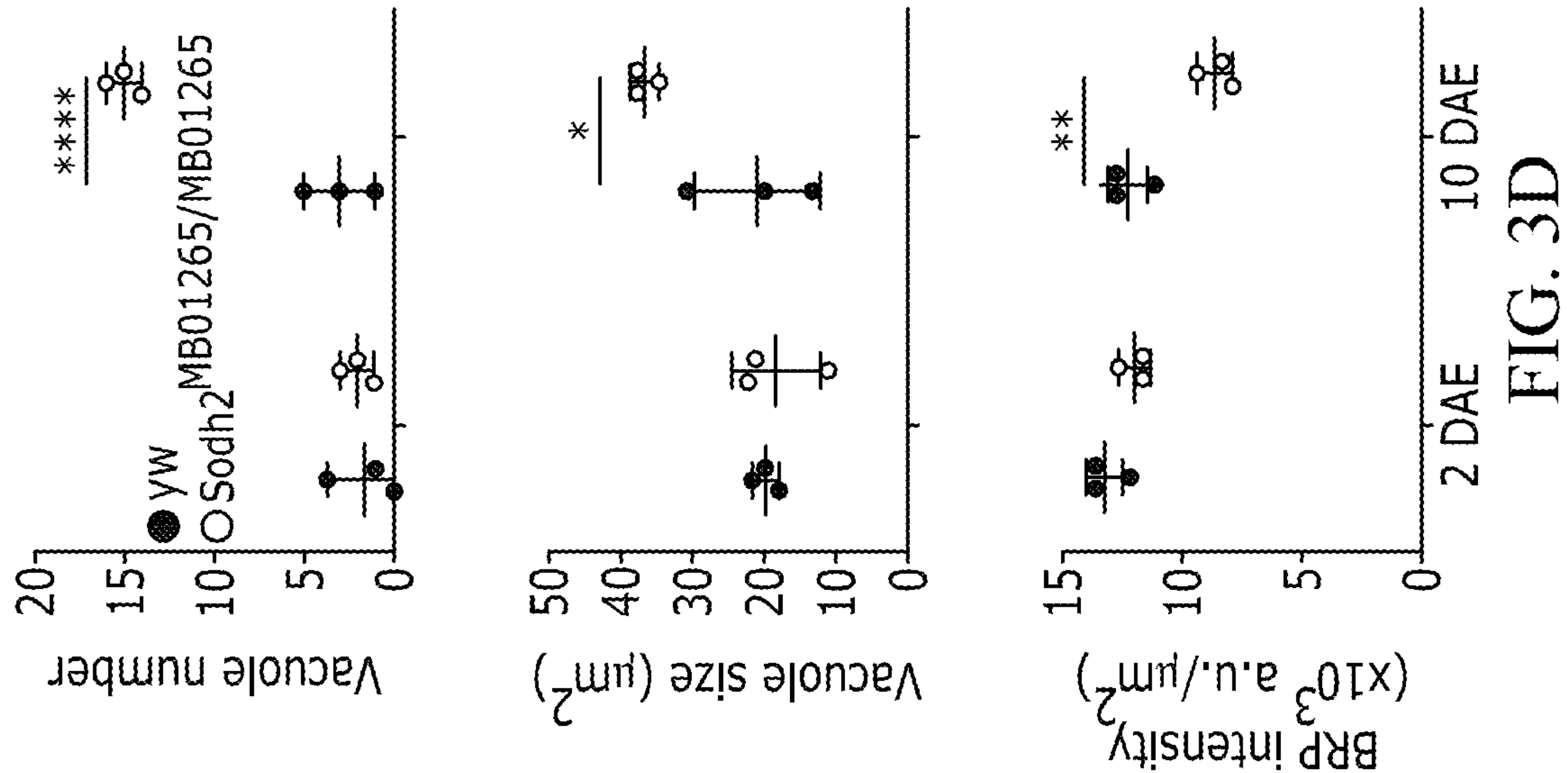


FIG. 3E

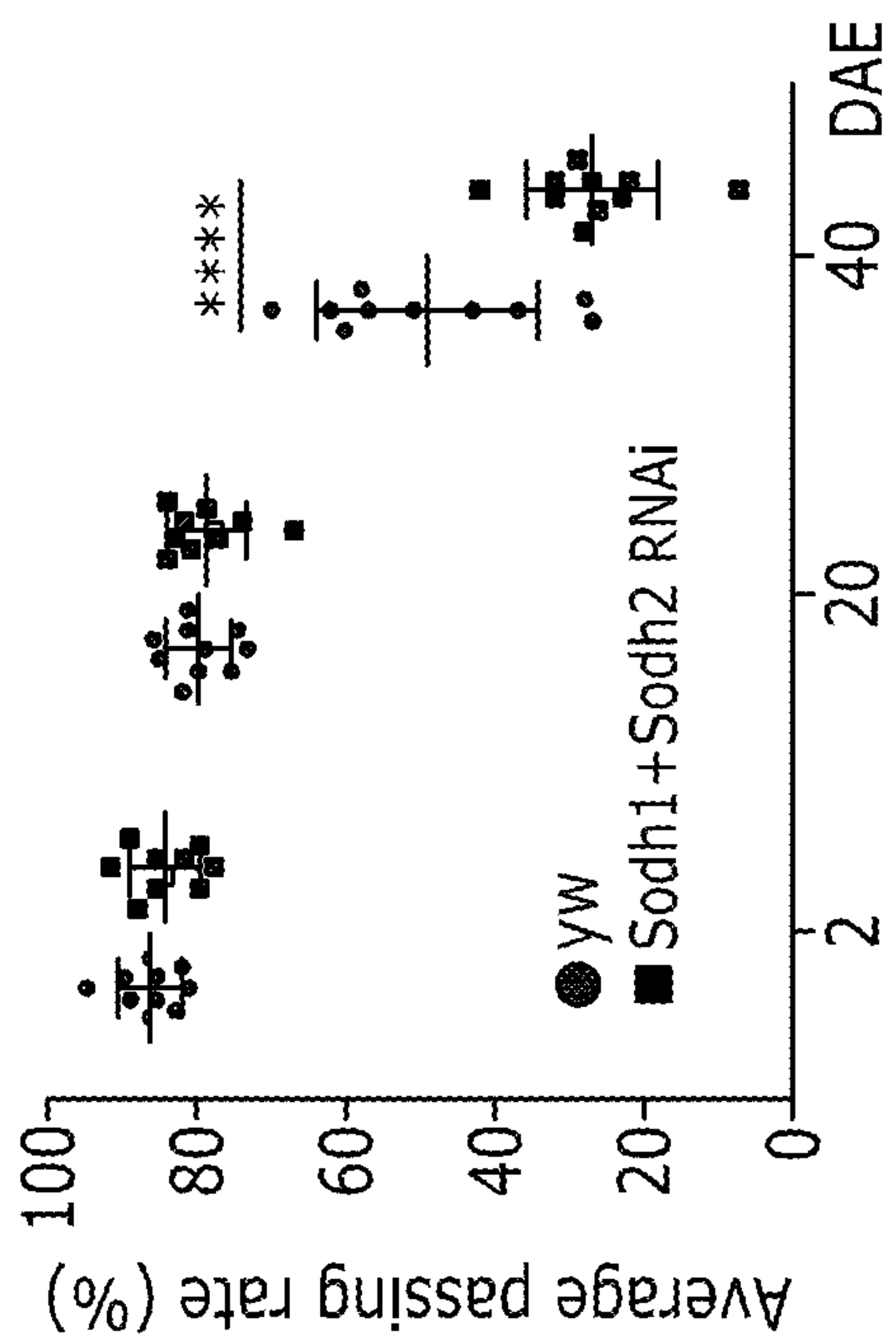


FIG. 3F

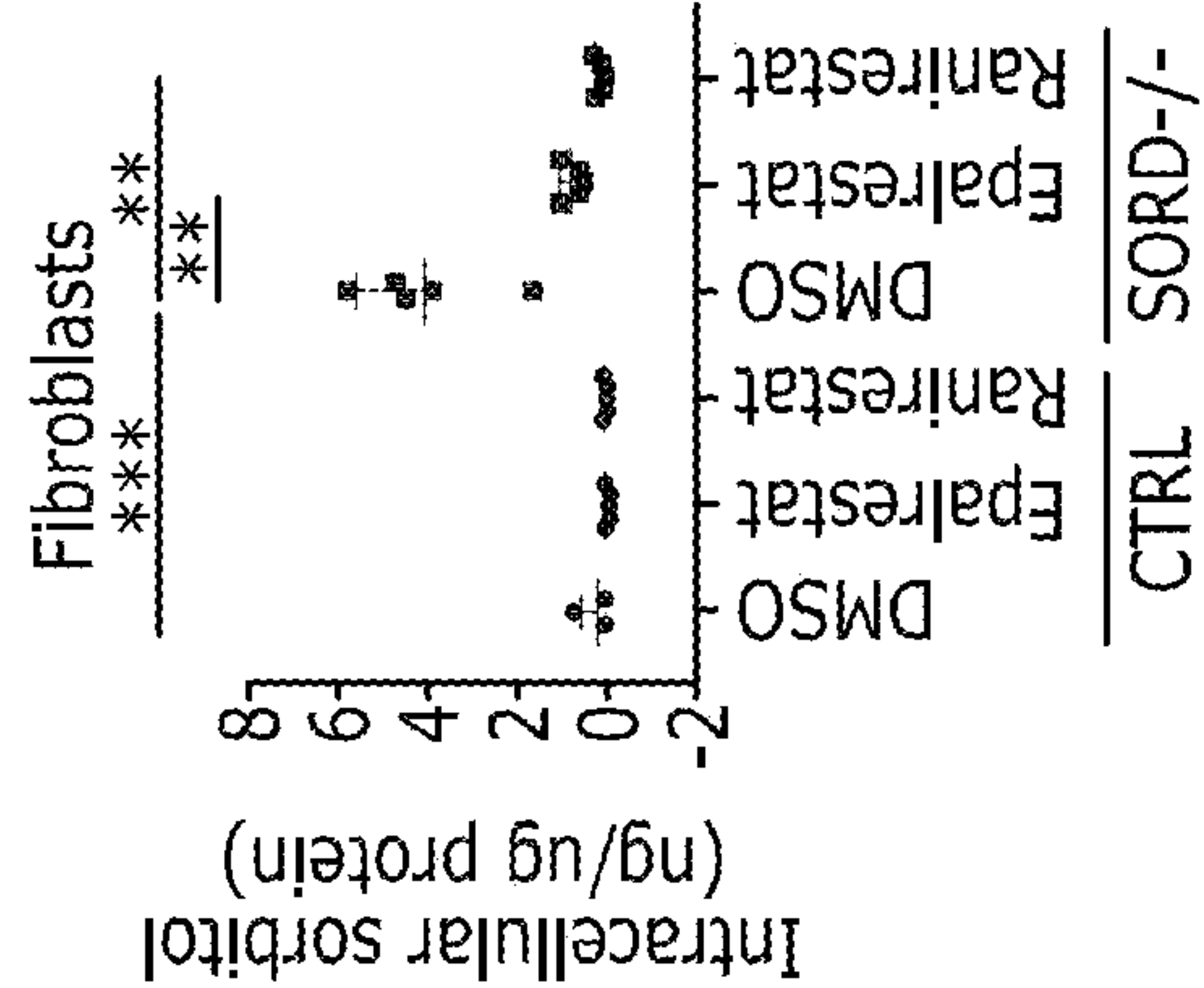


FIG. 4A

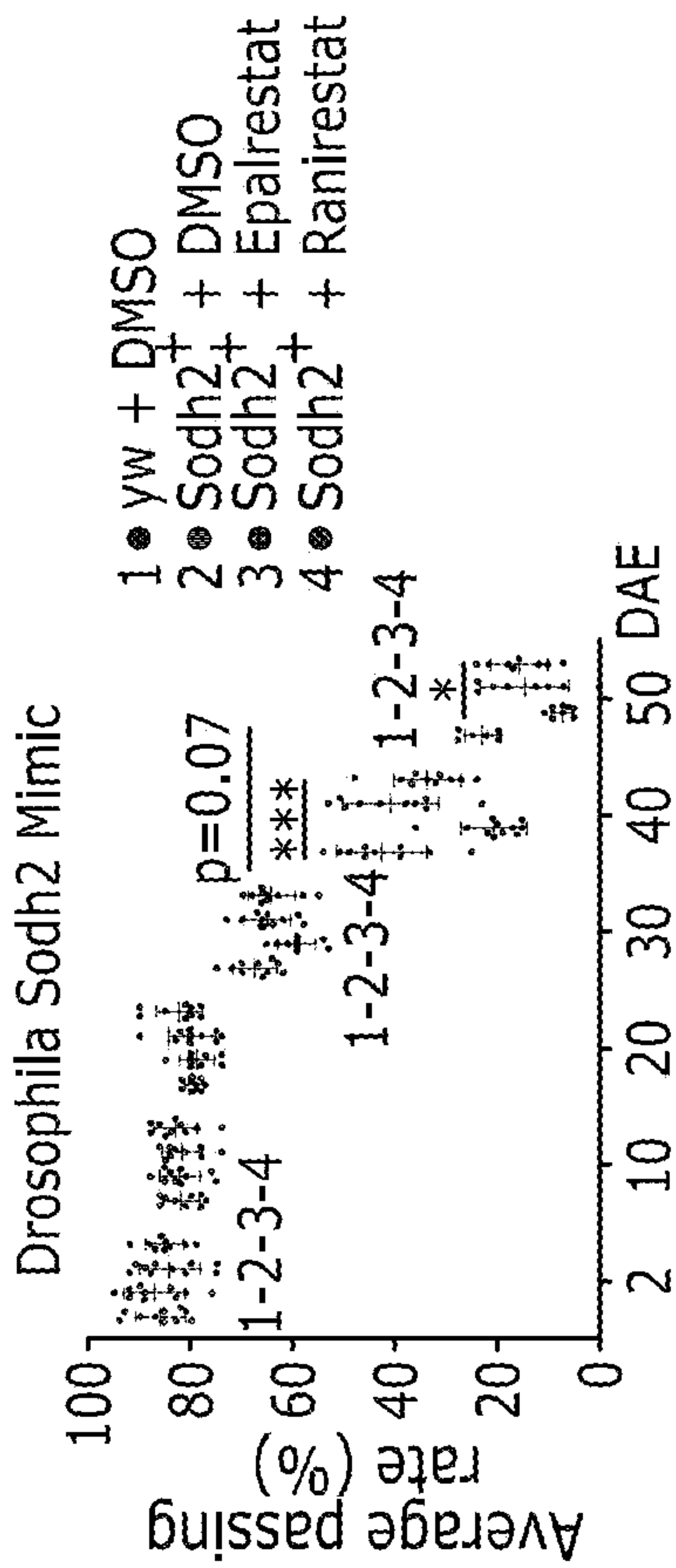


FIG. 4C

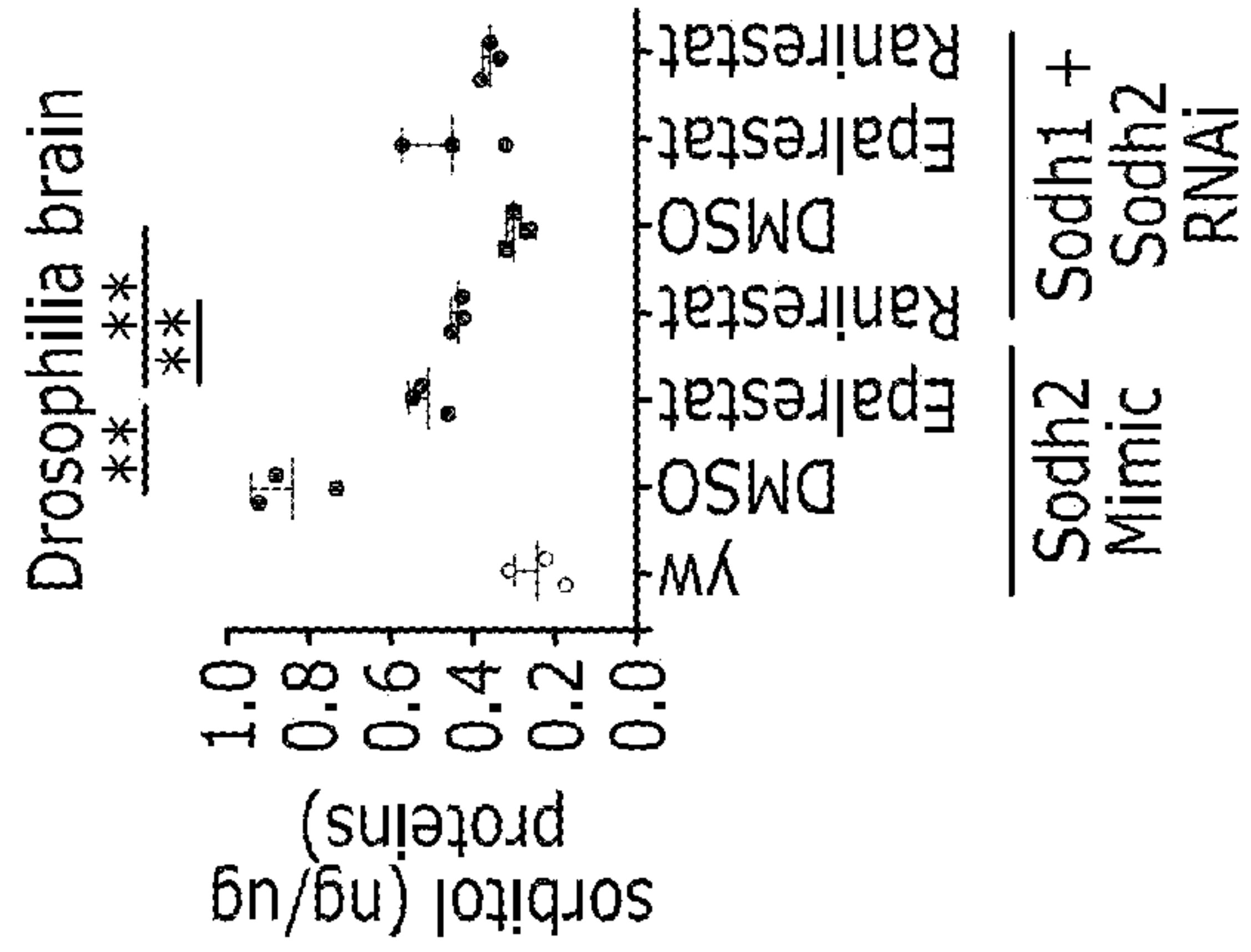


FIG. 4B

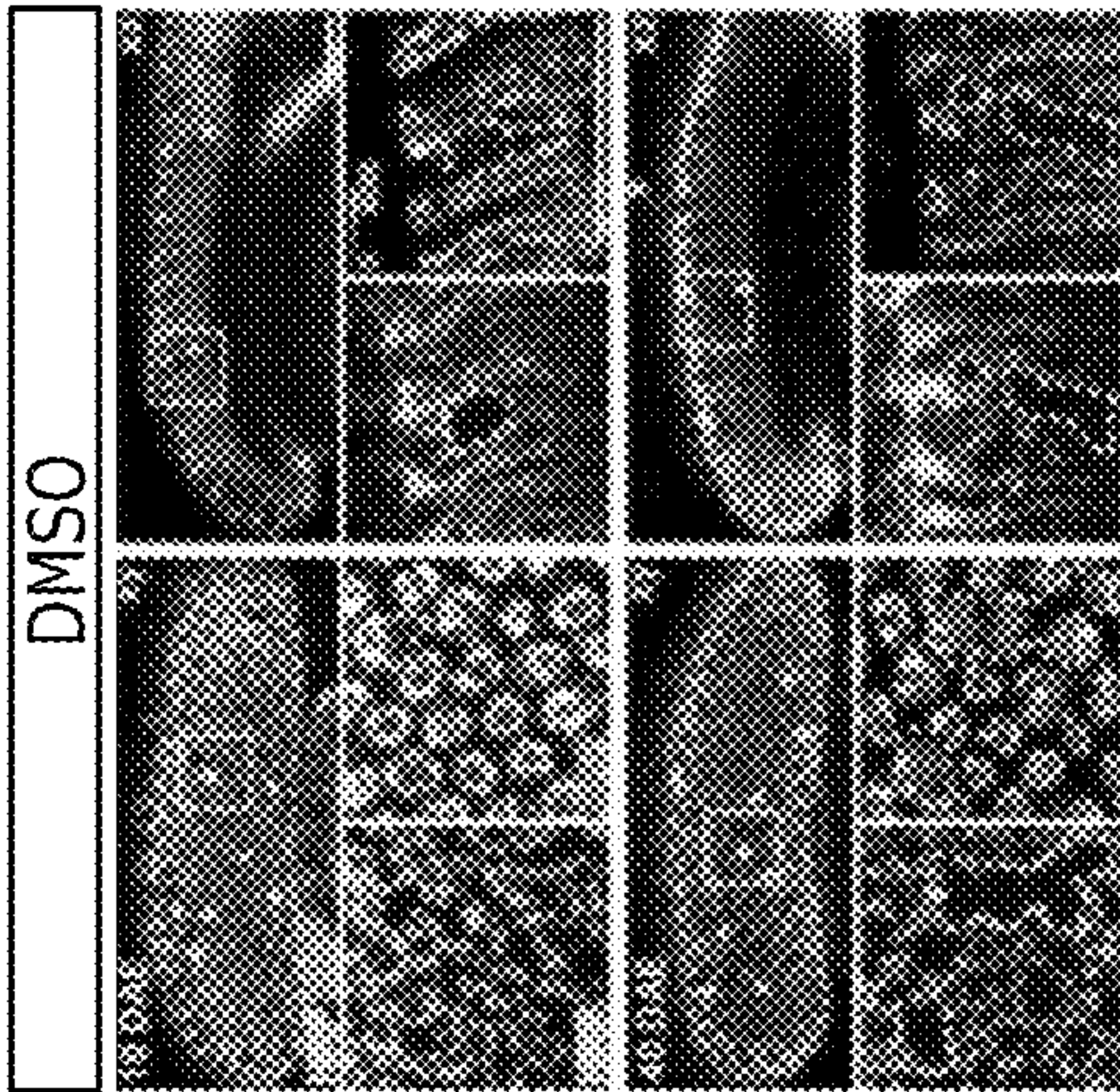


FIG. 4D

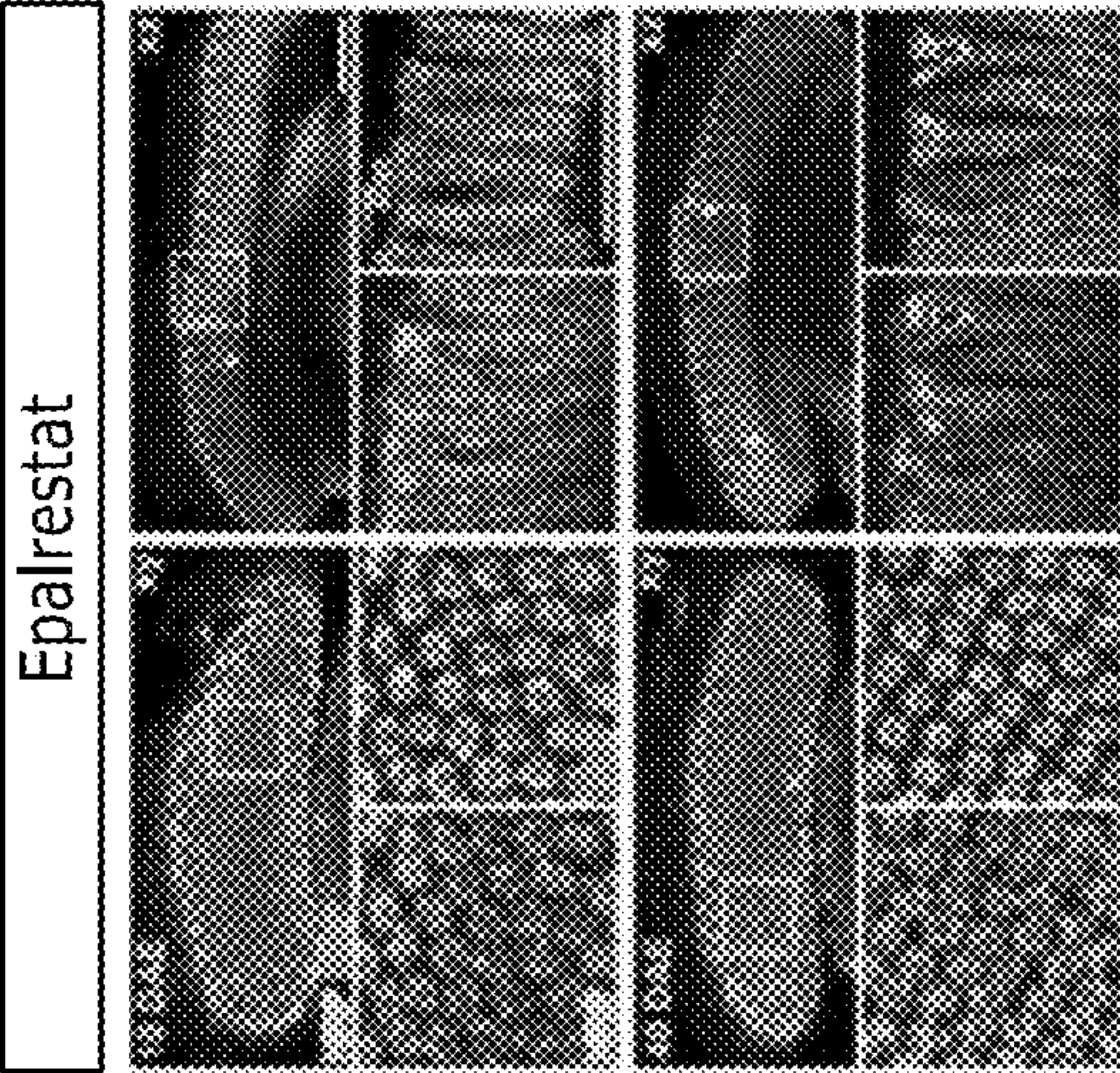


