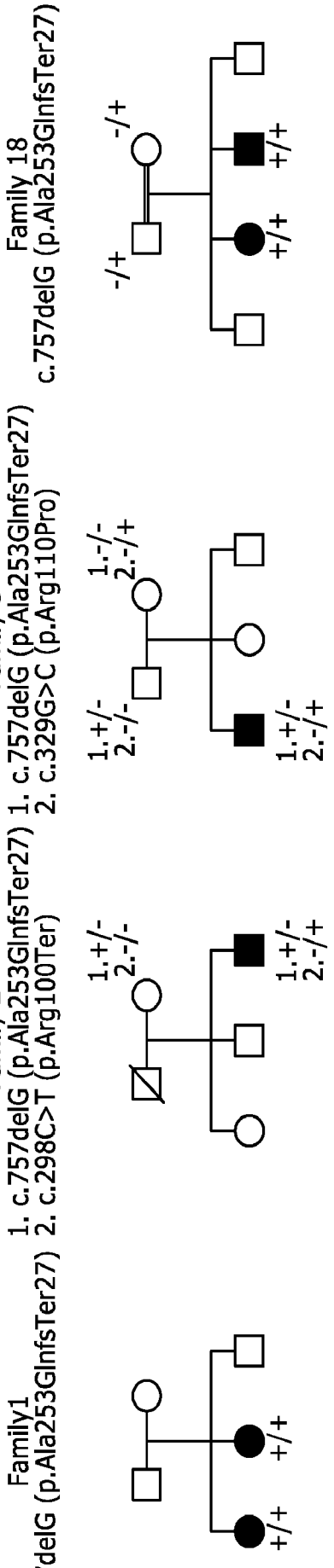

Family1
c.757delG (p.Ala253GlnfsTer27)
+/+
+/+
Family 2
1. c.757delG (p.Ala253GlnfsTer27)
2. c.298C>T (p.Arg100Ter)
1.+/-
2.-/-
1.+/-
2.-/+
Family 3
1. c.757delG (p.Ala253GlnfsTer27)
2. c.329G>C (p.Arg110Pro)
1.+/-
2.-/-
1.-/-
2.-/+
1.+/-
2.-/+
Family 18
c.757delG (p.Ala253GlnfsTer27)
-/+
-/+
+/+
+/+

FIG. 1A