FIG. 4E

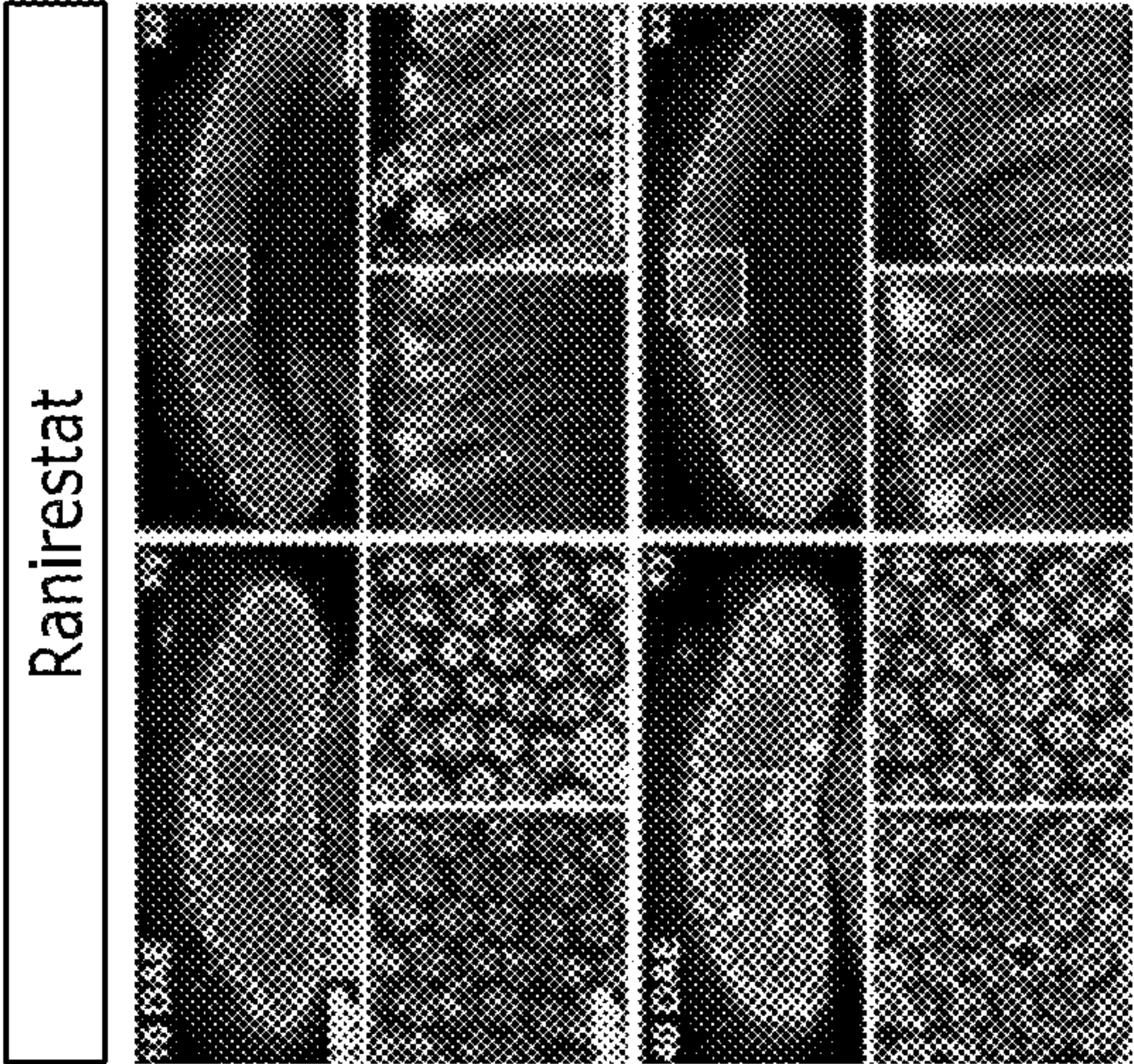


FIG. 4F

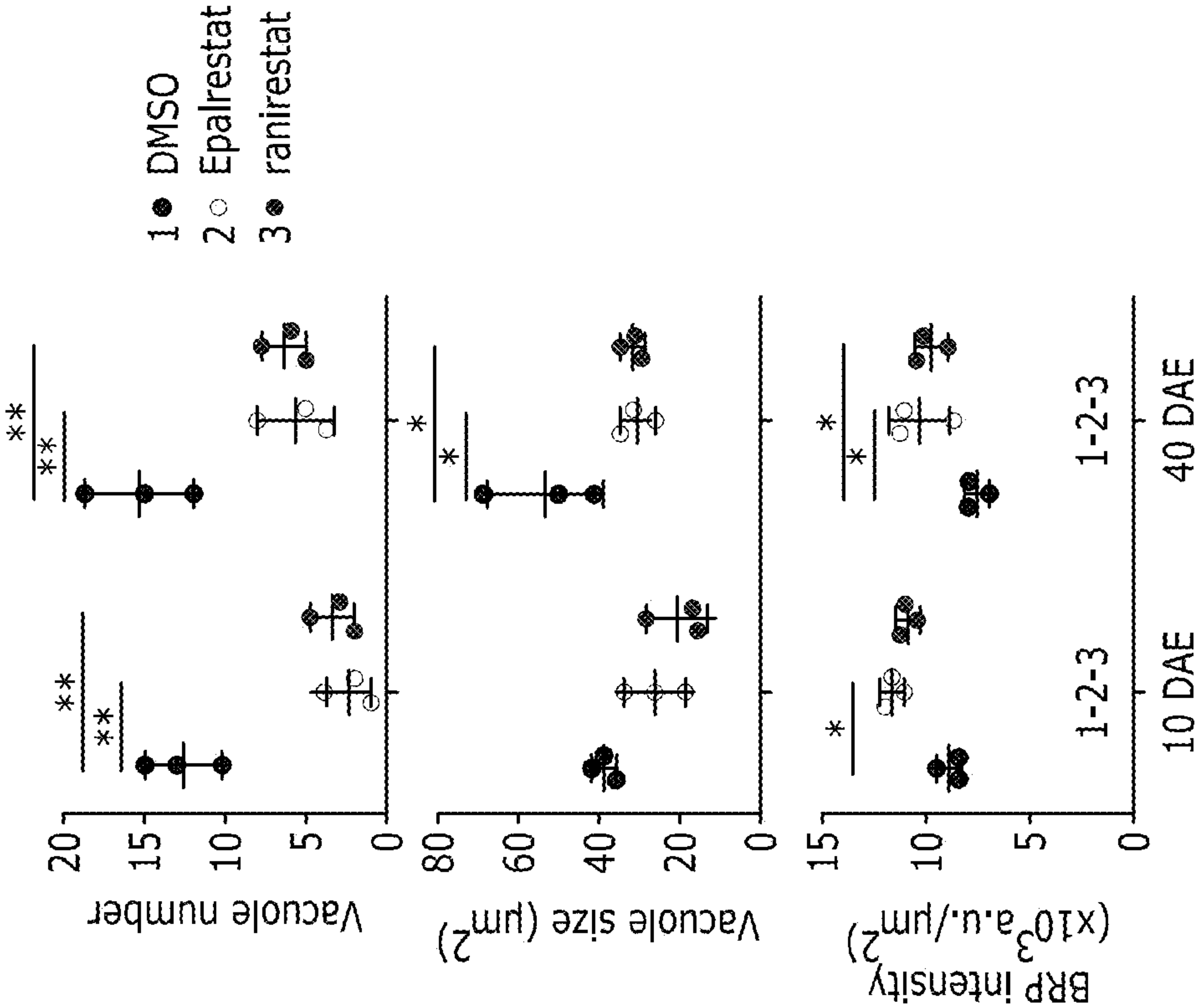


FIG. 4G

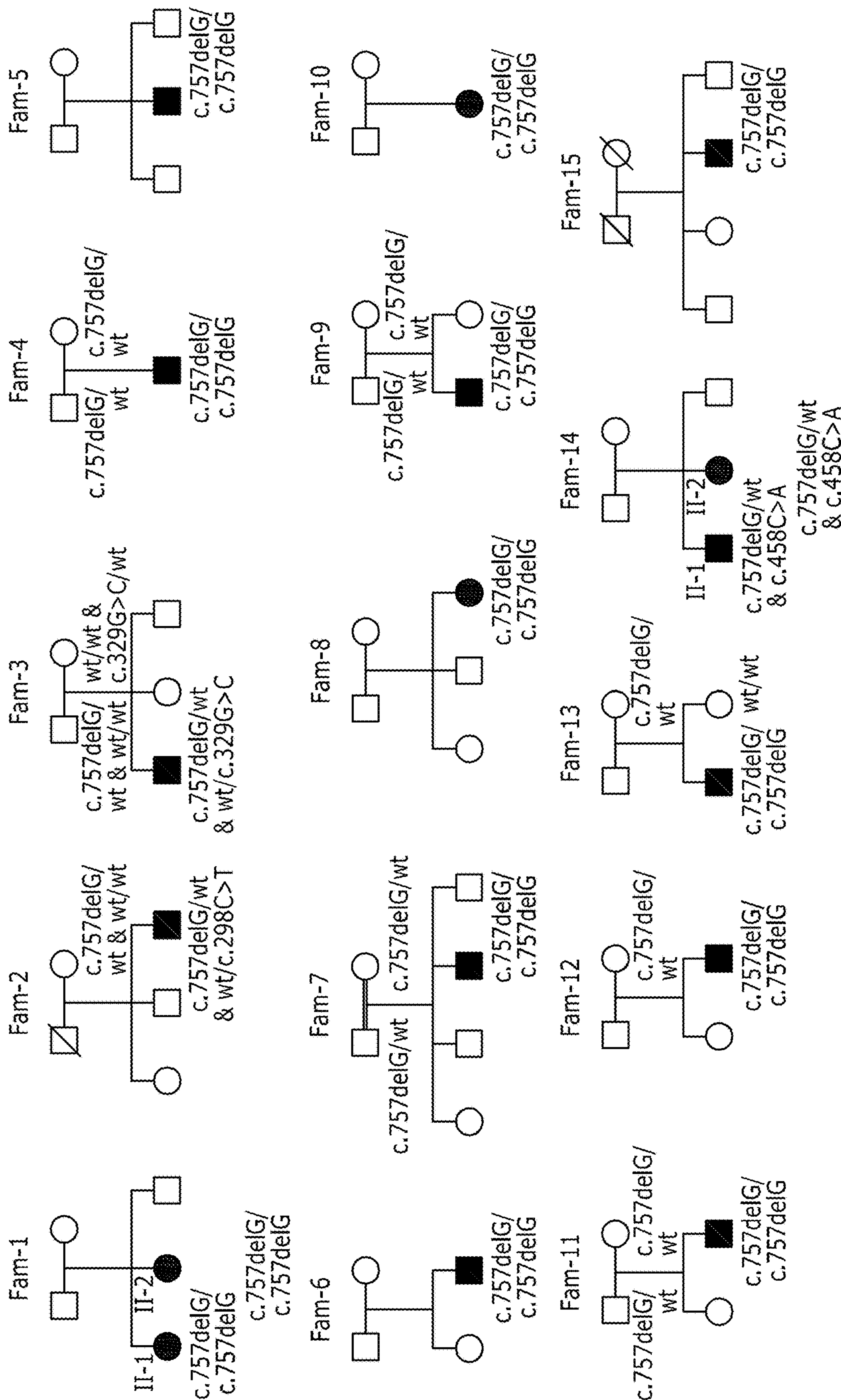


FIG. 5

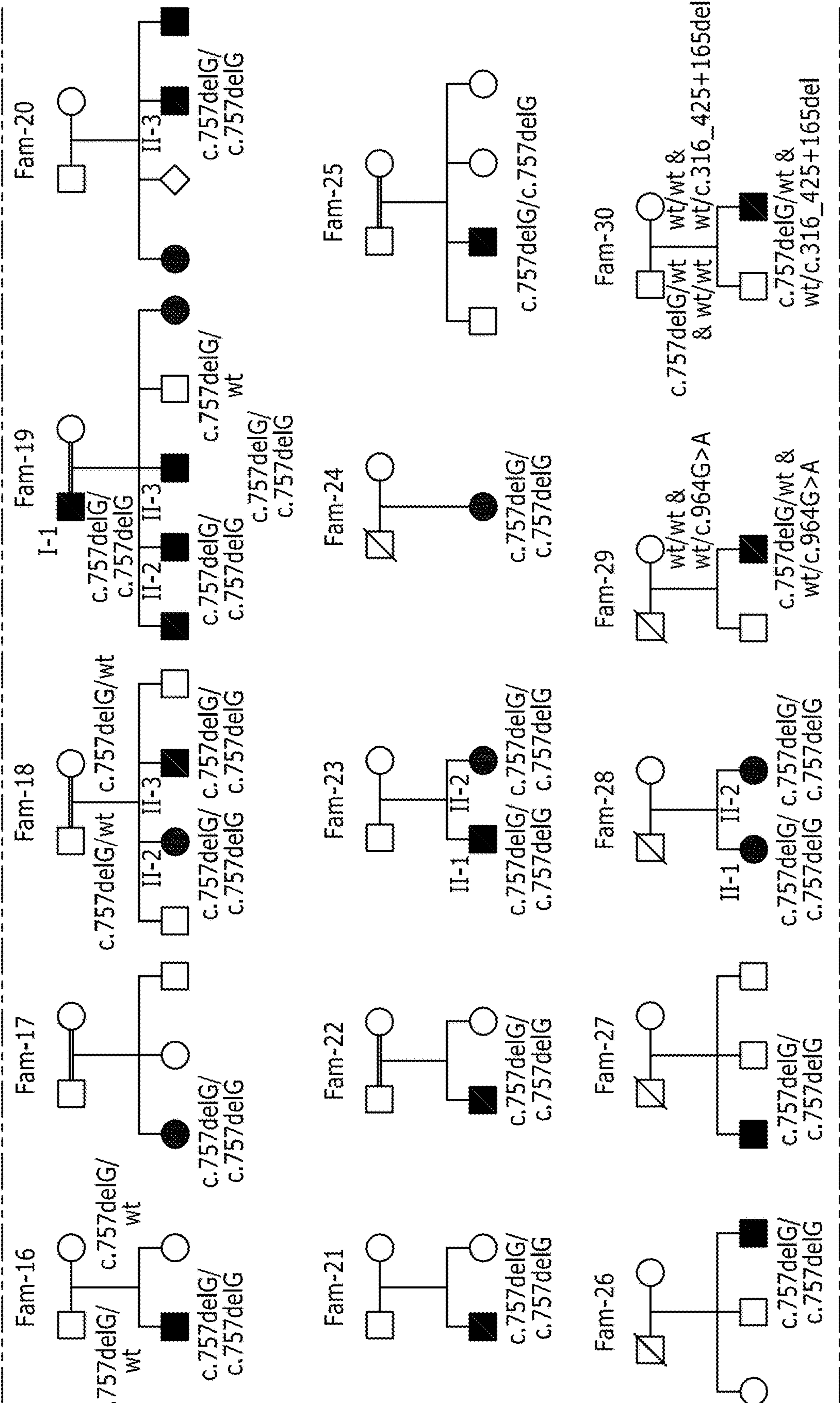


FIG. 5CONT.

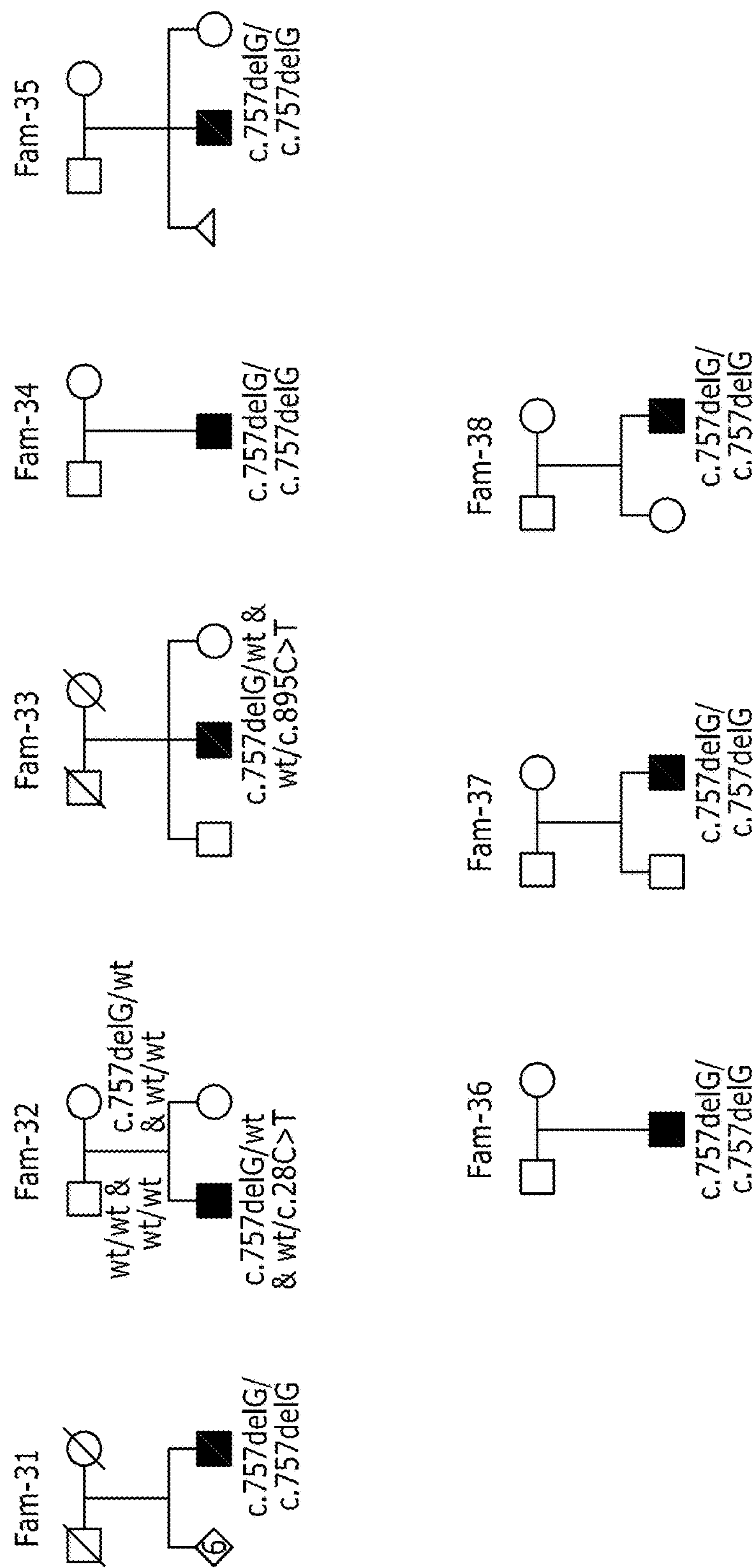


FIG. 5CONT.

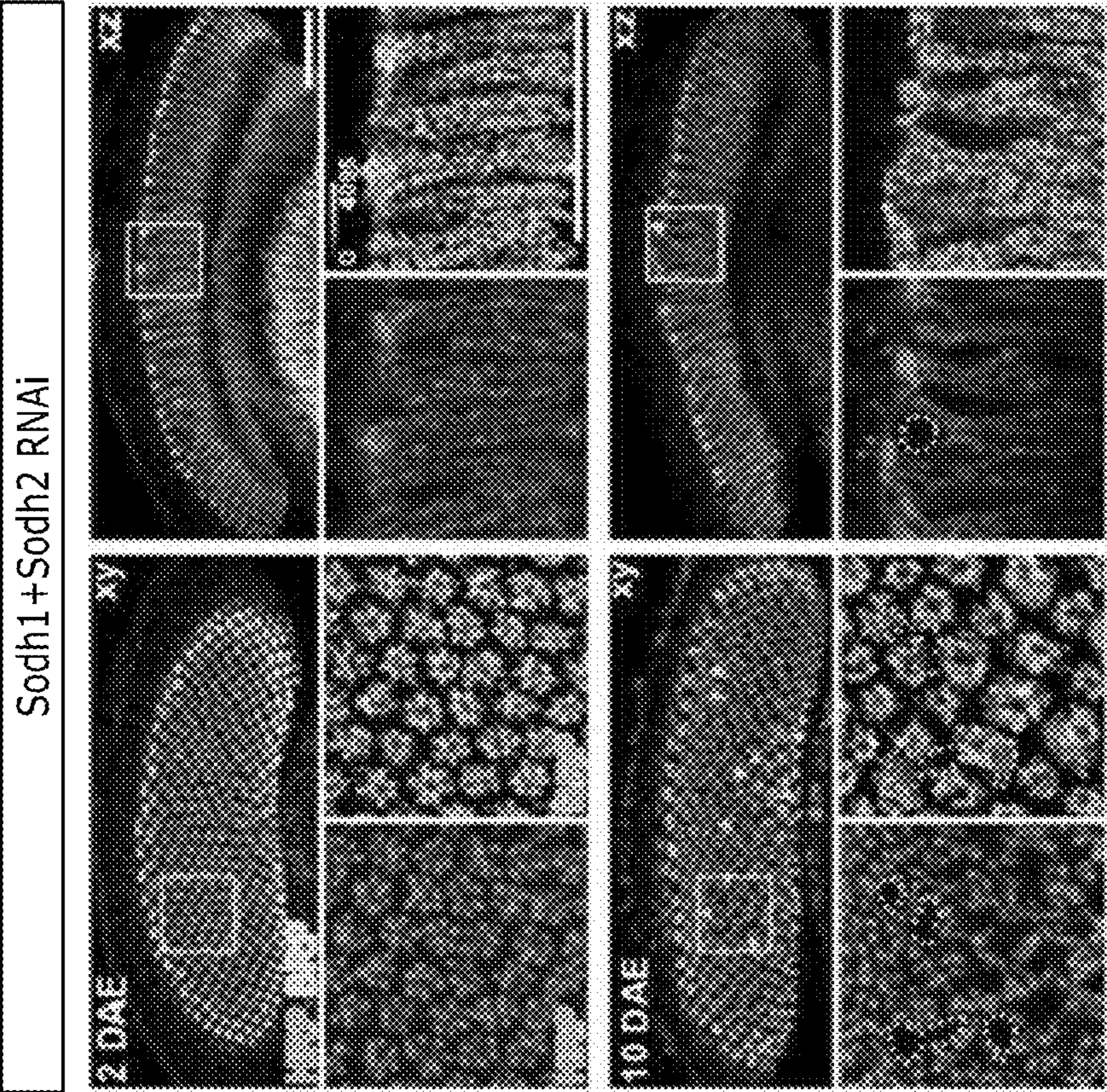
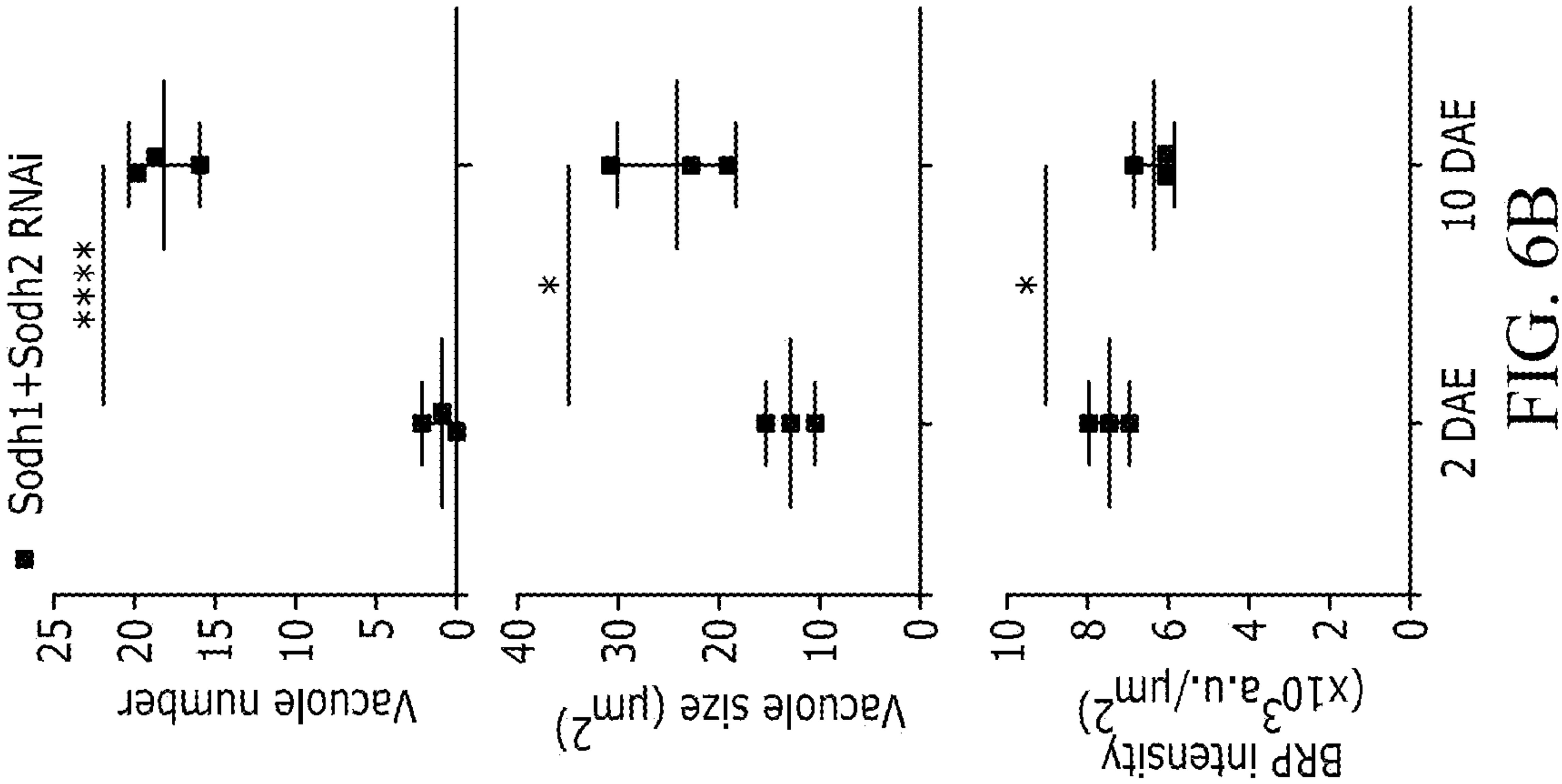


FIG. 6A



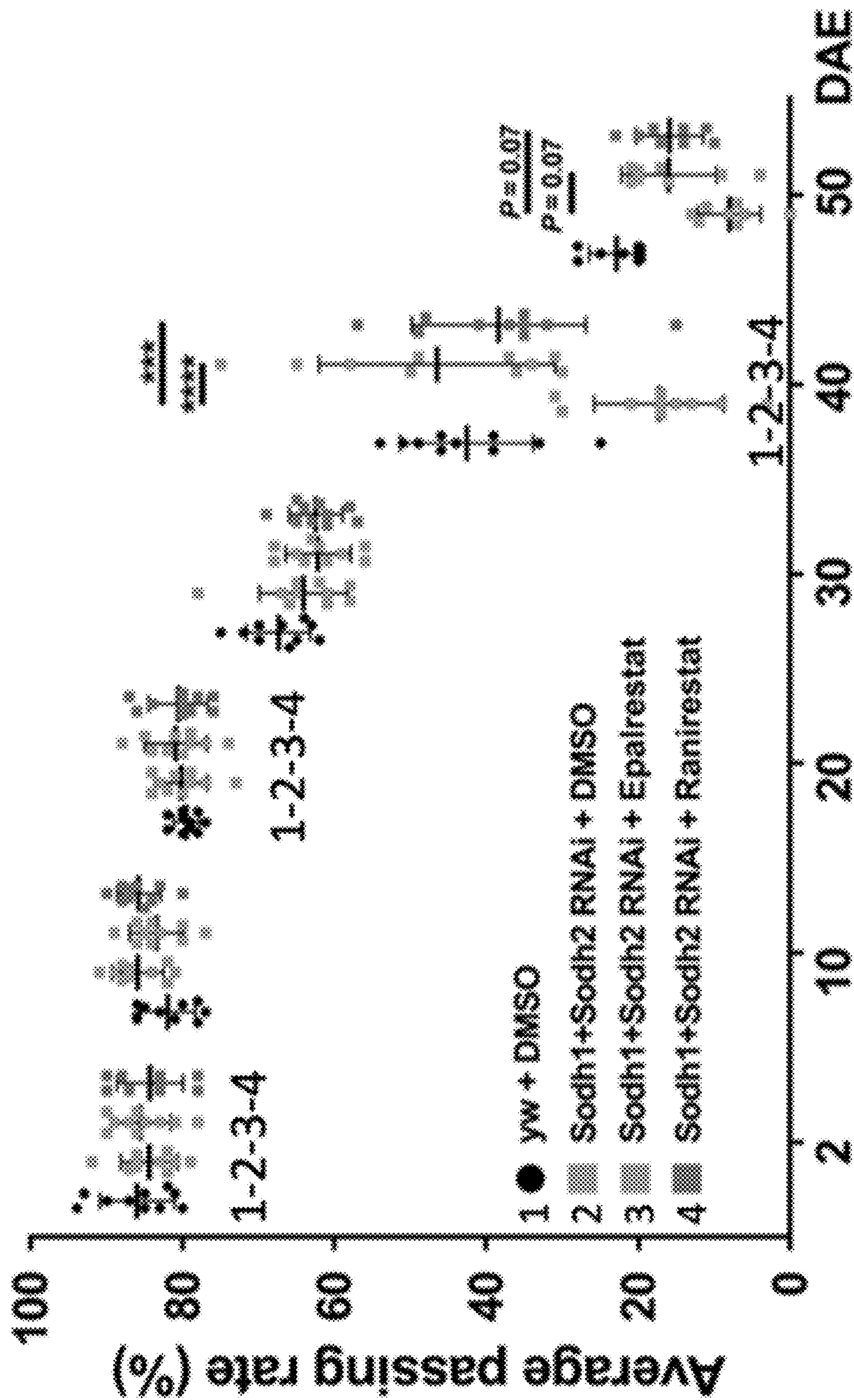


FIG. 7

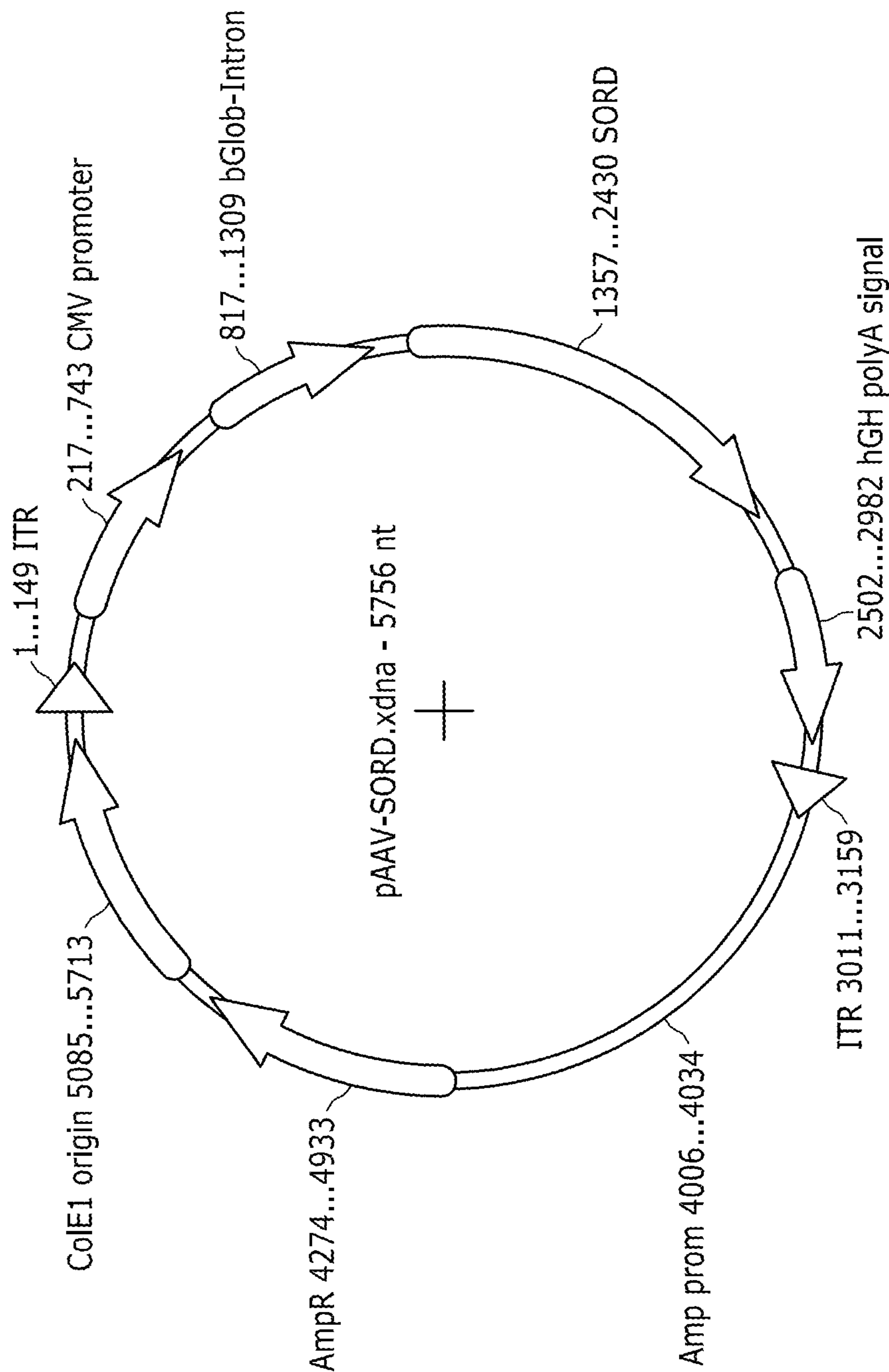


FIG. 8

> [pAAV-SORD.xdna] - 5756 bp SEQ ID NO: 48
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTGGGGCGACCTTTGGTGGCCCCG
GCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAATCCATCACTAGGGGTTCTGCGGCCGCAACCGTCTAGT
TATTAATAGTAATCAATTACGGGGTCATTAGTTATAGCCCATATATGGAGTTCGCGTTACATAACTTACGGTAAATGG
CCCGCTGGCTGACCGCCCAACGACCCCGCCCATTTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGA
CTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGT
ACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCCCTGGCATTATGCCAGTACATGACCTTATGGGACTTTCCTAC
TTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGC
GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCATTGACGTCAATGGGAGTTTGTGGCACCAAAATCAACGGGAC
TTTCCAAAATGTCGTAACAACTCCGCCCATTTGACGCAAAATGGGCGGTAGGCGGTACGCGTGGGAGGTCTATATAAGCAG
AGCTCGTTAGTGAACCGTCAGATCGCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGAT
CCAGCCTCCGCGGATTGCAATCCCGGCCGGGAACGGTGATTGGAACGCGGATTCCCGTGCCAAGAGTGACGTAAGTAC
CGCTATAGAGTCTATAGGCCACAAAAAATGCTTTCTTTTAAATACTTTTGTATCTTATTTCTAATACTTT
CCCTAATCTCTTTTTCAGGGCAATAATGATACAATGTATCGCTCTTGCACCATCTAAAGAATAACAGTGATAA
TTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATTTCTGCATATAAATTGTAAGTGTATGTAAGAGGTTTCAT
ATTGCTAATAGCAGTACAATCCAGCTACCATCTGCTTTTATTTATGTTGGGATAAGGCTGGATTATTCTGAGTCCA
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CGGCGGCGGCCAAGCCCAACACCTTTCCCTGGTGGTGACGGACCGGGGGACTTGGCCTGGAGAACTATCCTATCCCT
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CGGTAAAGCACCTAAACAGGTGATCGTGTGGCCATCGAGCCTGGTGCTCCCGAGAAAATGATGAATCTGCAAGATG
GGCCGATACAATCTGTACCTTCCATCTTCTGTGCCACGCCCCCGATGACGGGAACCTCTGCCGGTCTATAAGCA
CAATGCAGCCTTTGTTACAAGCTTCTGACATGTACCTTTGAGGAAGGCGCCCTGATCGAGCCACTTCTGTGGGGA
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GATTGGGGCTGATTTAGTCTCCAGATCTCAAGGAGAGCCCTCAGGAAATCGCCAGGAAAGTAGAAGGTGAGCTGGGGT
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AACCTCGTGCTTGTGGGGCTGGGCTCTGAGATGACCACCGTACCCCTACTGCATGCAGCCATCCGGGAGGTGGATATCAA
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TCACCCATAGGTTTCTCTGGAGAAAGCTCTGGAGGCCCTTGAACATTTAAAAAGGGATTGGGGTTGAAATCATGCTC
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CAGTGCCCAACAGCCTGTCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCTTCTATAATATTATGGGG
TGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTG
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GGCCACTCCCTCTCTGCGGCTCGCTCGCTCACTGAGGCGGGCGACCAAGGTGCGCCGACGCGCGGGCTTTGCCCGGG
CGGCCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCTTACGCATCTGTGCGGT
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CGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCGCTCTTTCGCTTCTTCCCTTCTTCTGCGCACGTTGCG
CGGCTTTCCCGCTCAAGCTCTAAATCGGGGGCTCCCTTAGGGTCCGATTAGTGCTTTACGGCACCTCGACCCCAAAA
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TTTGCCGATTTGGGTCTATTGGTTAAAAAATGAGCTGATTTAACAATAATTTAACGCAATTTTAACAAAATATTAACGT
TTACAATTTTATGGTGCATCTCAGTACAATCTGCTCTGATGCCCATAGTTAAGCCAGCCCCGACACCCGCCAACACCC
GCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGCATCCGCTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTG
TCAGAGGTTTTACCGTCATACCGAAACGCGGAGACGAAAGGGCCTGTGATACGCTATTTTATAGGTTAATGTCA
TGATAAATATGGTTTTCTAGACGTCAAGGTGGCACTTTTCGGGGAATGTGCGCGGAACCCCTATTTGTTATTTTCTAA
ATACATTTCAATATGTATCCGCTCATGAGACAATAACCTGATAAATGCTTCAATAATATTGAAAAAGGAAGATATGAG
TATTAACATTTCCGTGTCGCCCTTATCCCTTTTTTGGCGCATTTTGCTTCTGTTTGTCTACCCAGAAACGCTGG
TGAAAGTAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTT
GAGAGTTTTGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTAT
TGACGCCGGCAAGAGCAACTCGGTCGCCCATACACTATTTCTCAGAACTGAGTTGGTTGAGTACTACCAAGTACAGAAA
AGCATCTTACGGATGGCATGACAGTAAGAGAATTATGAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTA
CTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTGCTTGTGCG
TTGGGAACCGGAGCTGAATGAAGCATACCAACGACGAGCGTGACACCATGCTGTAGCAATGGCAACAACGTTGC
GCAAACTATTAACTGGCGAACTACTTACTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCA
GGACCACTTCTGCGCTCGGCCCTTCCGGCTGGTGGTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGG
TATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCGCTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGG
ATGAACGAAATAGACAGATCGCTGAGATAGGTGCTCACTGATTAAGCATTGGTAACGTGACAGCAAGTTTACTCATAT
ATACTTTAGATTGATTTAAACCTTCATTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTGATAATCTCATGACCAA
AATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTT
TTCTGCGCGTAATCTGCTGCTTGCAACAAAAAACCACCGCTACCAGCGGTGGTTTTGTTGCGGATCAAGAGCTACCA
ACTCTTTTTCCGAAGGTAACCTGGCTTACGACAGCGCAGATACCAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCA
CCACTTCAAGAATCTGTAGCACCGCTACATACCTCGCTGCTAATCTGTACCAAGTGGCTGCTGCCAGTGGCGATA
AGTCGTGCTTACCAGGTTGGACTCAAGACGATAGTTACCGGATAAGGGCGACGGTGGGCTGAACGGGGGGTTCTGTGC
ACACAGCCAGCTTGGAGCGAACGACCTACCCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCC
CGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGA
ACGCTGGTATCTTTATAGTCTGTGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTGTCAGGGGGG
CGGAGCCTATGGAACACGCCAGCAACGCGGCCCTTTTACGGTCTCTGGCCTTTGCTGGCCTTTGCTCACATGT

FIG. 9

Supplemental Table 1 | Primers sequences and thermocycling conditions

	Primers	SEQ ID NO:	Reagents	Thermocycling conditions		
SORD Exon 1	Fw/sequencing: CAGGCTGGCACAAAGGAG Rv: AGTGAGGCAGGATCGGTATG	2	Faststart Master Mix 2X (Roche) Primers 0.5 mM genomic DNA 50 ng	95°C 4 min [95°C 30 s 65°C 30 s - Each cycle decreasing by 0.5°C 72°C 1 min] X18 cycles [95°C 30s 55°C 30s 72°C 1 min] X18 cycles 72°C 5 min		
		3				
SORD Exon 2	Fw/sequencing: AGCGTGCCATTIAGCGTATC Rv: GCAGTAGACTCTGTTCTCAGCCTAAC	4				
		5				
SORD Exon 3	Fw ACCTTTTCTCATAAAATAGATACGAATCC Rv/sequencing TCTTGTTCCCTGCTGTACCC	6				
		7				
SORD Exon 4	Fw and sequencing GCATGCAAGCCTTCATAACA Rv CGAGGTCATTGTTGTTATGACG	8				
		9				
SORD Exon 5	Fw/sequencing CGTGGCCAIGTTAACTCCTT Rv GTTCCCTGAATCCCAGTCA	10				
		11				
SORD Exon 6	Fw/sequencing ATGTTTAATATTTCACGAACATATTCC Rv GCTGTTTCCCGACTCAAGGAG	12				
		13				
SORD exon 7	Fw TGAGTCATCAGATTCTCTTGTTG Rv AGCCTGGCGACTGAGTGAG Sequencing AAAAGAAAACATAGATGGCAAAAGA	14				
		15				
		16				
SORD exon 8	Fw/sequencing TCCCGCTCAGTTAAGTTTGG Rv GCTTCAAAATCCCCTCCTTC	17				
		18				
SORD exon 9	Fw/sequencing CACCTGGCTCTTTCCTCTTG Rv CCCTGAGATCCCAAGACTG	19				
		20				
SORD2P exon 7	Fw Rv					

PCR: polymerase chain reaction; Fw: forward; Rv: reverse

FIG. 10

Case ID	Family ID	Gender	Age of onset	Age at exam	Ethnicity and origin	Family history	Diagnosis	Symptom at onset	Additional symptoms and signs	motor NCS	sensory NCS UL/LL	Disease severity	c.753delG; p.(Ala253GlnfsTer27) variant in SORD	Second variant in SORD
1	Fam 1	female	10	43	White American	yes	CMT2	walking difficulties		axonal	not available	mild	homozygous	
2	Fam 1	female	10	38	White American	yes	CMT2	distal atrophy of lower limbs		axonal	not available	mild	homozygous	c.298C>T; p.(Arg100Ter) (absent in the mother, father deceased)
3	Fam 2	male	15	39	White Greek	no	CMT2 (motor predominant)	unable to stand on toes and heels	Rapid onset after flu-like syndrome, upper limb tremor	axonal	reduced/absent	mild	heterozygous (maternal)	
4	Fam 3	male	13	17	White French	no	CMT intermediate	difficulties running and jumping, ankle sprains	upper limb tremor, mild hearing loss	intermediate	reduced/reduced	moderate	heterozygous (paternal)	c.329G>C; p.(Arg110Pro) (maternal)
5	Fam 4	male	14	20	White American	no	CMT2 (motor predominant)	unable to stand on toes, walking difficulties	muscle ache, raised CK up to 1200 IU, scapular winging	axonal	reduced/normal	mild	homozygous	
6	Fam 5	male	12	23	White American	no	dHMN	walking and running difficulties, decreased sport performance	upper limb tremor	axonal	normal/normal	mild	homozygous	
7	Fam 6	female	28	59	White American	no	dHMN	unsteadiness		axonal	normal/normal	mild	homozygous	
8	Fam 7	male	14	29	Middle Eastern Iraqi	yes	dHMN	not available		axonal	normal/reduced	mild	homozygous	
9	Fam 8	female	20	32	White American	no	dHMN	balance problems during pregnancy	rapid worsening	intermediate	normal/normal	mild	homozygous	
10	Fam 9	male	12	15	White American	no	CMT intermediate	walking difficulty	upper limb tremor	intermediate	reduced/normal	mild	homozygous	
11	Fam 10	female	12	23	Mixed White and African American	no	CMT2	walking difficulty		intermediate	normal/reduced	mild	homozygous	
12	Fam 11	male	15	34	White British	no	dHMN	unable to stand on toes	stress fractures	axonal	reduced/normal	mild	homozygous	

FIG. 11

13	Fam 12	male	13	43	White British	no	dHMN	unable to stand on toes	Left peroneal nerve mononeuropathy	axonal	reduced/normal	moderate	homozygous	
14	Fam 13	male	29	34	White German	no	Complex CMT2	walking difficulties	Complex ataxo-spastic syndrome entailing mental retardation (since age 3), coarse facial features, bulky stature	axonal	not available/normal	mild	homozygous	c.458C>A; p.(Ala153Asp) (parents unavailable)
15	Fam 14 II-1	male	10	27	White Austrian	no	CMT2	walking difficulties	upper limb distal weakness and tremor	intermediate	reduced/not available	moderate	heterozygous (parents unavailable)	c.458C>A; p.(Ala153Asp) (parents unavailable)
16	Fam 14 II-2	female	20	36	White Austrian	no	CMT2	walking difficulties		intermediate	reduced/not available	mild	heterozygous (parents unavailable)	
17	Fam 15	female	18	28	Middle Eastern (Bedouin) Egyptian	no	dHMN	unable to stand on toes, unable to wear high heels	upper limb tremor	axonal	reduced/reduced	mild	homozygous	
18	Fam 16	male	15	55	White British	no	dHMN	walking difficulties		axonal	absent/normal	mild	homozygous	
19	Fam 17	male	12	23	East Asian Singaporean	no	CMT intermediate	walking and running difficulties		axonal	reduced/normal	moderate	homozygous	
20	Fam 18 II-2	female	12	20	Middle Eastern Egyptian	yes	CMT2	walking difficulties	burning pain in hands and feet	axonal	normal/absent	moderate	homozygous	
21	Fam 18 II-3	male	15	17	Middle Eastern Egyptian	yes	CMT2	walking difficulties		intermediate	normal/absent	moderate	homozygous	
22	Fam 19 I-1	male	40	70	Middle Eastern Egyptian	yes	CMT2	walking difficulties		not available	not available	severe	homozygous	
23	Fam 19 II-2	male	29	39	Middle Eastern Egyptian	yes	CMT2	walking difficulties		not available	not available	moderate	homozygous	
24	Fam 19 II-3	male	16	19	Middle Eastern Egyptian	yes	CMT2	walking difficulties		not available	not available	mild	homozygous	
25	Fam 19 II-3	male	18	26	Middle Eastern Kuwaiti	yes	CMT2 (motor predominant)	Difficulties running and jumping		intermediate	normal/reduced	mild	homozygous	

FIG. 11 CONT.

26	Fam 21	female	20		29	White Italian	no		CMT2 (motor predominant)	walking difficulties		axonal	normal/reduced	moderate	homozygous	
27	Fam 22	male	15		31	White Italian	yes		dHMN	distal atrophy of lower limbs		axonal	normal/normal	mild	homozygous	
28	Fam 23 II-1	male	25		52	White Italian	no		dHMN	walking difficulties	epilepsy, vascular encephalopathy, upper limb tremor, scoliosis. Has a normal sural nerve biopsy	axonal	normal/normal	mild	homozygous	
29	Fam 23 II-2	female	20		45	White Italian	yes		CMT2	pes cavus		axonal	reduced/reduced	mild	homozygous	
30	Fam 24	female	20		42	White Italian	no		dHMN	walking difficulties	brisk reflexes	axonal	normal/normal	moderate	homozygous	
31	Fam 25	male	14		46	White Italian	no		dHMN	walking difficulties		axonal	normal/normal	mild	homozygous	
32	Fam 26	male	12		41	White Italian	no		CMT2 (motor predominant)	walking difficulties	split hand	axonal	reduced/normal	moderate	homozygous	
33	Fam 27	male	13		28	White Italian	no		dHMN	walking difficulties	scoliosis, raised CK	axonal	normal/normal	moderate	homozygous	
34	28 II-1	female	40		48	White Italian	yes		dHMN	walking difficulties	brisk reflexes	axonal	normal/normal	mild	homozygous	
35	28 II-2	female	20		52	White Italian	yes		dHMN	walking difficulties	brisk reflexes	axonal	normal/normal	mild	homozygous	
36	Fam 29	male	2		10	White Italian	no		CMT2	retarded developmental milestone		axonal	absent/absent	moderate	heterozygous (absent in the mother, father unavailable)	c.964G>A; p.(Val322Ile) [maternal]
37	Fam 30	male	15		18	White Italian	no		CMT2	falls		intermediate	reduced/absent	mild	heterozygous (paternal)	c.316_425+165del (maternal)
38	Fam 31	male	30		42	White Italian	no		CMT2	walking difficulties	scoliosis	intermediate	reduced/absent	moderate	homozygous	
39	Fam 32	male	18		29	White Italian	no		dHMN	walking difficulties, cramps	raised CK	axonal	normal/normal	mild	heterozygous (mother)	c.28C>T, p.(Leu10Phe) (de novo)
40	Fam 33	male	15		60	White Italian	no		CMT2 (motor predominant)	falls	mild hearing loss	axonal	normal/reduced	moderate	heterozygous (parents unavailable)	c.895C>T; p.(Arg299Ter)
41	Fam 34	male	25		36	White American	no		CMT intermediate	distal atrophy of lower limbs		intermediate	normal/normal	mild	homozygous	
42	Fam 35	male	12		16	Mixed, Native American (Alaska) and White American	no		dHMN	running difficulties		axonal	reduced/normal	mild	homozygous	

FIG. 11 CONT.

43	Fam 36	male	10	29	East Asian (Han) Chinese	sporadic	CMT2 (motor predominant)	foot drop and walking difficulties		axonal	normal/normal	mild	homozygous	
44	Fam 37	male	10	24	East Asian (Han) Chinese	sporadic	CMT2	walking difficulties		axonal	normal/reduced	mild	homozygous	
45	Fam 38	male	16	26	East Asian (Han) Chinese	sporadic	CMT2	walking difficulties		axonal	normal/reduced	mild	homozygous	

FIG. 11 CONT.

	N=45
Male	32 (71%)
Age of onset	17 ± 8 (2-40)
Age at examination	34 ± 14 (10-70)
Family history of neuropathy	13 (29%)
CMT subtype	
CMT2	23 (51%)
dHMN	18 (40%)
CMT intermediate	4 (9%)
Foot deformities	31 (69%)
Upper limb weakness	
Proximal muscle groups	0/44 (0%)
Distal muscle groups	26/44 (59%)
Lower limb weakness	
Proximal muscle groups	2/44 (5%)
Distal muscle groups	43/44 (98%)
Prominent involvement of foot plantar flexion	15/37 (41%)
Reduced vibratory sensation	17/40 (42%)
Reduced pinprick superficial sensation	13/39 (33%)
Disease severity	
Mild	30 (67%)
Moderate	14 (31%)
Severe	1 (2%)
Use of ankle-foot orthoses (AFOs)	19 (42%)
Other walking aids	2 (4%)
Nerve conduction study	
Reduced motor conduction velocity	11/42 (26%)
Reduced sensory action potentials	26/40 (65%)

FIG. 12

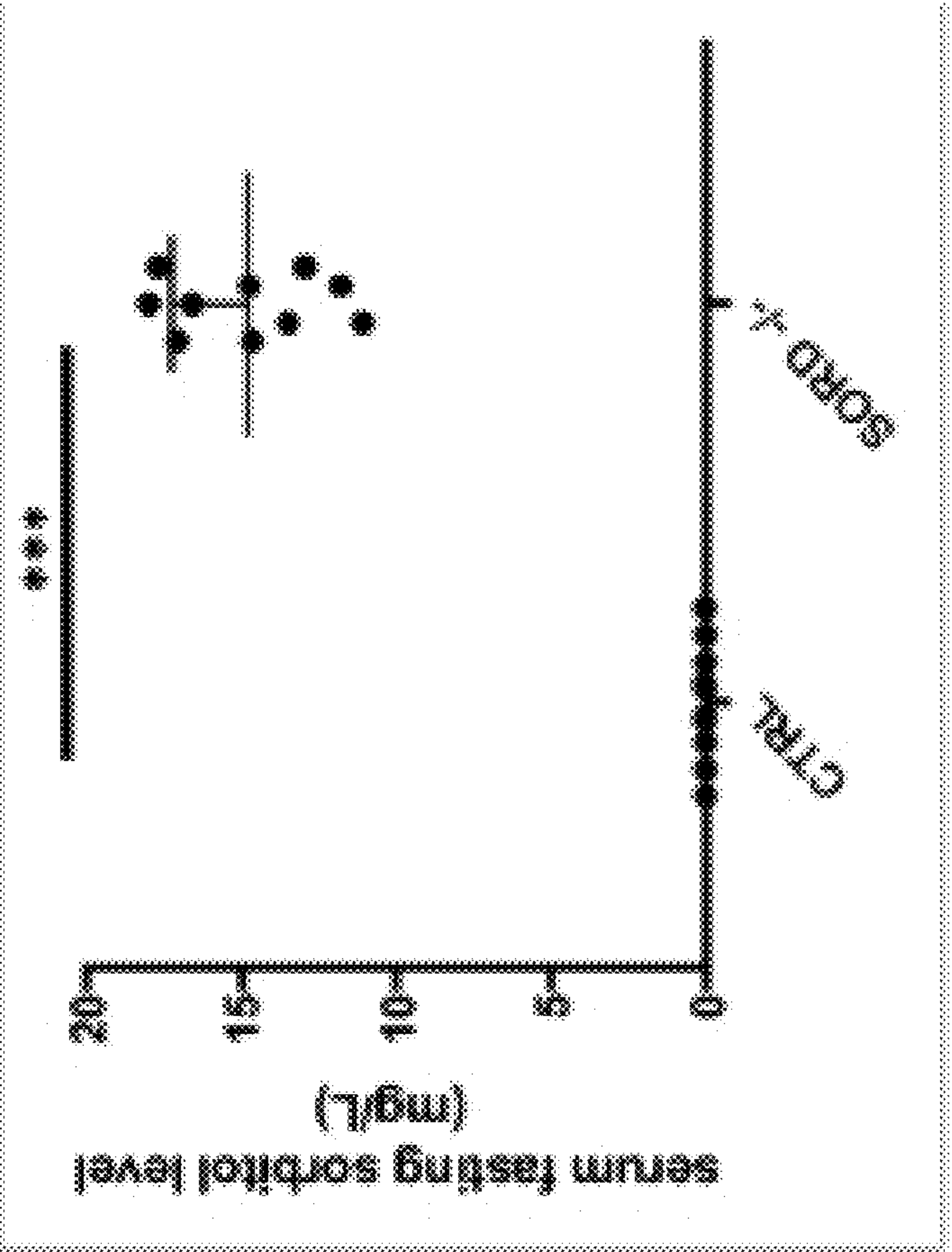


FIG. 13

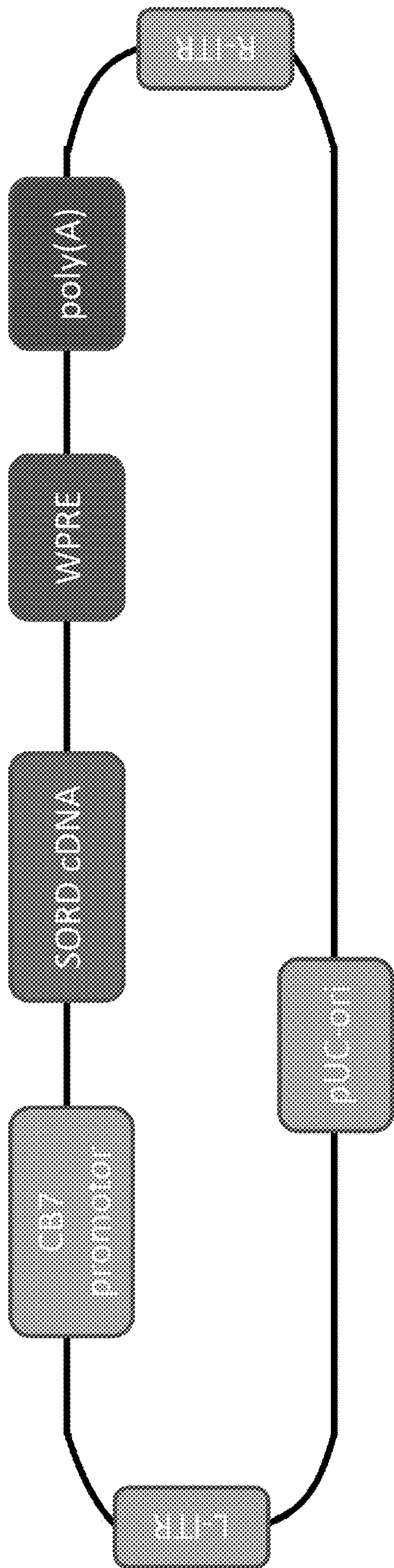


FIG. 14A

atggcggcgccgaagcccaaaccttccctgggtggtgcacggaccgggggacttgccgctggagaaactatcctatccctgaaccaggcccaaatgaggctcttgctgaggatgcattctgttggaatctgtggctcag
atgtccactactgggagtagtgcgaattgggaattttatttgaaagcccatgggtgctgggacatgaagcttcggggaacagtcgaaagtggggacatcaggtaagcacctaaaccagggtgatcgtgttgccatcga
ggcctgtgctccccgagaaatgatgaattctgcaagatgggacgatacaaatctgtcaccttccatcttctgtgccacgcccccgatgacgggaacctctgcgggttctataagcacaaatgcagccctttgtttacaagctt
cctgaacaatgtcacctttgaggaaaggccctgatcgagccactttctgtggggatccatgctgcaggagagcgaggttaacctggggacacaaaggtccttgtgtgaggctggggccaatcggggatggtcactttgctcgt
ggccaaaggcaatgggagcagctcaagtagtggtagctgatctgtctgctacccgattgtccaaagccaaggagattggggctgatttagtctccagatctccaaggagagagccctcaggaaatcgccaggaaagtagaag
gtcagctgggggtgcaagccggaagtcacatcgagtgacgggggagagccctccatccaggcgggcatctacgcccactgctgtgggaaacctgtgtgtggggctggggctctgagatgaccaccgtaccctact
gcatgcagccatccgggaggtggatatcaaggcggtgttttcgatactgcaacacgctggccagtgcgatttcgctgctcaaatgctgtgaatgtataaacccctcgtcacccatagggttctctctggagaaaagctctggg
aggcctttgaaacatttaaaaagggttgaaatcatgctcaagtgtgaccccgtagccagaaatccctga

FIG. 14B (SEQ ID NO: 45)

MAAAKPNLNLVHGPDLRLNYPPEGPNEVLLRMHHSVIGCGSDVHYWEYGRIGNFIVKPMVLGHEASGTVEKVGSVKHLKPGDRVAIEPGAPRENDEFCKMGRYN
LSPSIFFCATPPDDGNLCRFYKHNAFCYKLPDNLVTFEEGALIEPLSVGIHACRRGGVTLGHKVLVCGAGPIGMVTLVAKAMGAAQVVVTDLSATRLSKAKEIGADLVLQJSKES
PQEARKVEGQLGCKPEVTIETGAEASIQAGIYATRSGNLVLVGLGSEMTTVPLLHAAIREVDIKGVFRYCNTWPVAISMLASKSVNVKPLVTHRFPLEKALEAFETFKKGLGLKI
MLKCDPSDQNP

FIG. 14C (SEQ ID NO: 46)

AR 1A

G*T*T*T*A*AG**A*T*C*A*T*C*T*CC*A*C*C*T
[SEQ ID NO: 22]

AR-S 1A

T*A*T*T*AC*A**G*C*T*A*C*A*T*CC*TG*T*C
[SEQ ID NO: 47]

FIG. 15A

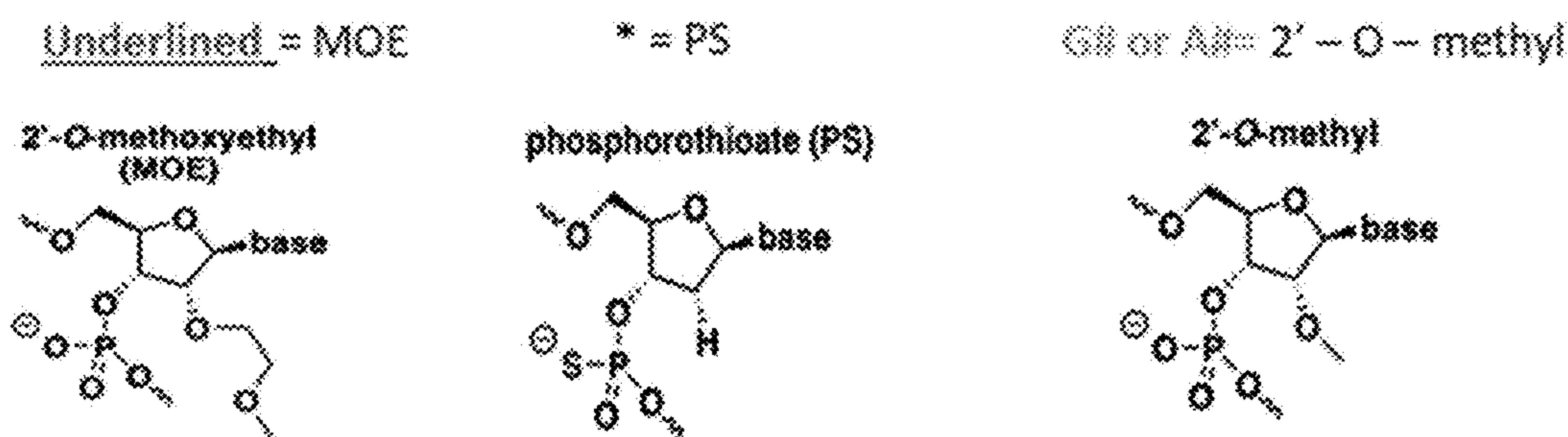


FIG. 15B

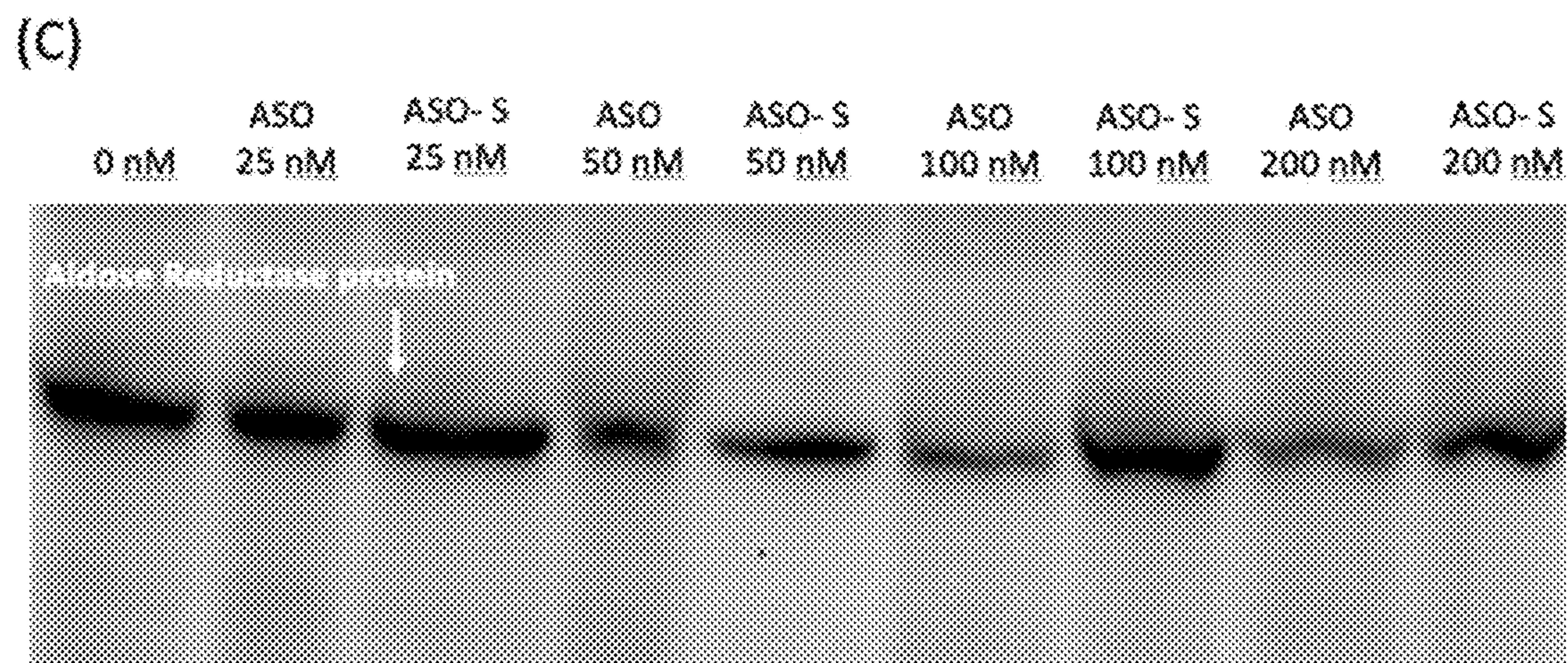


FIG. 15C

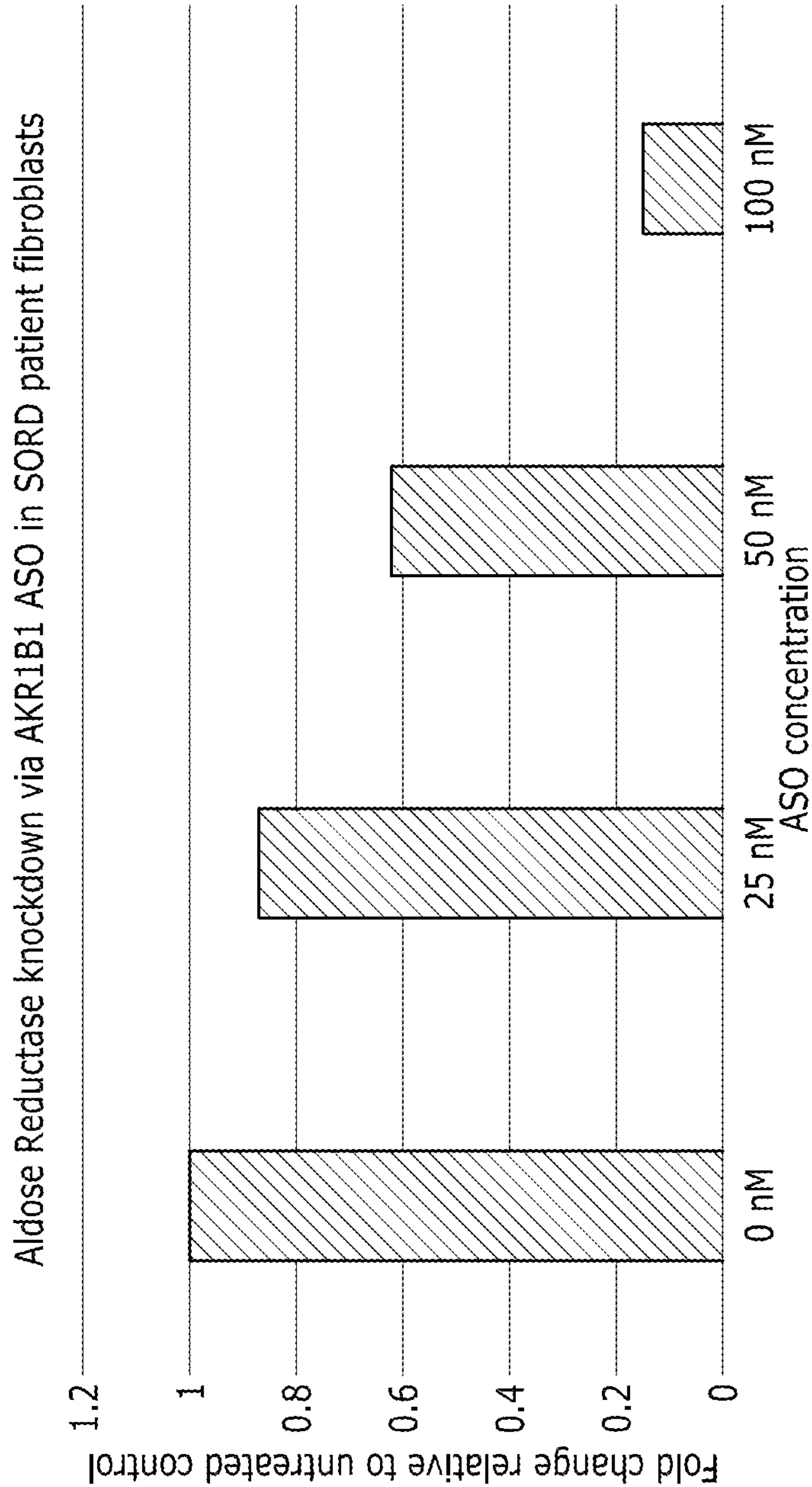


FIG. 15D

ASO sequences and corresponding target sites in *Homo sapiens* aldo-keto reductase family 1 member B (AKR1B1), exon targets only

Rank	SEQ ID NO:	target sequence (5p --> 3p)	antisense oligo (5p --> 3p)	SEQ ID NO:	GC content	oligo binding energy (kcal/mol)
1	49	UCGCAGCCCAAGCACAAUAAA	TTTATTGTGCTTGGCTGCGA	50	45.00%	-16.3
2	51	GCAGCCCAAGCACAAUAAAAC	GTTTATTGTGCTTGGCTGC	52	45.00%	-16.3
3	53	GAUCGCAGCCCAAGCACAAUA	TATTGTGCTTGGCTGCGATC	54	50.00%	-16.2
4	55	AUCGCAGCCCAAGCACAAUAA	TTATTGTGCTTGGCTGCGAT	56	45.00%	-16.1
5	57	CGCAGCCCAAGCACAAUAAAA	TTTTATTGTGCTTGGCTGCG	58	45.00%	-15.9
6	59	GCCAAGCACAAUAAAACUAC	GTAGTTTTATTGTGCTTGGC	60	40.00%	-15.7
7	61	CGAUCGCAGCCCAAGCACAAU	ATTGTGCTTGGCTGCGATCG	62	55.00%	-15.6
8	63	AGCACAAUAAAACUACAGCC	GGCTGTAGTTTTATTGTGCT	64	40.00%	-15.2
9	65	CAGCCAAAGCACAAUAAAACU	AGTTTTATTGTGCTTGGCTG	66	40.00%	-14.8
10	67	GCGAUCGCAGCCCAAGCACAA	TTGTGCTTGGCTGCGATCGC	68	60.00%	-14.7
11	69	GCACAAUAAAACUACAGCCC	GGGCTGTAGTTTTATTGTGC	70	45.00%	-13.6
12	71	AACCAGAUUGAGUGCCACCC	GGGTGGCACTCAATCTGTT	72	55.00%	-13
13	73	ACCAGAUUGAGUGCCACCCA	TGGGTGGCACTCAATCTGGT	74	55.00%	-13
14	75	ACCUCCCACAAGGAUUACCC	GGGTAATCCTTGTGGGAGGT	76	55.00%	-12.7
15	77	CCUCCCACAAGGAUUACCCC	GGGGTAATCCTTGTGGGAGG	78	60.00%	-12.6
16	79	ACAACCUUGAAUACCCUUUUC	GAAAGGGTATTTCAGGTTGT	80	40.00%	-12.3
17	81	CUCCCACAAGGAUUACCCCU	AGGGGTAATCCTTGTGGGAG	82	55.00%	-12.2
18	83	CCAGAUUGAGUGCCACCCCAU	ATGGGTGGCACTCAATCTGG	84	55.00%	-12.1
19	85	CAACCUGAAUACCCUUUUCU	AGAAAAGGGTATTCAGGTTG	86	40.00%	-12.1
20	87	AGUACAACCUUGAAUACCCUU	AAGGGTATTTCAGGTTGTACT	88	40.00%	-11.9
21	89	GUACAACCUUGAAUACCCUUU	AAAGGGTATTTCAGGTTGTAC	90	40.00%	-11.9
22	91	AAGGCGAUCGCAGCCCAAGCA	TGCTTGGCTGCGATCGCCTT	92	60.00%	-11.8
23	93	UCCCACAAGGAUUACCCCUU	AAGGGGTAATCCTTGTGGGA	94	50.00%	-11.8

FIG. 16

24	95	AAGUACAACCUUGAAUACCCU	AGGGTATTCAGGTTGTACTT	96	40.00%	-11.8
25	97	AACCUGAAUACCCUUUUCUG	CAGAAAAGGTATTACAGTT	98	40.00%	-11.8
26	99	ACCUGAAUACCCUUUUCUGA	TCAGAAAAGGTATTACAGGT	100	40.00%	-11.7
27	101	UACCUCCCCACAAGGAUUACC	GGTAATCCTTGTGGGAGGTA	102	50.00%	-11.5
28	103	AAAGUACAACCUUGAAUACCC	GGGTATTCAGGTTGTACTTT	104	40.00%	-11.5
29	105	CCUGAAUACCCUUUUCUGAC	GTCAGAAAAGGTATTACAGG	106	45.00%	-11.5
30	107	UAACCAGAUUGAGUGCCACC	GGTGGCACTCAATCTGGTTA	108	50.00%	-11.2
31	109	AUUGAGUGGCCACCCAUUUCU	AGATATGGGTGGCACTCAAT	110	45.00%	-11.2
32	111	GUGCCACCCAUUUCUCACUC	GAGTGAGATATGGGTGGCAC	112	55.00%	-11.2
33	113	UGCCACCCAUUUCUCACUCA	TGAGTGAGATATGGGTGGCA	114	50.00%	-11.2
34	115	CACAAUAAAACUACAGCCCA	TGGGCTGTAGTTTIAATTGTG	116	40.00%	-11.2
35	117	CCCACAAGGAUUACCCCUUC	GAAGGGTAATCCTTGIGGG	118	55.00%	-11.2
36	119	CUGAAUACCCUUUUCUGACC	GGTCAGAAAAGGTATTACAG	120	45.00%	-11.2
37	121	GAUUGAGUGGCCACCCAUUUC	GATATGGGTGGCACTCAATC	122	50.00%	-11.1
38	123	AGUGCCACCCAUUUCUCACU	AGTGAGATATGGGTGGCACT	124	50.00%	-11.1
39	125	GCCACCCAUUUCUCACUCAG	CTGAGTGAGATATGGGTGGC	126	55.00%	-11.1
40	127	GAGUGCCACCCAUUUCUCAC	GTGAGATATGGGTGGCACTC	128	55.00%	-11
41	129	UGAAUACCCUUUUCUGACCA	TGGTCAGAAAAGGTATTCA	130	40.00%	-11
42	131	UUGAGUGGCCACCCAUUUCUC	GAGATATGGGTGGCACTCAA	132	50.00%	-10.9
43	133	UGAGUGCCACCCAUUUCUCA	TGAGATATGGGTGGCACTCA	134	50.00%	-10.9
44	135	AGAUUGAGUGGCCACCCAUU	ATATGGGTGGCACTCAATCT	136	45.00%	-10.8
45	137	CCACCCAUUUCUCACUCAGG	CCTGAGTGAGATATGGGTGG	138	55.00%	-10.8
46	139	CAGAUUGAGUGGCCACCCAU	TATGGGTGGCACTCAATCTG	140	50.00%	-10.7
47	141	CCACAAGGAUUUACCCCUUCC	GGAAGGGGTAATCCTTGTGG	142	55.00%	-10.6
48	143	GAAAGUACAACCUUGAAUACC	GGTATTCAGGTTGTACTTTC	144	40.00%	-10.6
49	145	GAAUACCCUUUUCUGACCAA	TTGGTCAGAAAAGGGTATTTC	146	40.00%	-10.5
50	147	ACAAUAAAACUACAGCCCCAG	CTGGGCTGTAGTTTATTGT	148	40.00%	-10.4
51	149	GUACCUCCCACAAGGAUUUAC	GTAATCCTTGTGGGAGGTAC	150	50.00%	-10.3
52	151	AAACAAACCUUGGCUUGAAGU	ACTTCAAGCCAGGTTTGTTT	152	40.00%	-10.1

FIG. 16 CONT.

53	153	UCAAGGCGAUCGCAGCCAAG	CTTGGCTGCGATCGCCTTGA	154	60.00%	-10.1
54	155	AUGGCAAGCCGUCUCCUGCU	AGCAGGAGACGGCTTGCCAT	156	60.00%	-10
55	157	GAUCUUAAACAACCCUGGCU	AGCCAGGTTTGTTTAAGATC	158	40.00%	-10
56	159	UGAUCUUAAACAACCCUGGC	GCCAGGTTTGTTTAAGATCA	160	40.00%	-9.9
57	161	UAAACAACCCUGGCUUGAAG	CTTCAAGCCAGGTTTGTTTA	162	40.00%	-9.8
58	163	AACAACCCUGGCUUGAAGUA	TACTTCAAGCCAGGTTTGTT	164	40.00%	-9.8
59	165	CUCAGCAGUGGGACAGCAAC	GTTGCTGTCCCACTGCTGAG	166	60.00%	-9.8
60	167	UCAGCAGUGGGACAGCAACC	GGTTGCTGTCCCACTGCTGA	168	60.00%	-9.8
61	169	CAGCAGUGGGACAGCAACCU	AGGTTGCTGTCCCACTGCTG	170	60.00%	-9.8
62	171	AGCAGUGGGACAGCAACCUG	CAGGTTGCTGTCCCACTGCT	172	60.00%	-9.8
63	173	GCAGUGGGACAGCAACCUGU	ACAGGTTGCTGTCCCACTGC	174	60.00%	-9.7
64	175	CAGUGGGACAGCAACCUGUA	TACAGGTTGCTGTCCCACTG	176	55.00%	-9.7
65	177	AGUGGGACAGCAACCUGUAG	CTACAGGTTGCTGTCCCACT	178	55.00%	-9.7
66	179	UGUACCUCCCCACAAGGAUUA	TAATCCTTGTGGGAGGTACA	180	45.00%	-9.6
67	181	AAGUGACCUAUACCUGUGUU	AACACAGGTATAGGTCACCT	182	40.00%	-9.6
68	183	GUGGGACAGCAACCUGUAGA	TCTACAGGTTGCTGTCCCACT	184	55.00%	-9.6
69	185	UAGUGCCACUAACGGUUGAG	CTCAACCGTTAGTGGCACATA	186	50.00%	-9.6
70	187	AGUGCCACUAACGGUUGAGU	ACTCAACCGTTAGTGGCACCT	188	50.00%	-9.6
71	189	AGGUGGAGAUGAUCUUAAAC	GTTTAAGATCATCTCCACCT	190	40.00%	-9.5
72	191	UGGGACAGCAACCUGUAGAG	CTCTACAGGTTGCTGTCCCA	192	55.00%	-9.5
73	193	AUAGUGCCACUAACGGUUGA	TCAACCGTTAGTGGCACATAT	194	45.00%	-9.5
74	195	CAAGUGACCUAUACCUGUGU	ACACAGGTATAGGTCACCTTG	196	45.00%	-9.4
75	197	AGUGACCUAUACCUGUGUUU	AAACACAGGTATAGGTCACCT	198	40.00%	-9.4
76	199	GCAAGCCGUCUCCUGCUCAA	TTGAGCAGGAGACGGCTTGC	200	60.00%	-9.3
77	201	CAAGCCGUCUCCUGCUCAAC	GTTGAGCAGGAGACGGCTTG	202	60.00%	-9.3
78	203	AAGCCGUCUCCUGCUCACAA	TGTTGAGCAGGAGACGGCTT	204	55.00%	-9.3
79	205	UCUUAAACAACCCUGGCUUG	CAAGCCAGGTTTGTTTAAGA	206	40.00%	-9.3
80	207	UCUGUGACACCCAGAACGCAU	ATGCGTTCGTGTGCACAGA	208	50.00%	-9.3
81	209	CUGUGACACCCAGAACGCAUU	AATGCGTTCTGTGTGCACAG	210	50.00%	-9.3

FIG. 16 CONT.

82	211	UGUGACACCAGAACGCAUUG	CAATGCGTTCTGGTGTACACA	212	50.00%	-9.3
83	213	AACUUAACCAUCUCCAGGU	ACCTGGAGATGTTGAAGTT	214	45.00%	-9.2
84	215	ACAAACCUGGCUUGAAGUAAU	ATACTTCAAGCCAGGTTTGT	216	40.00%	-9.2
85	217	UUAACCCAGAUUGAGUGCCAC	GTGGCACTCAATCTGGTTAA	218	45.00%	-9.2
86	219	GUGACACCAGAACGCAUUGC	GCAATGCGTTCTGGTGTAC	220	55.00%	-9.2
87	221	UGACACCAGAACGCAUUGCU	AGCAATGCGTTCTGGTGTCA	222	50.00%	-9.1
88	223	AUUACCCCUUCCAUGAAGAG	CTCTTCATGGAAGGGTAAT	224	45.00%	-9.1
89	225	GGGACAGCAACCUGUAGAGU	ACTCTACAGGTTGCTGTCCC	226	55.00%	-9.1
90	227	AUACCCUUUUCUGACCAAAG	CTTTGGTCAGAAAGGGTAT	228	40.00%	-9.1
91	229	AUCAAGGCGAUCGCAGCCAA	TTGGCTGCGATCGCCTTGAT	230	55.00%	-9
92	231	AGUCUGUGACACCAGAACGC	GCGTTCTGGTGTACAGACT	232	55.00%	-9
93	233	CUGUACCUCCACAAAGGAUU	AATCCTTGTGGGAGGTACAG	234	50.00%	-9
94	235	CACAAAGGAUUACCCCUUCCA	TGGAAGGGTAATCCTTGTG	236	50.00%	-9
95	237	GAUUACCCCUUCCAUGAAGA	TCCTTCATGGAAGGGTAATC	238	45.00%	-9
96	239	UUACCCCUUCCAUGAAGAGU	ACTCTTCATGGAAGGGGTAA	240	45.00%	-9
97	241	UACCCCUUCCAUGAAGAGUU	AACCTCTTCATGGAAGGGTA	242	45.00%	-9
98	243	CACCCAUUAUCUCACUCAGGA	TCCTGAGTGAGATATGGGTG	244	50.00%	-8.9
99	245	GGAUUACCCCUUCCAUGAAG	CTTCATGGAAGGGTAATCC	246	50.00%	-8.9
100	247	ACUCAGCAGUGGGACAGCAA	TTGCTGTCCCACTGCTGAGT	248	55.00%	-8.9
101	249	AAGCCUGCAGUUAAACCAGAU	ATCTGGTTAACTGCAGGCTT	250	45.00%	-8.8
102	251	GUCUGUGACACACAGAACGCA	TGCGTTCTGGTGTACAGAC	252	55.00%	-8.8
103	253	GCUGUACCUCCACAAAGGAU	ATCCTTGTGGGAGGTACAGC	254	55.00%	-8.8
104	255	AGGAUUACCCCUUCCAUGAA	TTTCATGGAAGGGTAATCCT	256	45.00%	-8.8
105	257	AGCCUGCAGUUAAACCAGAUU	AATCTGGTTAACTGCAGGCT	258	45.00%	-8.7
106	259	CCAAGUGACCUAUACCUUGUG	CACAGGTATAGTCACTTGG	260	50.00%	-8.7
107	261	ACUUAACCAUCUCCAGGUG	CACCTGGAGATGGTTGAAGT	262	50.00%	-8.6
108	263	UUAGAGCUGUACCUCCACAA	TTGTGGGAGGTACAGCTCAA	264	50.00%	-8.6
109	265	UGAGCUGUACCUCCACAAAG	CTTGTGGGAGGTACAGCTCA	266	55.00%	-8.6
110	267	GAGCUGUACCUCCACAAAGG	CCTTGTGGGAGGTACAGCTC	268	60.00%	-8.6

FIG. 16 CONT.

111	269	AGCUGUACCUCCACAAGGA	TCCTTGTGGAGGTACAGCT	270	55.00%	-8.6
112	271	ACCCUUCCAUGAAGAGUUU	AAACTCTTCATGGAAGGGT	272	45.00%	-8.6
113	273	GGAAAGUACAACCUGAUAC	GTATTCAGGTTGTACTTCC	274	40.00%	-8.6
114	275	GGAAUUUUUCCCAUUGGAUG	CATCCAATGGGAAAAATTCC	276	40.00%	-8.5
115	277	GGUGGAGAUGAUCUUAACA	TGTTTAAGATCATCTCCACC	278	40.00%	-8.5
116	279	GCCUGCAGUUAACCAUAUUG	CAATCTGGTTAACTGCAGGC	280	50.00%	-8.5
117	281	ACAAGGAUUACCCCUUCCAU	ATGGAAGGGTAATCCTTGT	282	45.00%	-8.5
118	283	AGCCGUCUCCUGCUCAACAA	TTGTTGAGCAGGAGACGGCT	284	55.00%	-8.4
119	285	AUUGGAUGAGUCGGGCAUUG	CATTGCCCCGACTCATCCAAT	286	50.00%	-8.4
120	287	UAAGCCUGCAGUUAACCAGA	TCTGGTTAACTGCAGGCTTA	288	45.00%	-8.4
121	289	CCCCAAGUCUGUGACACCCAG	CTGGTGTACAGACTTGGGG	290	60.00%	-8.4
122	291	GUGACCUAUACCUUGUGUUUC	GAAACACAGGTATAGGTAC	292	45.00%	-8.4
123	293	GGACAGCAACCUGUAGAGUG	CACCTACAGGTTGCTGTCC	294	55.00%	-8.4
124	295	CUUAAACAACCCUGGCUUGA	TCAAGCCAGGTTTGTTTAAG	296	40.00%	-8.3
125	297	CAUAAAACUACAGCCCCAGG	CCTGGGCTGTAGTTTATTG	298	45.00%	-8.3
126	299	AAGUCUGUGACACCAGAACG	CGTTCTGGTGTACAGACTT	300	50.00%	-8.3
127	301	GUUGAGCUGUACCUCCACACA	TGTGGGAGGTACAGCTCAAC	302	55.00%	-8.3
128	303	UACCCUUUUCUGACCAAAGA	TCCTTGGTTCAGAAAAGGTA	304	40.00%	-8.3
129	305	ACCCAUAUCUCACUCAGGAG	CTCCTGAGTGAGATATGGGT	306	50.00%	-8.2
130	307	AUCCCCAAGUCUGUGACACC	GGTGTCACAGACTTGGGGAT	308	55.00%	-8.2
131	309	UCCCCAAGUCUGUGACACCA	TGGTGTACAGACTTGGGGA	310	55.00%	-8.2
132	311	CAAGGAUUACCCCUUCCAUG	CATGGAAGGGTAATCCTTG	312	50.00%	-8.2
133	313	AAGGAUUACCCCUUCCAUGA	TCATGGAAGGGTAATCCTT	314	45.00%	-8.2
134	315	AAUAGUGCCACUAACGGUUG	CAACCGTTAGTGGCACTATT	316	45.00%	-8.2
135	317	UUGGAUGAGUCGGGCAUUGU	ACATTGCCCGACTCATCCAA	318	50.00%	-8.1
136	319	CAACUUCAACCAUCUCCAGG	CCTGGAGATGGTTGAAGTTG	320	50.00%	-8.1
137	321	AUAAGCCUGCAGUUAACCCAG	CTGGTTAACTGCAGGCTTAT	322	45.00%	-8.1
138	323	CCUGCAGUUAACCCAGAUUGA	TCAATCTGGTTAACTGCAGG	324	45.00%	-8.1
139	325	GAUCCCCAAGUCUGUGACAC	GTGTCACAGACTTGGGGATC	326	55.00%	-8.1

FIG. 16 CONT.

140	327	UGUUGAGCUGUACCUCCCAC	GTGGGAGGTACAGCTCAACA	328	55.00%	-8.1
141	329	CACUCAGCAGUGGGACAGCA	TGCTGTCCCACTGCTGAGTG	330	60.00%	-8.1
142	331	UGGAUGAGUCGGGCA AUGUG	CACATTGCCCGACTCATCCA	332	55.00%	-8
143	333	AAUGUGGUUCCCGAGUGACAC	GTGTCACTGGGAACCCACATT	334	50.00%	-8
144	335	GAUCAAGGCGAUCGCAGCCA	TGGCTGCGATCGCCTTGATC	336	60.00%	-8

FIG. 16 CONT.

ASO sites in homo sapiens aldo-keto reductase family 1 member B (AKR1B1), exon targets only

Rank	SEQ ID		antisense oligo (5p --> 3p)	SEQ ID NO:	GC content	average unpaired probability for target site nucleotides	binding site disruption energy (kcal/mol)
	NO:	target sequence (5p --> 3p)					
1	337	UCGCAGCCAAGCACAAUAAA	TTTATTGTGCTTGGCTGCGA	338	45.00%	0.819	8.6
2	339	CGCAGCCAAGCACAAUAAA	TTTATTGTGCTTGGCTGCG	340	45.00%	0.818	9
3	341	GCCCUUCUUUCUACCCUGCU	AGCAGGGTAGAAAGAGGGC	342	55.00%	0.735	9.9
4	343	GACCUCACGGGCUAUUUAAA	TTTAAATAGCCCCGTGAGGTC	344	45.00%	0.698	7.8
5	345	UACCUCCCACAAAGGAUUACC	GGTAATCCTTGTGGGAGGTA	346	50.00%	0.694	7.3
6	347	CCCUUUCUUUCUACCCUGCUG	CAGCAGGGTAGAAAGAGGG	348	55.00%	0.693	9.9
7	349	ACCUCCCACAAGGAUUACCC	GGGTAATCCTTGTGGGAGGT	350	55.00%	0.69	7.4
8	351	ACCUCACGGGCUAUUUAAAG	CTTTAAATAGCCCCGTGAGGT	352	45.00%	0.684	9.9
9	353	AUUGAGUGCCACCCCAUAUCU	AGATATGGGTGGCACTCAAT	354	45.00%	0.668	6.7
10	355	GAUCUUAAACAACCCUGGCU	AGCCAGGTTTGTTTAAGATC	356	40.00%	0.666	12
11	357	UGAUCUUAAACAACCCUGGC	GCCAGGTTTGTTTAAGATCA	358	40.00%	0.664	12.7
12	359	AAGGCGAUCGCAGCCCAAGCA	TGCTTGGCTGCGATCGCCTT	360	60.00%	0.663	9.4
13	361	GAUUGAGUGCCACCCCAUAUC	GATATGGGTGGCACTCAATC	362	50.00%	0.649	6.2
14	363	CAGAUUGAGUGCCACCCCAUA	TATGGGTGGCACTCAATCTG	364	50.00%	0.644	5.8
15	365	CCAGAUUGAGUGCCACCCCAU	ATGGGTGGCACTCAATCTGG	366	55.00%	0.643	5.6
16	367	UCAAGGCGAUCGCAGCCCAAG	CTTGGCTGCGATCGCCTTGA	368	60.00%	0.639	10.1
17	369	UAAACAACCCUGGCUUGAAG	CTTCAAGCCAGGTTTGTTTA	370	40.00%	0.636	9.3
18	371	UUACCCCUUCCAUGAAGAGU	ACTCTTCATGGAAGGGGTAA	372	45.00%	0.633	8.6
19	373	AAACAACCCUGGCUUGAAGU	ACTTCAAGCCAGGTTTGTTT	374	40.00%	0.631	8.5
20	375	UACCCCUUCCAUGAAGAGUU	AACCTTTCATGGAAGGGGTA	376	45.00%	0.627	8.6

FIG. 17

ASO sites in homo sapiens aldo-keto reductase family 1 member B (AKR1B1), hg19 dna range=chr7:134127102-134143944 (intronic targets only)

Rank	SEQ ID NO:	target sequence (5p --> 3p)	antisense oligo (5p --> 3p)	SEQ ID NO:	GC content	average unpaired probability for target site nucleotides	binding site disruption energy (kcal/mol)
1	377	AAUACAAAUAUAGCCCGGC	GCCGGGCTAATTTTGTATT	378	40.00%	0.859	7.5
2	379	AAUACCAUCUCCUCUUCGGC	GCCGAAGAGGAGATGGTATT	380	50.00%	0.818	3.8
3	381	AAUACCAUCUCCUCUUCGG	CCGAAGAGGAGATGGTATTT	382	45.00%	0.817	3.8
4	383	AUACCAUCUCCUCUUCGGCU	AGCCGAAGAGGAGATGGTAT	384	50.00%	0.812	3.8
5	385	CACUACCCUUAUUCUUGUCU	AGACAAGAATAAGGGTAGTG	386	40.00%	0.812	4.3
6	387	AUACAAAUAUAGCCCGGCA	TGCCGGGCTAATTTTGTAT	388	40.00%	0.811	7.6
7	389	UCACUACCCUUAUUCUUGUC	GACAAGAATAAGGGTAGTGA	390	40.00%	0.805	3
8	391	UACCAUCUCCUCUUCGGCUG	CAGCCGAAGAGGAGATGGTA	392	55.00%	0.802	4.1
9	393	ACACCCAUUCAGUCAUUUUG	CAAAATGACTGAATGGGTGT	394	40.00%	0.795	0.5
10	395	GACACCCAUUCAGUCAUUUU	AAAATGACTGAATGGGTGC	396	40.00%	0.787	1.9
11	397	UCAUGAUAAUCUCCAGAAC	GTTCTGGGAGATTATCATGA	398	40.00%	0.783	4
12	399	CAGUUUAUCUUAUCGCUCU	AGGAGCGATAAGATAAACTG	400	40.00%	0.783	10
13	401	AGUUUAUCUUAUCGCUCU	GAGGAGCGATAAGATAAACT	402	40.00%	0.782	9.9
14	403	ACCUCCCACAAGGAUUACCC	GGGTAATCCTTGTGGGAGGT	404	55.00%	0.777	7.3
15	405	CCUCCCACAAGGAUUACCCC	GGGGTAATCCTTGTGGGAGG	406	60.00%	0.767	7.3
16	407	CAUGAGGUCAGAGAUAUAGAG	CTCTATCTTCTGACCTCATG	408	45.00%	0.761	7.5
17	409	CUUCAUGAUAAUCUCCAGAG	TCTGGGAGATTATCATGAAG	410	40.00%	0.759	1.6
18	411	AUGAGGUCAGAGAUAUAGAGA	TCTCTATCTTCTGACCTCAT	412	40.00%	0.757	8
19	413	ACUGUUUUCUCCUUCUCCU	AGGAGAAAGGAGAAACACAGT	414	40.00%	0.755	7.2
20	415	UUCUCCUUCUCCUGACAGC	GCTGTCAGGAGAAAGGAGAA	416	50.00%	0.753	7.2
21	417	AGACCCAGCCUCCUUCUCCU	AGGGAAGGAGGCTGGGTCT	418	60.00%	0.751	10.9
22	419	CCCUUAUUUCUUGUCUGAGCU	AGCTCAGACAAGAATAAGGG	420	45.00%	0.75	3.4

FIG. 18

23	421	CUCUCCAUUCAUCCGUCUU	AAGACGGATGAATGGGAGAG	422	50.00%	0.749	5
24	423	CAUGAUAAUUCUCCAGAACC	GGTTCTGGGAGATTATCATG	424	45.00%	0.747	8.5
25	425	UCUCUCCCAUUCAUCCGUCU	AGACGGATGAATGGGAGAGA	426	50.00%	0.747	4.3
26	427	CCUUAUUCUUGUCUGAGCUC	GAGCTCAGACAAGAAAGG	428	45.00%	0.744	3.4
27	429	UCUCUCACUACCCUUAUUCU	AGAATAAGGTTAGTGAGAGA	430	40.00%	0.734	4.8
28	431	CCUUUCUUGGCCUCUCUGUC	GACAGAGAGGGCAAGAAAGG	432	55.00%	0.718	-0.1
29	433	CCAAUCUGUCCAUUCCAUUU	AAATGGAATGGACAGATTGG	434	40.00%	0.716	3.8
30	435	CUCUCUCCUUUAGUACUUC	GGAAGTACTAAAGGAGAGAG	436	45.00%	0.716	5.6
31	437	UCUCUCCUUUAGUACUUCU	AGGAAGTACTAAAGGAGAGA	438	40.00%	0.715	4.6
32	439	CCUGAGCCUGAUUAUCUGAA	TTCAGATAATCAGGCTCAGG	440	45.00%	0.709	2.7
33	441	CCAUCUUUUGCCAUGAUCAC	GTGATCATGGCAAAAGATGG	442	45.00%	0.709	1.6
34	443	UUUCUCCAUCUUUUGCCAUG	CATGGCAAAAGATGGAGAAA	444	40.00%	0.708	2.3
35	445	GCCAAUCUGUCCAUUCCAUU	AATGGAATGGACAGATTGGC	446	45.00%	0.708	3.8
36	447	UCCAUCUUUUGCCAUGAUCA	TGATCATGGCAAAAGATGGA	448	40.00%	0.707	1.6
37	449	CUGAGCCUGAUUAUCUGAAA	TTTCAGATAATCAGGCTCAG	450	40.00%	0.706	3
38	451	CUUCUUCGUGACCUCUUGCA	TGCAAGAGGTCACGAAGAAG	452	50.00%	0.696	5.3
39	453	AUUGACUUCUCCCAACAACA	TGTTGTTTGGGGAAGTCAAT	454	40.00%	0.691	13
40	455	CUAGAAAACCUCUCACAAAC	GTTGTGAGAGGTTTTTCTAG	456	40.00%	0.688	5.3
41	457	UUGACUUCUCCCAACAACAG	CTGTTGTTTGGGGAAGTCAA	458	45.00%	0.688	13.1
42	459	UAGCCUGAGCCUGAUUAUCU	AGATAATCAGGCTCAGGCTA	460	45.00%	0.686	2.9
43	461	AACGUUAUACCCACGGCCAU	ATGGCCGTGGGTGATACGTT	462	55.00%	0.684	8.3
44	463	ACACUCAAUACAGCUACACU	AGTGTAGCTGTATTGAGTGT	464	40.00%	0.68	5.9
45	465	GCUUCUUCGUGACCUCUUGC	GCAAGAGGTCACGAAGAAGC	466	55.00%	0.677	6.6
46	467	AUAGCCUGAGCCUGAUUAUC	GATAATCAGGCTCAGGCTAT	468	45.00%	0.676	2.5
47	469	GUAAACUAGCAAAGACCUGUAA	TTACAGGTCTTGCTAGTTAC	470	40.00%	0.676	5.3
48	471	AUAAGCAUCUCAAGCCGGUA	TACCGGCTTGAGATGCTTAT	472	45.00%	0.672	4.2
49	473	AAACGUUAUCACCCACGGCCA	TGGCCGTGGGTGATACGTTT	474	55.00%	0.672	8.7
50	475	CCGUAGCUAGUUGAUAAUUC	GAATTATCAACTAGCTACGG	476	40.00%	0.67	6.8
51	477	AUUUGUUUCUACCCCGAGCUC	GAGCTGGGGTAGAAACAAAT	478	45.00%	0.67	7.5

FIG. 18 CONT.

52	479	AAUAAGCAUCUCAAGCCGGU	ACCGGCTTGAGATGCTTATT	480	45.00%	0.669	4.2
53	481	UUUGUUUCUACCCAGCUCU	AGAGCTGGGTAGAAACAAA	482	45.00%	0.669	7.6
54	483	ACGUAUACCCACGGCCAUA	TATGGCCGTGGTGATACGT	484	55.00%	0.669	9.4
55	485	UAAACCUCUACACCCACACA	TGTGTGGTGTGAGGTTTTA	486	40.00%	0.668	6.7
56	487	GUCCCCUCUUAACCCACACC	GGTGTGGTTAAGAGGGGAC	488	60.00%	0.667	11.1
57	489	GUCUCAGCUCAGCCCGUUU	AAACGGGCTGGAGCTGAGAC	490	60.00%	0.663	8.3
58	491	AGUCUCAGCUCAGCCCGUU	AACGGGCTGGAGCTGAGACT	492	60.00%	0.656	5.3
59	493	AAAACCUCUACACCCACACAG	CTGTGTGGTGTGAGGTTTT	494	45.00%	0.65	8.6
60	495	CCCGUAGCUAGUUGAUAAUU	AATTATCACTAGCTACGGG	496	40.00%	0.644	8.9
61	497	UAGUGUCCAUUGUCUCCGUCU	AGACGGAGACATGGACACTA	498	50.00%	0.644	9.2
62	499	CUCACAACCAUUCACAGCAU	ATGCTGTGAATGGTTGTGAG	500	45.00%	0.643	13.6
63	501	ACAACCAUUCACAGCAUCAU	ATGATGCTGTGAATGGTTGT	502	40.00%	0.641	12.4
64	503	GCAUUUUGUUUUAUUCUGUCCC	GGGACAGAAATAACAAAATGC	504	40.00%	0.633	8.6
65	505	UCCGUCUGACAGUCUCAGCU	AGCTGAGACTGTCAGACGGA	506	55.00%	0.632	9.5
66	507	CAUUCCAUUUUGUGUCCUCU	AGAGGACACAAAATGGAATG	508	40.00%	0.631	9
67	509	UUAGAGUCCCGUGCUGAUGA	TCATCAGCACGGGACTCTAA	510	50.00%	0.627	6.8
68	511	GUUUUUAUUGCACCCACAGCAU	ATGCTGTGGTGCAATAAAC	512	40.00%	0.626	6.1
69	513	UAAGCAUCUCAAGCCGGUAG	CTACCGGCTTGAGATGCTTA	514	50.00%	0.624	6.5
70	515	UGCCCUUCACAACCAUUCACA	TGTGAATGTTGTGAGGGCA	516	50.00%	0.623	11.9
71	517	UAUCACCCACGGCCAUAACAG	CTGTATGGCCGTGGTGATA	518	55.00%	0.621	14.3
72	519	AUGACACCAAGCUAAUUUCC	GGAAATTAGCTTGGTGTCAT	520	40.00%	0.618	9
73	521	UUUUUUGCACCCACAGCAUAUC	GATATGCTGTGGTGCAATAA	522	40.00%	0.616	6.4
74	523	GCAUGGGCUCUUAGAUUAAU	ATTAATCTAAGAGCCCATGC	524	40.00%	0.616	9.9
75	525	AUCCAUUUUGUGUCCUCUG	CAGAGGACACAAAATGGAAT	526	40.00%	0.613	11.3
76	527	GGCUAAUCUUUUUUUCUUCCC	GGGAAGAAAAAGATTAGCC	528	40.00%	0.601	14.3
77	528	ACAGAUGCUCGACAGAAAGAU	ATCTTCTGTCGAGCATCTGT	530	45.00%	0.6	7.2
78	531	GAUGCUCGACAGAGAUGUG	CACATCTTCTGTCGAGCATC	532	50.00%	0.599	8.6
79	533	UUGUUUCCUCCCAAAACUCC	GGAGTTTTTGGAGGAAACAA	534	40.00%	0.597	9.6
80	535	GUACUUAACCUAUGUAGGCU	AGCCTACATAGGTTAAGTAC	536	40.00%	0.594	6.6

FIG. 18 CONT.

TREATMENT AND DETECTION OF INHERITED NEUROPATHIES AND ASSOCIATED DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS AND INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0001] This application is a Continuation of International Patent Application No. PCT/US2020/031708, filed May 6, 2020, which claims the benefit of U.S. Provisional Patent Application No. 62/844,370, filed May 7, 2019, and U.S. Provisional Patent Application No. 62/987,151, filed Mar. 9, 2020, each of the foregoing are incorporated herein by reference in their entireties.

GRANT FUNDING DISCLOSURE

[0002] This invention was made with government support under grant numbers NS065712, NS075764 and GM119018 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

SEQUENCE LISTING

[0003] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: Filename: 761350_000281_SL.txt; Size: 147,687 bytes; Created: Dec. 15, 2021.

FIELD OF THE INVENTION

[0004] The present disclosure relates to methods of detecting and treating inherited neuropathy.

BACKGROUND

[0005] Peripheral neuropathies are amongst the most frequent neurodegenerative diseases, with diabetic neuropathy and hereditary origins amongst the most common mechanisms of action. For the inherited neuropathies, also known as Charcot-Marie-Tooth disease (CMT), the remaining diagnostic gap of patients is ~50%. In our understanding, CMT represents an umbrella concept for clinically and genetically heterogeneous inherited monogenic highly phenotypically penetrant conditions affecting the peripheral nerves. CMT is classified depending on conduction velocity as demyelinating (CMT1) and axonal (CMT2) types. Distal hereditary motor neuropathy (dHMN) represents a form of CMT2 in which the burden of disease falls predominantly or exclusively on motor nerves (Rossor, Tomaselli, and Reilly 2016). A similar condition includes ALS4 (juvenile dHMN+brisk reflexes as sign of upper motoneuron involvement). As opposed to CMT1, for which over 90% of cases have mutations in known genes, only 20 to 30% of CMT2 and distal HMN patients receive a genetic diagnosis (Fridman et al. 2015).

SUMMARY

[0006] The disclosure provides a method of treating and/or detecting inherited neuropathy. In various aspects, the method comprises detecting the presence of a mutation in the sorbitol dehydrogenase (SORD) gene in a sample from a subject. In various embodiments, the SORD mutation is a DNA variant classified as pathogenic or likely pathogenic

according to American College of Medical Genetics and Genomics (ACMG) criteria. Optionally, the method comprises diagnosing the subject with inherited neuropathy when the presence of a mutation in the SORD gene is detected. Optionally, the method comprises administering to the subject a composition that comprises an agent selected from the group consisting of an aldose reductase inhibitor; an aldose reductase antisense oligonucleotide; a polynucleotide that encodes a SORD peptide; a SORD peptide; an agent that blocks expression of a mutant SORD gene; and an agent that corrects the mutation in SORD gene. In various aspects, the method comprises administering to the subject Alrestatin, Epalrestat, Diepalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, Salfredin B₁₁, Sorbinil, Tolrestat, Zenarestat, or Zopolrestat (or a combination thereof). In various aspects, the method comprises administering to the subject an aldose reductase antisense oligonucleotide; a polynucleotide that encodes a SORD peptide; an agent that blocks expression of a mutant SORD gene; an agent that corrects the mutation in SORD gene; or a combination of any of the foregoing. In various aspects, the method comprises administering to the subject a SORD peptide. Administration of a combination of any of the foregoing is also contemplated. Optionally, the method comprises measuring sorbitol levels in a sample from the subject.

[0007] Also provided is use of an (i) aldose reductase inhibitor (e.g., Alrestatin, Epalrestat, Diepalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, Salfredin B₁₁, Sorbinil, Tolrestat, Zenarestat, and/or Zopolrestat); (ii) an aldose reductase antisense oligonucleotide, a polynucleotide that encodes a SORD peptide, an agent that blocks expression of a mutant SORD gene, and/or an agent that corrects the mutation in a SORD gene; and/or (iii) a SORD peptide for the treatment of inherited neuropathy (or use in the preparation of a medicament for treatment of inherited neuropathy) in a subject which has been tested for the presence of a mutation in the sorbitol dehydrogenase (SORD) gene.

[0008] The disclosure further provides a method of characterizing a neuropathy in a mammalian subject, the method comprising measuring the level of sorbitol in a subject suffering from a neuropathy, wherein a sorbitol level of greater than about 10 g/L indicates that the neuropathy is associated with a mutation in the sorbitol dehydrogenase (SORD) gene. The disclosure also provides a method of evaluating the efficacy of a treatment for an inherited neuropathy in a subject, the method comprising administering to the subject an agent selected from the group consisting of an aldose reductase inhibitor (e.g., Alrestatin, Epalrestat, Diepalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, Salfredin B₁₁, Sorbinil, Tolrestat, Zenarestat, and/or Zopolrestat), an aldose reductase antisense oligonucleotide, a polynucleotide that encodes a SORD peptide, a SORD peptide, an agent that blocks expression of a mutant SORD gene, and an agent that corrects the mutation in SORD gene (or a combination of any of the foregoing); and measuring the level of sorbitol in a subject.

[0009] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the disclosure and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For

example, where features are described with language such as “one embodiment,” “some embodiments,” “various embodiments,” “related embodiments,” each of these types of embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the invention.

[0010] The headings herein are for the convenience of the reader and not intended to be limiting. Additional aspects, embodiments, and variations of the invention will be apparent from the Detailed Description and/or drawings and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIGS. 1A-F. SORD gene and pedigrees. Biallelic mutation in SORD cause autosomal recessive dHMN/CMT2. (FIG. 1A) Representative pedigrees of dHMN/CMT2 families carrying biallelic mutations in SORD. The squares indicate males and the circles females. The diagonal lines are used for deceased individuals. Patients are indicated with filled shapes. (FIG. 1B) Schematic diagram showing all exons, introns and untranslated regions (UTRs) of SORD on the basis of NCBI Reference Sequence: NM_003104.6. The gray and white boxes represent the coding sequence and UTRs of SORD, respectively. Variants identified in the families considered in the present study map throughout the coding region of the gene. The nonsense c.757delG; p.(Ala253GlnfsTer27) variant on exon 7, was identified at particular high frequency. (FIG. 1C) Distribution of mutation across SORD protein domains. (FIG. 1D) SORD protein orthologs alignments showing that the four missense substitutions identified in dHMN/CMT2 families in this study are located at highly conserved residues across species from humans to elephants (FIGS. 1E and 1F) Magnification the nucleotide sequence of a highly homologous region in exon 7 in SORD (reverse strand) and SORD2P (forward strand). Nucleotides differing in SORD2P from SORD are indicated with an arrow, including a FIG. 1C deletion in SORD2P. Representative electropherograms shows that in SORD the c.757delG; p.(Ala253GlnfsTer27) variant found in homozygous state in dHMN/CMT2 patients and heterozygous state in available patents (right box, upper plot) is absent in biallelic state from healthy controls (right box, lower plot), but it is fixated in SORD2P (left box, lower plot).

[0012] FIGS. 2A-C. Decreased SORD expression and sorbitol accumulation in patients fibroblasts. (FIG. 2A) Schematic representation of the two-step polyol pathway converting glucose to fructose. (FIG. 2B) Immunoblot showing protein level of SORD using the polyclonal antibody ab189248 and normalized to Tubulin in healthy control (n=4, lane 1-4), heterozygous carriers of c.757delG; p.(Ala253GlnfsTer27) variant in SORD (n=2, lane 10-11) and patients carrying homozygous c.757delG; p.(Ala253GlnfsTer27) change (n=4, lane 5-8) or compound heterozygous c.757delG; p.(Ala253GlnfsTer27) variant together with a second nonsense c.895C>T; p.(Arg299Ter) mutation (n=1, lane 9). (FIG. 2C) Levels of intracellular sorbitol as measured by UPLC and normalised to protein content in healthy controls (n=5) and patients carrying biallelic nonsense mutations in SORD (n=5). The graphs show the mean±s.d. and data distribution (dots). A two-tailed t-test was performed to compare SORD encoded protein

(FIG. 2B) or sorbitol level (FIG. 2C) across groups. Statistical significance is indicated as *, ** or *** if P-value <0.05, <0.01 or <0.001, respectively. All experiments were repeated independently twice with similar results.

[0013] FIGS. 3A-F. Loss of *Drosophila* Sord2 causes age-dependent synaptic degeneration. (FIG. 3A) 3D structure of *Drosophila* visual system showing the lamina, medulla, and lobula. The xy- and xz-planes showing the photoreceptor terminals and lamina neurons are indicated. (FIG. 3B) Lamina of yw control fly at 2 DAE. The organized lamina cartridges and columnar photoreceptor neurons are shown in the xy-plane and xz-plane, respectively. (FIG. 3C) Laminae of Sodh2^{MB01265/MB01265} homozygous flies at 2 DAE and 10 DAE. Arrowheads indicate the lamina vacuoles. Boxes indicate higher magnification areas of the lamina. The intensity of BRP is indicated. Dotted lines indicate the area of lamina vacuoles. Scale bar: 30 μm. (FIG. 3D) Quantification of the vacuole number, size, and BRP intensity. A total of 3 laminae of each group were quantified. Data are presented as mean±s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. *P<0.05, **P<0.01, ****P<0.0001. (FIGS. 3E-3F) Locomotor activity of control flies (yw) and Sodh2^{MB01265/MB01265} (FIG. 3E) or Sodh1 and Sodh2 pan-neuronal double knockdown (RNAi) (FIG. 3F) flies. n=10 in each group. Data are presented as mean±s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. ****P<0.0001

[0014] FIGS. 4A-G. Treatment with aldose reductase inhibitors Epalrestat and Ranirestat decrease sorbitol level and restore function. (FIG. 4A) Intracellular sorbitol level as measured by UPLC and normalised to protein content in fibroblasts from healthy controls (n=5, circle dots) and patients carrying biallelic nonsense mutations in SORD (n=5, square dots) after three days of treatment with Epalrestat 100 μM, Ranirestat 10 μM or DMSO. (FIG. 4B) Sorbitol level as measured by UPLC from brain/head homogenates and normalised to protein concentration from wild-type (yw, empty circle dots), Sodh2^{MB01265/MB01265} (full circle dots) and neuron-specific knock-down of Sodh1 and Sodh1 by RNAi (square dots) *Drosophilae* at 10 days after eggs enclosure. Sodh2 Mimic and Sodh1 and Sodh2 RNAi *Drosophilae* were fed with either 80 μM Epalrestat, 80 μM Ranirestat or DMSO. The graphs show the mean±s.d. A two-tailed t-test was performed to compare sorbitol level. Statistical significance is indicated as *, ** or *** if P-value <0.05, <0.01 or <0.001, respectively, unless otherwise specified. All experiments were repeated independently twice with similar results. (FIG. 4C) Locomotor activity of control flies (yw) feeding with DMSO, Sodh2^{MB01265/MB01265} flies feeding with DMSO, 80 μM Epalrestat, or 80 μM Ranirestat (n=10 in each group). Data are presented as mean±s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. *P<0.05, ***P<0.001 (FIGS. 4D-4F) Laminae of Sodh2^{MB01265/MB01265} homozygous flies at 10 DAE and 40 DAE fed with DMSO (FIG. 4D), 80 μM Epalrestat (FIG. 4E), or 80 μM Ranirestat (FIG. 4F). Arrowheads indicate the lamina vacuoles. Boxes indicate higher magnification areas of the lamina. The intensity of BRP is indicated. Dotted lines indicate the area of lamina vacuoles. Scale bar: 30 μm. (FIG. 4G) Quantification of the vacuole number, size, and BRP intensity of (FIGS. 4D-4F). n=3. Data are presented as

mean $\pm$ s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. *P<0.05, **P<0.01, ****P<0.0001.

[0015] FIG. 5. Pedigrees of families carrying biallelic mutations in SORD. The squares indicate males and the circles females. The diagonal lines are used for deceased individuals. Patients are indicated with filled shapes.

[0016] FIGS. 6A-B. Double knockdown of *Drosophila* Sodh1 and Sodh2 lead to age-dependent synaptic degeneration. (FIG. 6A) Laminae of Sodh1 and Sodh2 double knockdown homozygous flies at 2 DAE and 10 DAE. Arrowheads indicate the lamina vacuoles. Boxes indicate higher magnification areas of the lamina. The intensity of BRP is indicated. Dotted lines indicate the area of lamina vacuoles. Scale bar: 30 μ m. (FIG. 6B) Quantification of the vacuole number, size, and BRP intensity. A total of 3 laminae of each group were quantified. Data are presented as mean $\pm$ s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. *P<0.05, **P<0.01, ****P<0.0001.

[0017] FIG. 7. Treatment with aldose reductase inhibitors Epalrestat and Ranirestat restore locomotor function in Sodh1 and Sodh2 double knockdown flies. Locomotor activity of control flies (yw) feeding with DMSO (dots, first data point from the left for each DAE point indicated), or flies with neuronal specific knockdown of Sodh1 and Sodh2 feeding with DMSO (squares, second data point from the left for each DAE point indicated), 80 μ M Epalrestat (squares, third data point from the left for each DAE point indicated), or 80 μ M Ranirestat (squares, fourth data point from the left for each DAE point indicated). n=10 in each group. Data are presented as mean $\pm$ s.d. Statistical analysis was performed using Two-Way ANOVA followed by post-hoc Tukey's multiple comparison test. ***P<0.001, ****P<0.0001.

[0018] FIG. 8. An illustration of an exemplary expression vector encoding the SORD peptide (pAAV-SORD).

[0019] FIG. 9. An exemplary complete AAV vector DNA sequence including the SORD coding sequence (pAAV-SORD) (SEQ ID NO: 1).

[0020] FIG. 10. SORD primer sequences and thermocycling conditions. PCR: polymerase chain reaction; Fw: forward; Rv: reverse.

[0021] FIG. 11. Clinical features of patients with hereditary neuropathy and carrying biallelic mutations in SORD.

[0022] FIG. 12. Clinical features of patients affected by hereditary neuropathy and carrying the biallelic mutations in SORD. Categorical data are expressed as N (%) if data is available in all individuals or N/number individuals considered (%). Continuous variables are expressed as mean $\pm$ standard deviation (min-max). CMT, Charcot-Marie-Tooth, dHMN, distal hereditary motor neuropathy.

[0023] FIG. 13. Fasting sorbitol level in serum from ten unrelated healthy controls and ten patients carrying biallelic p.Ala253GlnfsTer27 mutations in SORD. The graphs show the mean $\pm$ s.d. and data distribution (dots), and the p-value of two-tailed t-tests comparing SORD protein and sorbitol levels across groups—*p<0.05, **p<0.01, and ***p<0.001. All experiments were twice repeated independently.

[0024] FIGS. 14A-14C. Exemplary vector design for SORD gene replacement therapy. (FIG. 14A) AAV-9 packaged vector design for a SORD gene replacement therapy. CB7 promoters have been shown to be effective in driving high expression, followed by the SORD cDNA (NCBI

Reference Sequence: NM_003104.6), a Posttranscriptional Regulatory Element (WPRES) to further enhance expression and target specificity, and the transcription termination poly (A) element. Further origin of replication (pUC-ori) and ITR sequences (inverted terminal repeat). (FIG. 14B) SORD cDNA sequence. (FIG. 14C) SORD polypeptide sequence.

[0025] FIGS. 15A-15D. Significant knock-down of aldose reductase (AR) (AKR1B1 gene) via an antisense oligonucleotide (ASO) (AR 1A, (SEQ ID NO: 22)). Targeting ASO (AR 1A) sequence and ASO-S scrambled sequence (AR-S 1A, (SEQ ID NO: 47)) are shown in FIG. 15A. FIG. 15B shows the modifications to the nucleotide backbone of the ASOs. This was carried out in a SORD patient fibroblast and control fibroblasts and normalized to β -tubulin and measured via Western blot (FIGS. 15C-15D). A further control is a scrambled version of the ASO-S (AR-S 1A) exhibiting random nucleotides was used (FIG. 15C).

[0026] FIG. 16. A table of antisense oligonucleotide sequences and target sites in *Homo sapiens* aldose reductase family 1 member B (AKR1B1), exon targets only. Filter criteria: A) 40% $\leq$ GC % $\leq$ 60%; B) Antisense oligo binding energy $\leq$ -8 kcal/mol; C) No GGGG in the target sequence.

[0027] FIG. 17. A table of antisense oligonucleotide (ASO) sequences and target sites in *Homo sapiens* aldose reductase family 1 member B (AKR1B1), exon targets only. Filter criteria: A) 40% $\leq$ GC % $\leq$ 60%; B) No GGGG in the target sequence; C) Average unpaired probability for target site nucleotides $\geq$ 0.5; D) For each peak in the accessibility profile that is above the threshold probability of 0.5, all sites targeted to this same peak are ranked by their average unpaired probability (the higher the better) and at most n sites are selected for each peak, where n is determined by max([width of peak/site length], 2); E) Among sites satisfying criteria A-D, the top 20 unique ones with the highest average unpaired probability are listed.

[0028] FIG. 18. A table of antisense oligonucleotide (ASO) sequences and target sites in *Homo sapiens* aldose reductase family 1 member B (AKR1B1), hg19_dna range=chr7:134127102-134143944 (intronic targets only). Filter criteria: A) 40% $\leq$ GC % $\leq$ 60%; B) No GGGG in the target sequence; C) Average unpaired probability for target site nucleotides $\geq$ 0.5; D) For each peak in the accessibility profile that is above the threshold probability of 0.5, all sites targeted to this same peak are ranked by their average unpaired probability (the higher the better) and at most n sites are selected for each peak, where n is determined by max([width of peak/site length], 2); E) Among sites satisfying criteria A-D, the top 20 unique ones with the highest average unpaired probability are listed.

DETAILED DESCRIPTION

[0029] The disclosure provides a method of detecting and/or treating inherited neuropathy and related inherited conditions.

[0030] Inherited (or hereditary) neuropathies include, but are not limited to Charcot-Marie-Tooth disease (CMT), hereditary motor and sensory neuropathy, hereditary motor neuropathy, distal hereditary motor neuropathy (dHMN), axonal neuropathies, intermediate neuropathies, and amyotrophic lateral sclerosis type ALS4.

[0031] In various aspects, the disclosure provides a method wherein the presence of a mutation in the sorbitol dehydrogenase (SORD) gene is detected in a sample from a

subject. The mutation may be detected by examining the DNA sequence of the gene, examining RNA, or examining proteins with mutations that result in some loss of function.

[0032] Disclosed herein is the identification of biallelic mutations in the Sorbitol dehydrogenase gene (SORD) associated with the most frequent recessive form of CMT. SORD encodes sorbitol dehydrogenase, an enzyme which converts sorbitol to fructose. It belongs to the two-step polyol pathway previously identified as pivotal to nerve damage in hyperglycemic condition of diabetes. Forty-two cases of CMT across different ethnicities were identified as carrying a nonsense mutation in SORD, c.757delG; p.Ala253GlnfsTer27, either in homozygous or compound heterozygous state. By screening the p.Ala253GlnfsTer27 change in additional cases and multiple control sets, this variant was established as one of the most common pathogenic alleles in men inherited according to Mendel's law (MAF=0.003). Patient fibroblast cultures exhibit a complete loss of SORD protein as well as loss of intracellular sorbitol accumulation, which causes tissue damage. Loss of Sodh1 in *Drosophila* led to synaptic degeneration and progressive motor impairment. Notably, reduction of polyol influx by treatment with aldose reductase inhibitors fully rescued intracellular sorbitol levels in patient fibroblasts and a Sodh1 *Drosophila* model. In the latter model, the treatment also completely ameliorated motor and eye phenotypes. Together, these findings demonstrate a major role of the polyol pathway and sorbitol accumulation in hereditary neuropathies and establish the molecular cause for a potentially treatable condition in a significant fraction of cases. These findings also represent an example of converging pathomechanisms of hereditary and acquired neuropathies with a broader impact in the field of diabetes.

[0033] Thus, in various aspects of the disclosure, the method comprises detecting the SORD gene mutation 753delG; p.(Ala253GlnfsTer27), c.757delG; p.Ala253GlnfsTer27, c.28C>T; p.Leu10Phe, c.316_425+165del; p.Cys106Ter, c.329G>C; p.Arg110Pro, c.298C>T; p.Arg100Ter, c.295C>T; p.Arg299Ter, c.964G>A; p.Val322Ile, c.458C>A; p.Ala153Asp; a deletion of individual or multiple coding exons or the entire SORD gene via a copy number variation; or any protein truncating mutation and/or mutation that leads to a "loss of function" or a hypomorphic function of the protein.

[0034] In various aspects, the SORD mutation is detected using DNA sequencing methods such as whole exome sequencing, whole genome sequencing (WGS) and/or next-generation sequencing (NGS), allele specific oligonucleotides, polymerase chain reaction (PCR), quantitative or real-time PCR (qPCR), multiplex PCR, nested PCR, Amplification Refractory Mutation System (ARMS) PCR, Multiplex ligation-dependent probe amplification (MLPA), Denaturing gradient gel electrophoresis (DGGE), Single-Strand Conformation Polymorphism (SSCP), Protein Truncation Test (PTT), RFLP, DNA microarray, RNA-seq, using CRISPR-based mutation detection (e.g., CRISPR-Chip, Hajian et al., *Nature Biomedical Engineering* 3, 427-437 (2019)) or other DNA or RNA mutation detection methods suitable for mutation detection.

[0035] In various aspects, the SORD mutation is detected by examining proteins using western blotting (immunoblot), High-performance liquid chromatography (HPLC), Liquid chromatography-mass spectrometry (LC/MS), antibody dependent methods such as enzyme-linked immunosorbent

assay (ELISA), protein immunoprecipitation, protein immunostaining, protein chip methods or other protein detection methods suitable for mutation detection.

[0036] Optionally, the method further comprises measuring sorbitol levels in a sample of the subject. Methods of measuring sorbitol include, e.g., enzymatic assays, fluorimetric assays, chromatography-based methods, and spectroscopy-based methods. An exemplary method of sorbitol measurement is provided in the Examples.

[0037] The disclosure further provides a method of characterizing a neuropathy (e.g., inherited neuropathy) and related conditions involving a SORD mutation. In various aspects, the method comprises measuring sorbitol levels in a biological sample of a subject suffering from a neuropathy. In various aspects, the method comprises detecting increased levels of sorbitol in the biological sample. By "increased levels of sorbitol" is meant, e.g., sorbitol levels above about 10 mg/L. SORD-related neuropathy leads to high levels of sorbitol in patients, as described in the Examples and FIG. 13. As such, detection of sorbitol levels above about 10 mg/L indicates that the neuropathy is an inherited neuropathy associated with a SORD mutation, thereby allowing a clinician to characterize the neuropathy afflicting the subject. Optionally, the method comprises a treatment step comprising administering to the subject an agent selected from the group consisting of an aldose reductase inhibitor; an aldose reductase antisense oligonucleotide; a polynucleotide that encodes a SORD peptide; a SORD peptide; an agent that blocks expression of a mutant SORD gene; and an agent that corrects the mutation in SORD gene.

[0038] In various aspects, the disclosure provides a method comprising identifying a mutation in the sorbitol dehydrogenase (SORD) gene in a sample from a subject before or after a step of measuring sorbitol levels in the subject. In this regard, the method may be used to confirm a diagnosis of inherited neuropathy. Similarly, the disclosure provides a method for identifying a SORD mutation that is pathogenic, the method comprising measuring sorbitol levels in a subject comprising a mutation in the SORD gene. The presence of increased sorbitol levels (e.g., greater than about 10 mg/L) indicates that the SORD mutation is pathogenic.

[0039] Alternatively (or in addition), the method may be used to evaluate the efficacy of a treatment for an inherited neuropathy in a subject. In this regard, the method comprises administering a therapy to the subject, then measuring sorbitol levels in a biological sample. A decrease in sorbitol levels compared to the level of sorbitol observed pre-treatment (e.g., a reduction of sorbitol levels below about 10 g/L) indicates an improvement in the subject's condition. The materials and methods described herein may also characterize patient compliance in taking medication for treatment of SORD-related inherited neuropathies or monitor the success of candidate therapeutics in clinical trials.

[0040] The sample may be any biological sample taken from the subject, including, but not limited to, any tissue, cell, or fluid (e.g., blood, plasma, serum, or urine) which can be analyzed for a trait of interest, such as the presence or amount of a nucleic acid (e.g., SORD mRNA), a protein (e.g., SORD protein), or sorbitol. In various embodiments, the biological sample is a plasma, serum, saliva, urine, or skin sample.

[0041] A “subject” as referred to herein, can be any mammal, such as humans. Animals of agricultural importance, such as bovine, equine, and porcine animals, are contemplated, as well as animals important as domestic pets, including canines and felines; animals important in research, including rodents and primates; and large endangered species and zoo animals such as primates, felines, giraffes, elephants, rhinos.

[0042] In various aspects, the method comprises treating the subject by administering to the subject a composition that comprises one or more aldose reductase inhibitors. In some embodiments, the aldose reductase inhibitor is Alrestatin, Epalrestat, Diepalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, Salfredin B₁₁, Sorbinil, Tolrestat, Zenarestat, or Zopolrestat. Aldose reductase inhibitors are reviewed in *Expert Opin Ther Pat.* 2019; 29(3):199-213; Chatzopoulou et al., *Expert Opin Ther Pat.* 2012; 22(11):1303-23 (incorporated by reference in their entirety).

[0043] In some embodiments, enzyme replacement therapy is employed, and a SORD peptide is administered to the subject. As such, the therapy supplements SORD peptide

(A) element, origin of replication (pUC-ori) and/or ITR sequences (inverted terminal repeat)). In various aspects, the constructs described herein include one or more of vector features listed in Table 1. Vector features are also reviewed in Powell et al., *Discov Med.* 2015; 19(102): 49-57 (incorporated by reference in its entirety). For example, the Cre-loxP system may be utilized to express a peptide of interest (e.g., a SORD peptides, optionally in a specific tissue of interest). Expression vectors may be viral-based (e.g., retrovirus-, adenovirus-, or adeno-associated virus-based) or non-viral vectors (e.g., plasmids). Non-vector based methods (e.g., using naked DNA, DNA complexes, etc.) also may be employed. Optionally, the vector is a viral vector, such as a lentiviral vector or baculoviral vector, and in various preferred embodiments the vector is an adeno-associated viral vector (AAV). The expression vector may be based on any AAV serotype, including AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12, or AAV-13. Polynucleotides also may be delivered via liposomes, nanoparticles, exosomes, microvesicles, hydrodynamic-based gene delivery, or via a “gene-gun.”

TABLE 1

Vector feature elements					
Ubiquitous Promoters	Neuronal specific promoter	Introns (enhanced expression)	Post-transcriptional regulatory elements	Polyadenylation signal enhancers	Bacterial resistance
CMV, Cba, CAG, CBh, EF1- α , PGK, UBC	NFL, NFH, synapsin, CaMKII, Hb9, MeCP2	b-Glob, MVM, I.IX, adenovirus SD/immuno-globulin SA, SV40 late SD/SA	HPRE, WPRE	hGH, bGHpA, SPA, SV40 late	Ampicillin Kanamycin

levels where endogenous SORD levels are inadequate or absent. An exemplary SORD peptide is provided in SEQ ID NO: 46. The disclosure contemplates use of a peptide that comprises at least 80%, at least 85%, at least 90%, at least 95%, or 100% identity to SEQ ID NO: 46.

[0044] In various embodiments, the method comprises administering to the subject a polynucleotide (e.g., an aldose reductase antisense oligonucleotide, a polynucleotide that encodes the SORD peptide/protein, an agent that blocks expression of a mutant SORD gene, and/or an agent that corrects the mutation in SORD gene). Polynucleotides are typically delivered to a host cell via an expression vector, which includes the regulatory sequences necessary for delivery and expression, although use of expression vectors are not required in the context of the disclosure. In some aspects, the constructs described herein include a promoter (e.g., cytomegalovirus (CMV) promoter or CB7 promoter), a protein coding region (optionally with non-coding (e.g. 3'-UTR) regions that facilitate expression), transcription termination sequences, and/or regulator elements sequences (e.g., Posttranscriptional Regulatory Element (WPRE), poly

[0045] Titers of AAV to be administered in methods of the disclosure will vary depending, for example, on the particular AAV, the mode of administration, the treatment goal, the individual, and the cell type(s) being targeted, and may be determined by methods known in the art. Titers of AAV may range from about 1×10^6 , about 1×10^7 , about 1×10^8 , about 1×10^9 , about 1×10^{10} , about 1×10^{11} , about 1×10^{12} , about 1×10^{13} to about 1×10^{14} or more DNase resistant particles (DRP) per ml. Dosages may also be expressed in units of viral genomes (vg).

[0046] In various embodiments, a polynucleotide that encodes a SORD peptide is administered to the subject. The amino acid sequence of SORD is provided as SEQ ID NO: 46 (FIG. 14C, NCBI Reference Sequence: NP_003095.2). The polynucleotide used in the method optionally encodes the amino acid sequence of SEQ ID NO: 46 or a sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to the amino acid sequence of SEQ ID NO: 46 (which retains the function of SORD). Optionally, the polynucleotide comprises SEQ ID NO: 45 (FIG. 14B) or a sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to the polynucleotide sequence of SEQ ID NO: 45 (and which encodes SORD).

Exemplary expression vectors comprising a polynucleotide encoding the SORD peptide are illustrated in FIGS. 8 and 14A. The polynucleotide, in at least one aspect of the disclosure, comprises the nucleic acid sequence shown in FIG. 9 (SEQ ID NO: 1), which corresponds to the sequence of an AAV vector comprising a polynucleotide encoding SORD.

[0047] In various embodiments, the method comprises administering to the subject an agent that blocks expression of a mutant SORD gene. An agent that blocks expression of a mutant SORD gene refers to an agent that interferes with expression of a SORD gene so that SORD gene expression and/or SORD protein levels are reduced compared to basal/wild-type levels. It will be appreciated that “blocking” expression of a mutant SORD gene does not require 100% abolition of expression and SORD production; any level of reduced expression of aberrant SORD may be beneficial to a subject. Exemplary agents include, but are not limited to, antisense oligonucleotides (ASO), short hairpin RNA (shRNA), small interfering RNA (siRNA), or micro RNA (miRNA).

reductase antisense oligonucleotide that reduces the expression of aldose reductase. An ASO is a single-stranded deoxyribonucleotide, which is complementary to an mRNA target sequence. In various aspects, the aldose reductase antisense oligonucleotide targets an exonic or intronic sequence of the aldose reductase gene.

[0049] In an exemplary method for identifying ASO sequences targeting aldose reductase, the following criteria were used: A) sequences targeting aldose reductase (AKR1B1) were selected which contained $\leq 40\%$ GC or $\leq 60\%$ GC content; B) sequences containing GGGG nucleotides were excluded; C) sequences with an average unpaired probability for target site nucleotides ≥ 0.5 were selected; D) for each peak in the accessibility profile that was above the threshold probability of 0.5, all sites targeted to the same peak were ranked by their average unpaired probability (the higher the better) and at most n sites are selected for each peak, where n is determined by max width of peak/site length. Exemplary agents satisfying these criteria are provided in Table 2. Additional exemplary ASO sequences and filter criteria are shown in FIGS. 16-18.

TABLE 2

ASO sequences targeting AKR1B1/ aldose reductase.							
Starting target position	Ending target position	Target Seq (5'-3')	SEQ ID NO antisense oligo (5'-3')	SEQ ID NO	GC content	Average unpaired probability	Binding site disruption
475		AGGUGGAGAUGAUCUUAAC	21 GTTTAAGATCATCTCCACCT	22	40.00%	0.594	12.5
476	495	GGUGGAGAUGAUCUUAACA	23 TGTTTAAGATCATCTCCACC	24	40.00%	0.592	12.6
484	503	UGAUCUUAACAAACCUGGC	25 GCCAGGTTTGTTTAAGATCA	26	40.00%	0.66	12.5
490	509	UAAACAAACCUGGCUUGAAG	27 CTTCAAGCCAGGTTTGTTTA	28	40.00%	0.633	9.2
534	555	CAGGUGGAGAUGAUCUUAACA	29 TGTTTAAGATCATCTCCACCTG	30	40.90%	0.584	12.6
545	566	GAUCUUAACAAACCUGGCUUG	31 CAAGCCAGGTTTGTTTAAGATC	32	40.90%	0.611	10.3
548	569	CUUAAACAAACCUGGCUUGAAG	33 CTTCAAGCCAGGTTTGTTTAAG	34	40.90%	0.646	9.5
567	588	AAGUAUAAGCCUGCAGUUAACC	35 GGTTAAGTGCAGGCTTATACTT	36	40.90%	0.584	7.7
739	760	UCAAGGCGAUCGCAGCCAAGCA	37 TGCTTGGCTGCGATCGCCTTGA	38	59.10%	0.669	10
741	762	AAGGCGAUCGCAGCCAAGCACA	39 TGTGCTTGGCTGCGATCGCCTT	40	59.10%	0.694	9.3
1025	1046	ACCUGUGUUUCUUGCCUCAUUU	41 AAATGAGGCAAGAAACACAGGT	42	40.90%	0.641	5.5

[0048] In various embodiments, the method comprises administering to the subject an aldose reductase antisense oligonucleotide which targets the aldose reductase sequence such that expression of the enzyme is blocked. An aldose reductase, aldo-keto reductase family 1 member B (AKR1B1), is encoded by SEQ ID NO: 48 (NCBI Reference Sequence: NM_001628). An aldose reductase antisense oligonucleotide interferes with expression of an aldose reductase gene (AKR1B1), so that AKR1B1 gene expression and/or aldose reductase protein levels are reduced compared to basal/wild-type levels. It will be appreciated that “blocking” expression of an aldose reductase gene (the AKR1B1 gene) does not require 100% abolition of expression and aldose reductase production; any level of reduced expression of aldose reductase may be beneficial to a subject. For example, in various aspects, the aldose

[0050] In various embodiments, the nucleotide backbone of ASO sequences are modified to a chimeric or gapmer design to reduce gene expression when compared to basal/wild-type levels. In various embodiments, a gapmer design requires a designation of 3-5 nucleotides on each end of the antisense oligonucleotide sequence to harbor modifications in the ribose sugar moiety resistant to RNase H recognition and other nucleases, while all other nucleotides contain an RNase H compatible modification. RNase H is responsible for cleaving RNA-DNA duplexes such as those formed between aberrant mRNA transcripts and synthetically designed DNA antisense oligonucleotides. In various embodiments, the modification to the ASO sequences includes, but is not limited to Phosphorothioate (PS)—RNase H recognizable, phosphorodiamidate morpholino (PMO)—RNase H resistant, 2'-O-methyl—RNase H resis-

tant, 2'-O-methoxyethyl (MOE)—RNase H resistant, locked Nucleic Acid (LNA)—RNase H resistant, ethylene-bridged nucleic acid (ENA)—RNase H resistant, or (S)-constrained ethyl (cEt)—RNase H resistant. Exemplary modification of an ASO sequence is shown in FIGS. 15A-15B. Modifications to ASO sequences are reviewed in Scoles et al., *Neurol Genet.* 2019; 5(2):e323. (incorporated by reference in its entirety).

[0051] In various aspects, the method employs RNA interference (RNAi) to regulate expression of SORD. The RNAi pathway is summarized in Duan (Ed.), Section 7.3 of Chapter 7 in *Muscle Gene Therapy*, Springer Science+Business Media, LLC (2010). Suitable agents include, e.g., siRNA, miRNA, and shRNA. A shRNA/Hairpin Vector is an artificial RNA molecule (nucleotide) with a tight hairpin turn that can be used to silence target gene expression via RNAi. shRNA is an advantageous mediator of RNAi in that it has a relatively low rate of degradation and turnover, but it often requires use of an expression vector. In exemplary aspects, the disclosure includes the production and administration of an AAV vector expressing one or more shRNAs targeting SORD. The expression of shRNAs is regulated by the use of various promoters. In various aspects, polymerase II promoters, such as U6 and H1, and polymerase III promoters are used. In some aspects, U6 shRNAs are used. It will be appreciated that RNAi also may be used to downregulate (i.e., block) expression of aldose reductase (e.g., AKR1B1); as such, the disclosure contemplates use of siRNA, miRNA, and shRNA which targets aldose reductase intronic or extronic sequences to block the expression of aldose reductase.

[0052] Traditional small/short hairpin RNA (shRNA) sequences are usually transcribed inside the cell nucleus from a vector containing a Pol III promoter such as U6. The endogenous U6 promoter normally controls expression of the U6 RNA, a small RNA involved in splicing, and has been well-characterized (Kunkel et al., *Nature.* 322(6074): 73-7 (1986); Kunkel et al., *Genes Dev.* 2(2):196-204 (1988); Paule et al., *Nucleic Acids Res.* 28(6):1283-98 (2000)). The disclosure includes both murine and human U6 or H1 promoters. The shRNA containing the sense and antisense sequences from a target gene connected by a loop is transported from the nucleus into the cytoplasm where Dicer processes it into siRNAs.

[0053] In some aspects of the disclosure, an agent that corrects the mutation in the SORD gene is employed. An agent that corrects the mutation in SORD gene refers to an agent capable of modifying the SORD coding sequence or a regulatory element and/or non-coding region associated with the SORD gene to achieve a desired change in the sequence. In various aspects, genome editing may be used to replace part or all of the SORD gene sequence or alter SORD protein expression levels. In various embodiments, the agent may comprise components employed in genome-editing techniques, such as designer zinc fingers, transcription activator-like effectors nucleases (TALENs), or CRISPR-Cas (clustered regularly interspaced short palindromic repeats-CRISPR associated) systems. An exemplary agent for use in the method of the disclosure is, DNA encoding Cas9 molecules and/or gRNA molecules. Cas9 and gRNA can be present in a single expression vector or separate expression vectors. Adenoviral delivery of the

CRISPR/Cas9 system is described in Holkers et al., *Nature Methods* (2014), 11(10):1051-1057 which is incorporated by reference in its entirety.

[0054] Other publications describing the CRISPR systems and Cas9 include the following: Cong et al. *Science* (2013) 339:819-23; Jinek et al., *Elife.* (2013) 2:e00471; Lei et al. *Cell* (2013) 152: 1173-1183; Gilbert et al. *Cell* (2013) 154:442-51; Lei et al. *Elife* (2014) 3:e04766; Perez-Pinela et al. *Nat Methods* (2013) 10: 973-976; Maider et al. *Nature Methods* (2013) 10, 977-979; U.S. Pat. Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; U.S. Application Publication No. 2014/0068797; and International Patent Publication No. WO 2014/197568, all incorporated by reference in their entirety.

[0055] In some embodiments, CRISPR/Cas9 multiplexing may be used to target multiple genomic loci wherein two or more guide RNAs are expressed as described in CRISPR 101: A Desktop Resource (1st Edition), *Addgene*, January 2016 which is incorporated by reference in its entirety.

[0056] The terms “treating” or “treatment” refer to reducing or ameliorating inherited neuropathy and/or associated disorders and/or symptoms associated therewith. These terms include reducing or delaying the frequency of occurrence or recurrence of the neuropathy or symptoms associated therewith (i.e., lengthening the period of remission in a patient who had suffered from the disorder), as well as reducing the severity of the disorder or any symptoms associated therewith. It is appreciated that, although not precluded, “treating” or “treatment” of a disorder or condition does not require that the disorder, condition, or symptoms associated therewith be completely eliminated.

[0057] A dose of an active agent (e.g., an aldose reductase inhibitor, an aldose reductase antisense oligonucleotide, a polynucleotide that encodes a SORD peptide, a SORD peptide, an agent that blocks expression of a mutant SORD gene, or an agent that corrects the mutation in SORD gene) will depend on factors such as route of administration (e.g., local vs. systemic), patient characteristics (e.g., gender, weight, health, side effects), the nature and extent of the inherited neuropathy or associated disorder, and the particular active agent or combination of active agents selected for administration.

[0058] The active agents described herein are provided in a composition (e.g., a pharmaceutically-acceptable composition) which may contain formulation components suitable for administration to a subject, as well as additional therapeutic agents. Suitable methods of administering a physiologically-acceptable composition, such as a pharmaceutical composition comprising an agent described herein, are well known in the art. In various aspects, more than one route can be used to administer one or more of the agents disclosed herein. A particular route can provide a more immediate and more effective reaction than another route. For example, in certain circumstances, it will be desirable to deliver the composition orally; through injection or infusion by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, intralesional, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, urethral, vaginal, or rectal means; by controlled, delayed, sustained or otherwise modified release systems; by implantation devices; using nanoparticles; or as a conjugate.

[0059] It is contemplated the two or more active agents described herein may be administered as part of a therapeutic regimen. Alternatively or in addition, one or more of the active agents may be administered with other therapeutics as part of a therapeutic regimen. The active agent(s) may be administered as a monotherapy or as a combination therapy with other treatments administered simultaneously or metronomically. The term “simultaneous” or “simultaneously” refers to administration of two agents within six hours or less (e.g., within three hours or within one hour each other). In this regard, multiple active (or therapeutic) agents may be administered the same composition or in separate compositions provided within a short period of time (e.g., within 30 minutes). The term “metronomically” means the administration of different agents at different times and at a frequency relative to repeat administration. Active agents need not be administered at the same time or by the same route; preferably, in various embodiments, there is an overlap in the time period during which different active agents are exerting their therapeutic effect. Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting.

EXAMPLES

General Methods

Families

[0060] All families provided written informed consent to participate in the study. The study protocol was approved by the institutional review board of giving institutions. All patients were clinically evaluated by neurologists.

Whole Exome and Sanger Sequencing

[0061] Whole exome sequencing was performed in index individuals from sporadic and recessive CMT and dHMN families. The SureSelect Human All Exon 50 MB Kit (Agilent) was used for in-solution enrichment, and the HiSeq 2500 instrument (Illumina) was used to produce about 120 bp paired-end sequence reads. The Burrows-Wheeler aligner, and Freebayes were used to align sequence reads and call variants. Final data were uploaded into GENESIS software for analysis. A filtering approach to search for families sharing the same homozygous variants were applied across all exomes in the database. Sanger sequencing, performed by Eurofins Genomics, confirmed segregation of the SORD variants. Polymerase chain reaction (PCR) was carried out in the Veriti Thermocycler (Applied Biosystem) and Platinum Taq (ThermoFisher) was used to amplify the regions containing the target mutations. The following primers were used to target specifically SORD and not SOR2P (FIG. 10).

Fibroblasts Culture

[0062] Fibroblasts were obtained from patients and cultured in Dulbecco's Modified Eagle Medium (ThermoFisher) supplemented with 10% fetal bovine serum (FBS), penicillin and streptomycin (Gibco). Cells were maintained in 5% CO₂ at 37° C. in a humidified incubator. Asynchronous cell cultures were grown to approximately 80% confluency and treated with epalrestat (100 μM), rani-

restat (10 μM) or DMSO for 72 hours. Media containing the drugs or DMSO were changed every 24 hours.

Western Blot

[0063] Fibroblasts were lysed in RIPA buffer (ThermoFisher) containing protease inhibitor (Roche) and sonicated for 5 minutes with the Bioruptor sonication device (Diagenode). Cell lysates were centrifuged at 13,000×g for 10 minutes at 4° C., and the supernatant was collected for protein quantification (Pierce BCA Protein Assay Kit). 30 μg of protein sample was mixed with Bolt LDS Sample Buffer and Sample Reducing Agent (ThermoFisher) and heated at 90° C. for 5 min. Samples were loaded on Bolt 4-12% Bis-Tris Plus mini-gel followed by transfer into a nitrocellulose membrane (Bio-Rad). Membrane was blocked with 5% non-fat milk and incubated with anti-SORD (ab189248, Abcam) antibody for 2 hours, washed with TBS containing 0.01% Tween 20 (Bio-Rad) and incubated with a secondary anti-rabbit antibody (Cell Signaling). Membrane was subsequently incubated with GAPDH primary antibody (Santa Cruz) and secondary anti-mouse antibody (Cell Signaling). Chemoluminescence detection was performed with the SuperSignal West Pico PLUS Chemiluminescent Substrate and imaged with the FluorChem E (ProteinSimple).

Sorbitol Measurement

[0064] Fibroblasts were collected and lysed as described in Western blot section in the absence of proteinase inhibitor. Sorbitol determination in human fibroblast lysates was performed in ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) (Waters Acquity UPLC & TQD mass spectrometer—Waters, Milford, Mass., USA). Fibroblasts were collected and lysed as described in Western blot section in the absence of proteinase inhibitor. Proteinase inhibitor contains high concentration mannitol, which is a sorbitol enantiomer, and can interfere with UPLC-MS/MS sorbitol determination. Lysate samples underwent protein precipitation with Acetonitrile (1:5), ten-time dilution with Acetonitrile-water (50/50) and clean up on Oasis HLB cartridges (10 mg/1 ml), before injection in UPLC (3 μL). UPLC conditions: column, BEH Amide 1.7 μm (2.1×100 mm) at 88° C., eluent A, Acetonitrile 90%-water 5%-Isopropanol 5%, eluent B, Acetonitrile 80%-water 20%, gradient elution 0 min., 100% A, 3.6 min. 100% B, flow rate, 0.45 ml/min. The retention time of sorbitol was 2.7 min. MS/MS conditions: interface, Electrospray interface in negative ion mode, Multiple Reaction Monitoring acquisition, m/z 180.9→88.9 (CV 24, CE 15).

[0065] For fasting sorbitol level testing, blood was collected after overnight fasting (last meal the evening before) in serum separator tubes. Samples were centrifuged at 500 g for 10 min. Serum was separated and frozen within an hour from blood collection. Sorbitol level was tested by UPLC using a method adapted from Li et al. *Biochem Biophys Res Commun.* 2009 October 2; 387(4):778-83. Conditions were as follows: column, BEH Amide 1.7 μm maintained at 25° C. (instead of 45° C.); eluent A, 10 mM ammonium acetate pH10; eluent B, Acetonitrile. Flow rate, 0.6 ml/min with the 20 same gradient. The retention time of Sorbitol was 6.0 min. MS/MS conditions were the same of fibroblast analysis. Serum samples underwent protein precipitation with cold Methanol (1:5), five time dilution with Acetonitrile-water (50/50) and clean up on Oasis HLB cartridges (10

mg/1 ml), before injection in UPLC (3 μ L). Calibration curve was done in serum in sorbitol concentration range 0.1-20 mg/L.

Drosophila Stocks and Genetics

[0066] Unless specified, all flies were kept on cornmeal-molasses-yeast medium at 25° C., 65% humidity, with 12 h light/12 h dark cycles. The following fly strains used in this study were obtained from Bloomington *Drosophila* Stock Center: *elav^{C155}-GAL4*, *GMR-GAL4*, *Sdh2^{MB01265}*, *UAS-Sdh1RNAi*, and *UAS-Sdh2RNAi*.

Drug Feeding

[0067] Epalrestat or ranirestat was dissolved in dimethyl sulfoxide (DMSO) to achieve a stock concentration of 10 mg/ml, and then mixed into 10 ml fly food at a final concentration of 80 μ g/ml. Equal amount of DMSO was mixed into the fly food as control. The vials were dried at room temperature for 12 h before feeding.

Drosophila Lifespan Assay and Negative Geotaxis Assay

[0068] For lifespan assay, 100 newly enclosed female flies of each group were collected and placed in vials of 20 individuals. Flies were transferred into new vials every 2 days and the number of dead flies was counted. Survival data was plotted using Kaplan-Meier plot and compared between groups using log-rank test. For negative geotaxis behavior assay, 10 age-matched female flies were placed in a vial marked with a black line drawn horizontally 8 cm above the bottom. Flies were given 60 min to fully recover from CO₂ anesthesia, and were gently tapped onto the bottom and given 10 s to climb. Flies that crossed the 8 cm line were counted. For each vial, this assay was repeated 10 times, and 10 independent vials of each group (a total 100 flies per group) were tested. To minimize observer-expectancy bias, this assay was performed with the examiner masked to the group assignment.

Drosophila Brain Dissection, Immunostaining, and Confocal Microscopy

[0069] Brain dissection and staining were carried out as previously described (Brazill et al., J Vis Exp. 2018; (138)). Briefly, fly brains were dissected in phosphate-buffered saline (PBS, pH 7.4), fixed in 4% formaldehyde for 10 min, and washed in PBTX (PBS containing 0.4% v/v Triton X-100) for 3 times (15 mins each). Brains were then incubated with primary mouse anti-BRP antibody (nc82, Developmental Studies Hybridoma Bank) at 1:250 dilution in 0.4% PBTX with 5% normal goat serum at 4° C. overnight with gentle shaking. After that, brains were incubated with Cy3-conjugated anti-mouse secondary antibody (Rockland) and Cy5-conjugated anti-HRP (Jackson ImmunoLab) at 1:250 dilution at 4° C. overnight with gentle shaking, followed by 4',6-diamidino-2-phenylindole (DAPI, 1:300, Invitrogen) staining at room temperature for 10 min. Samples were mounted on glass slides with VECTASHIELD Antifade Mounting Medium (Vector Laboratories Inc.). Fly brain slides were imaged using an Olympus IX81 confocal microscope with 60 $\times$ oil immersion objective lens with a scan speed of 8.0 μ s per pixel and spatial resolution of 1024 $\times$ 1024 pixels. Images were processed and analyzed using FluoView 10-ASW (Olympus).

[0070] Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting.

Example 1: Identification of DNA Variants in CMT Using GENESIS Analysis

[0071] Inherited neuropathies, including Charcot-Marie-Tooth disease (CMT), represent an umbrella concept for clinically and genetically heterogeneous conditions affecting the peripheral nerves. CMT is classified depending on conduction velocity as demyelinating (CMT1) and axonal (CMT2) types. Distal hereditary motor neuropathy (dHMN) represents a form of CMT2 in which the burden of disease falls predominantly or exclusively on motor nerves (Rossor, Tomaselli, and Reilly 2016). As opposed to CMT1, for which over 90% of cases have mutations in known genes, only 20 to 30% of CMT2 and distal HMN patients receive a genetic diagnosis (Fridman et al. 2015). Since up to 70% of CMT2 and dHMN cases are sporadic, it becomes more challenging to identify candidate pathogenic genes from single case whole exome and genomic sequences; therefore, large collective datasets are necessary. Using the data aggregation of over 1,100 CMT whole exome sequencing (WES) and whole genome sequencing (WGS) available at the GENESIS analysis platform provided the largest collection of such high quality data available (Gonzalez et al. 2015). Genes with significant DNA variants present in multiple families were identified, as well as individual alleles over-represented in CMT cases. When querying a subset of 598 undiagnosed CMT patients for recessive non-sense variants in genes shared by >3 families and with minor allele frequency in the gnomAD control database of <1%, 12 cases were identified from 11 unrelated families carrying a homozygous c.757delG; p.(Ala253GlnfsTer27) mutation in SORD. Four more cases from three unrelated families carried the heterozygous c.757delG; p.(Ala253GlnfsTer27) variant together with a second variant, c.298C>T; p.(Arg100Ter) in family 2 c.329G>C; p.(Arg110Pro) in family 3, and c.458C>A; p.(Ala153Asp) in II-1 and II-2 of family 14 (FIG. 1A-D and FIG. 5). All mutations represented loss-of-function (LOF) alleles except c.329G>C; p.(Arg110Pro). Interestingly, the Arg110Pro change is adjacent to the previously reported Tyr111Phe (corresponding to Tyr110Phe in rat), which was shown to abolish SORD enzymatic activity and destabilize the protein (Hellgren et al. 2007).

[0072] Interestingly, SORD has a non-functional highly homologous paralogue, the pseudogene SORD2P, which is thought to arise from the duplication of SORD within a 0.5 Mb region on chromosome 15 (Carr et al. 2016) (FIG. 1E). In order to specifically amplify SORD, but not SORD2P, in Sanger confirmation studies, primers were designed that took advantage of nucleotide sequence differences and distinct retrotransposon insertions in both genic regions (FIG. 5). Notably, the c.757delG; p.(Ala253GlnfsTer27) mutation in exon 7 of SORD is fixated in the pseudogene SORD2P in over 95% of control chromosomes, along with numerous additional exonic indel mutations, which prevent effective translation of SORD2P (1000 Genomes Project Consortium et al. 2015; Lek et al. 2016). Because of the high similarity of the regions, a nested PCR approach was necessary to obtain specific amplification of exon 7 of SORD and distinguish it from the homologous region in SORD2P. The presence of the variants detected by WES was confirmed by

Sanger sequencing in all cases and segregation data in immediate relative carriers was provided. (FIG. 1F and FIG. 5).

[0073] An independent set of 103 unresolved CMT2/dHMN cases WES at the (UCL Institute of Neurology in London (UK)) were screened. Nine cases from six unrelated families were identified carrying the homozygous c.757delG; p.(Ala253GlnfsTer27) mutation in SORD (8.7%). A third independent set of 297 recessive or sporadic CMT2/dHMN patients was screened by targeted Sanger sequencing of exon 7 of SORD, which was extended to the other coding exons if one c.757delG; p.(Ala253GlnfsTer27) was identified, and revealed 20 additional cases (7%) from 18 families with biallelic mutations in SORD: 16 cases with a homozygous c.757delG; p.(Ala253GlnfsTer27) mutation and four cases with c.757delG; p.(Ala253GlnfsTer27) in compound heterozygous state with a second likely pathogenic variant. The latter included c.964G>A; p.(Val322Ile) in family 29, a 275 bp deletion c.316_425+165del in exon 4 in family 30, a de novo c.28C>T; p.(Leu10Phe) in family 32, and c.895C>T; p.(Arg299Ter) in family 33. All changes have a minor allele frequency (MAF) of <0.0001 in gnomAD (Lek et al. 2016). The residues affected by missense mutations are highly conserved across multiple species (FIG. 1D) with GERP scores greater than 3. Further, biallelic non-sense variants in SORD were absent from 4,598 index cases affected by distinct neurological disorders other than CMT present in the GENESIS database.

[0074] The allelic carrier frequency of the c.757delG; p.(Ala253GlnfsTer27) variant in the normal population is 0.003% based on an allelic count of 94 out of 30,872 in gnomAD genomes (Lek et al. 2016). Of note, the gnomAD exome set detected the c.757delG; p.(Ala253GlnfsTer27) change at a significantly lower rate at MAF=0.00008, due to failure to pass random forest filters. GENESIS uses the FreeBayes software for variant calling (Gonzalez et al. 2015), which may have resulted in an allele frequency closer to the gnomAD genome based call set (MAF_{GENESIS}=0.002, 22 out of 9,196). Sanger sequencing of 600 healthy controls was performed, including 200 samples of European, 100 samples of Turkish and 200 samples of Middle Eastern origin, and identified three heterozygous, but no homozygous, c.757delG; p.(Ala253GlnfsTer27) alleles (MAF=0.0025). These calculations support an estimated prevalence of the homozygous c.757delG; p.(Ala253GlnfsTer27) allele alone of ~1/100,000 individuals, making it the most common individual pathogenic allele in axonal neuropathies and one of the most common alleles for any Mendelian disease.

[0075] Overall 45 individuals affected by hereditary neuropathy from 38 unrelated families were identified in the present study to carry biallelic mutations in SORD (FIGS. 11 and 12). Of note, 71% of cases were sporadic with no evidence of family history or consanguinity. The formal clinical diagnosis was axonal CMT in 51% (n=16), distal HMN in 40% (n=18), and intermediate CMT in 9% (n=4) of cases. The mean age of onset of the neuropathy was 17±8 years and walking difficulties was the most common complaint at onset. Delayed motoric development milestones were uncommon, but two thirds of the patients reported foot deformities, indicating that the neuropathy probably started earlier in life. At first examination all individuals had limb weakness, but only half showed sensory impairment. Weakness was mild in distal upper limbs and ranged from mild to near complete paralysis in the distal lower limbs. Proximal muscles of the upper and lower limbs were typically unaffected. Seven patients had upper limb tremor, four had mild scoliosis and two had mild hearing loss. One case had a

concurrent and likely unrelated syndromic disorder encompassing dysmorphic features, non-progressive mental retardation since the age of three years, and spastic ataxia with evidence of cerebellar atrophy at brain MRI. None of the patients had cataract nor involvement of other organs. According to the CMT neuropathy score, the neuropathy was mild in 67% (n=30), moderate in 31% (n=14) and severe in one case. 42% of patients (n=19) needed ankle-foot orthosis to sustain feet during walking, one patient required unilateral support and one patient was wheelchair dependent. Detailed nerve conduction studies were available in 42 patients and invariably showed a motor axonal neuropathy, with intermediate reduction of conduction velocities in 26% (n=11) and decreased sensory action potentials in 26% (n=65).

Example 2: Assessing SORD Protein Expression in Human Fibroblasts and SORD Levels in Blood

[0076] Sorbitol dehydrogenase is a homotetrameric enzyme of 38-kDa subunits, which is widely distributed in mammalian tissues (Johansson et al. 2001; Hellgren et al. 2007; Lindstad, Teigen, and Skjeldal 2013). It represents the second enzyme of the two-step polyol pathway, in which glucose is converted to sorbitol, a relatively non-metabolizable sugar, by the enzyme aldose reductase (AR). Sorbitol is then oxidized to fructose by SORD (FIG. 2A). To gather further insights into the functional consequences of recessive mutations in SORD, next SORD expression was assessed in fibroblasts from five unrelated affected individuals with homozygous c.757delG; p.(Ala253GlnfsTer27) (n=4) or c.757delG; p.(Ala253GlnfsTer27) & c.895C>T; p.(Arg299Ter) (n=1) variants as well as two unaffected carriers of c.757delG; p.(Ala253GlnfsTer27) in heterozygous state. SORD protein was absent in all patients and the wild-type levels were reduced in unaffected carriers compared to controls (FIG. 2B). Accordingly, intracellular sorbitol concentrations were over 10 times higher in patients' fibroblasts compared to controls, in keeping with a loss of SORD enzymatic activity (FIG. 2C). Fasting sorbitol levels in serum from ten patients carrying the homozygous p.Ala253GlnfsTer27 mutation and ten unrelated controls and found it was over 100 times higher (14.82±0.780 vs 0.046±0.004 mg/L, p<0.0001) was determined, confirming the lack of SORD enzymatic activity in patients (FIG. 13). This study also demonstrates that sorbitol is a useful marker for detecting or characterizing inherited neuropathy associated with SORD mutation in a mammalian subject.

Example 3: Investigating the SORD Mutation in Models of SORD Deficiency

[0077] To further explore the pathophysiology of SORD mutation in vivo, *Drosophila melanogaster* models of SORD deficiency were established. *Drosophila* has two functional SORD genes (Sodh1 and Sodh2) that share 90% residue identity (Luque et al. 1998). SORD is conserved across distant phyla and *Drosophila* Sodh1 (NP_001287203.1) and Sodh2 (NCBI Reference Sequence: NP_524311.1) encoded proteins share 75% and 73% identity with human SORD protein (NCBI Reference Sequence: NP_003095.2 (SEQ ID NO: 46)), respectively. A mutant allele of Sodh2 was obtained where the gene is disrupted by a transposon Minos mediated integration cassette (MiMIC) insertion (Sodh2^{MB01265}) (Bellen et al. 2011). Homozygous Sodh2 (Sodh2^{MB01265/MB01265}) mutants are viable with normal life span. To characterize neurodegenerative phenotypes, the *Drosophila* visual system was used to take advantage of the

highly organized parallel axons of the compound eye that allow in vivo detection of subtle neuronal and synaptic pathological changes (Bausenwein, Dittrich, and Fischbach 1992). Axons of the outer photoreceptor axons traverse the lamina cortex and make synaptic connections with lamina monopolar neurons in the lamina layer (FIG. 3A). In the control flies (yw) at 2 days after eclosion (DAE), the organized lamina cartridges of photoreceptor synapses can be visualized in the xy- and xz-planes, respectively (FIG. 3B). A loss of photoreceptor terminals in the lamina layer of *Sodh2*^{MB01265/MB01265} mutants was observed at 2 days after eclosion (DAE) (FIG. 3C). The phenotype became progressively severe at 10 DAE, with vacuoles being more numerous and larger in size distributed across the synaptic lamina layer (FIG. 3C, D). These vacuoles exhibited a loss of neuronal membrane (marked by HRP labelling), as well as a reduced Bruchpilot (BRP, a synaptic active zone cytomatrix protein) labelling, indicating synaptic degeneration (FIG. 3C, D). To validate the findings described herein, a second SORD model was generated by specific knockdown of both *Sodh1* and *Sodh2* expression in neurons using a pan-neuronal driver *elav*^{C155}. Loss of both *Sodh1* and *Sodh2* resulted in age-dependent synapse degeneration, similar to that of homozygous *Sodh2* (*Sodh2*^{MB01265/MB01265}) (FIG. 6). The behavioral phenotypes of SORD deficiency the *Sodh2*^{MB01265/MB01265} homozygous flies with a systemic loss of function in *Sodh2* were characterized and although these flies exhibited a normal life-span, their locomotor activity was significantly compromised at a late-stage (40 DAE) (FIG. 3E, F). This indicated a progressive, age-dependent neuromuscular dysfunction reminiscent of hereditary neuropathies. Moreover, the sorbitol levels were measured in fly heads at 10 DAE and observed a significant increase in the *Sodh2*^{MB01265/MB01265} model (FIG. 4B), consistent with the observation in patient fibroblasts. Taken together, *Drosophila* models of SORD deficiency were successfully established that recapitulate typical pathological phenotypes in human patients, including (1) a normal lifespan, (2) progressive and age-dependent synaptic degeneration and locomotor deficiency, and (3) increased sorbitol levels.

[0078] After establishing loss-of-function as the mechanism of action and a known enzymatic pathway, treatment options for SORD associated hereditary neuropathy were investigated. It had previously been shown that the pharmacological inhibition of aldose reductase, the enzyme upstream of SORD, represents a successful strategy to reduce toxic sorbitol accumulation in cellular and animal model of diabetes (Kikkawa et al. 1983; Matsumoto et al. 2008; Ramirez and Borja 2008; Hao et al. 2015; Grewal et al. 2016) and, arguably, also humans (Chalk, Benstead, and Moore 2007; Polydefkis et al. 2015; Sekiguchi et al. 2019). The effect of two commercially available aldose reductase inhibitors (ARI), Epalrestat and Ranirestat, were tested on intracellular sorbitol accumulation in patient fibroblasts lacking functional SORD. Patient and control fibroblasts were grown for 72 hrs in the presence or absence of Epalrestat (100 μ M) or Ranirestat (10 μ M) and intracellular sorbitol levels were measured thereafter. Both ARI, Epalrestat and Ranirestat, achieved a significant reduction of sorbitol to a level comparable to controls (FIG. 4A). Further, *Drosophila* models of SORD were fed with Epalrestat and Ranirestat starting at 2 DAE. A significant reduction of sorbitol level was observed in the *Sodh2*^{MB01265/MB01265} fly heads at 10 DAE (FIG. 4B). Importantly, the locomotor activities of *Sodh2*^{MB01265/MB01265} flies and flies with neuronal specific knockdown of both *Sodh1* and *Sodh2* were

rescued to the levels of yw control flies (FIG. 4C, FIG. 7). Furthermore, Epalrestat or Ranirestat feeding restored the age-dependent synaptic defects in *Sodh2*^{MB01265/MB01265} mutant flies. In DMSO vehicle treated flies, the loss of synaptic termini was highly prominent in the advanced age of 40 DAE where the expansion of neighboring vacuoles resulted in fused, much larger vacuoles encompassing multiple synaptic cartridges (FIG. 4D). Remarkably, epalrestat/ranirestat feeding reduced the number of vacuoles and restored the localization of synaptic cytomatrix protein BRP at both 10 and 40 DAE (FIG. 4E-G).

[0079] In summary, SORD represents a novel recessive gene causing axonal/intermediate, motor predominant CMT. Genetic data from the cohort as well as from control databases suggest that the predominant pathogenic variant in SORD, c.757delG; p.(Ala253GlnfsTer27), with a carrier frequency in of ~3/1,000 individuals in the population, may represent one of the most common specific alleles causing a recessive Mendelian disease. Indeed, with a frequency in undiagnosed CMT2 and dHMN cases of up to ~10%, it will likely account for a significant portion of the diagnostic gap in inherited axonal neuropathies. It is intriguing that, despite their frequency, mutations in SORD were not identified as a cause of CMT by previous studies. The presence of the human SORD2P gene duplication may have hampered the detection of variants in the functional SORD, since available annotation programs are highly dependent on the unique mapping of 150-300 bp long reads generated by current next-generation sequencing technologies. Other known pathogenic variants have previously been shown to be concealed by the presence of pseudogenes (De Vos et al. 2004). The pathogenicity of SORD mutations is further supported by in vitro data in patient-derived fibroblasts, which showed absent SORD protein and intracellular sorbitol accumulation. Two in vivo *Drosophila* models recapitulated the human phenotype with progressive synaptic degeneration and motor impairment, SORD deficiency, and in increased sorbitol levels.

[0080] The studies described herein demonstrate that enzymatic loss-of-function and subsequent sorbitol accumulation is a mechanism of action for SORD associated CMT. Previous studies in cellular and animal models of diabetes have shown that an increased polyol influx with intracellular sorbitol accumulation is paralleled by an increase in cellular osmolarity, oxidative stress and decreased NADPH levels, which can all have a detrimental effects on peripheral nerves (Schmidt et al. 2001; Obrosova 2005; Sango et al. 2006). However, previous studies on adult C57BL/LiA mice expressing reduced level of SORD protein due to an intronic splicing mutation did not identify overt neurological defects (Holmes, Duley, and Hilgers 1982; Lee, Chung, and Chung 1995; Ng et al. 1998). Based on patient clinical data and the late-onset phenotype in flies, it will be important to extend the observation to aging C57BL/LiA mice or create complete knock-out SORD mouse or rat models. The study further unravels a central role of the polyol pathway in peripheral nerve metabolism and survival in normoglycemic conditions. Although the mechanism by which intracellular sorbitol accumulation can lead to selective degeneration of peripheral nerves is yet unknown, the observation of increased sorbitol levels in patient derived cells in this study has promising implications, both as a biomarker of the disease and as a target of future therapeutic interventions, including methods for substrate reduction, gene replacement or correction, and SORD enzyme substitution. Accordingly, disclosed herein are preclinical studies demonstrating the beneficial effects of substrate reduction via ARI application

in human derived cells and *Drosophila* models. Epalrestat is currently marketed in few countries for the treatment of diabetic complications (Grewal et al. 2016) while Ranirestat has been advanced into late stages of clinical trials (Polydefkis et al. 2015; Sekiguchi et al. 2019).

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<210> SEQ ID NO 554
<211> LENGTH: 7
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<400> SEQUENCE: 554

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<210> SEQ ID NO 555
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<400> SEQUENCE: 555

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<210> SEQ ID NO 557
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- 1-10. (canceled)
11. A method for treating inherited neuropathy in a mammalian subject, comprising administering to the subject an effective amount of an inhibitor of aldose reductase.
12. The method of claim 11, wherein the inhibitor of aldose reductase is selected from the group consisting of Alrestatin, Epalrestat, Diepalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, Salfredin B11, Sorbinil, Tolrestat, Zenarestat, and Zopolrestat.
13. The method of claim 11, wherein the inhibitor of aldose reductase is Epalrestat.
14. The method of claim 11, wherein the inhibitor of aldose reductase is Zopolrestat.
15. The method of claim 11, wherein the inhibitor of aldose reductase is Ranirestat.
16. the method of claim 11, wherein the subject has neuropathy associated with a mutation in the sorbitol dehydrogenase (SORD) gene.
17. The method of claim 11, wherein the subject has a mutation in the sorbitol dehydrogenase (SORD) gene selected from the group consisting of c.753delG;

- p.Ala253GlnfsTer27, c.329G>C; p.Arg110Pro, c.298C>T; p.Arg100Ter, or c.458C>A; p.Ala153Asp.
18. The method of claim 11, wherein the subject has a mutation in the sorbitol dehydrogenase (SORD) gene selected from the group consisting of c.757delG; p.Ala253GlnfsTer27, c.28C>T; p.Leu10Phe, c.316_425+165del; p.Cys106Ter, c.295C>T; p.Arg299Ter, c.964G>A; p.Val322Ile; a deletion of individual or multiple coding exons; a deletion of the entire SORD gene.
19. The method of claim 11, wherein the effective amount of an aldose reductase inhibitor reduces the level of intracellular sorbitol in the subject.
20. The method of claim 11, further comprising detecting a mutation in the sorbitol dehydrogenase gene of the subject.
21. The method of claim 11, further comprising measuring the level of sorbitol in a subject, wherein a sorbitol level of greater than about 10 g/L indicates that the subject has neuropathy associated with a mutation in the sorbitol dehydrogenase (SORD) gene.
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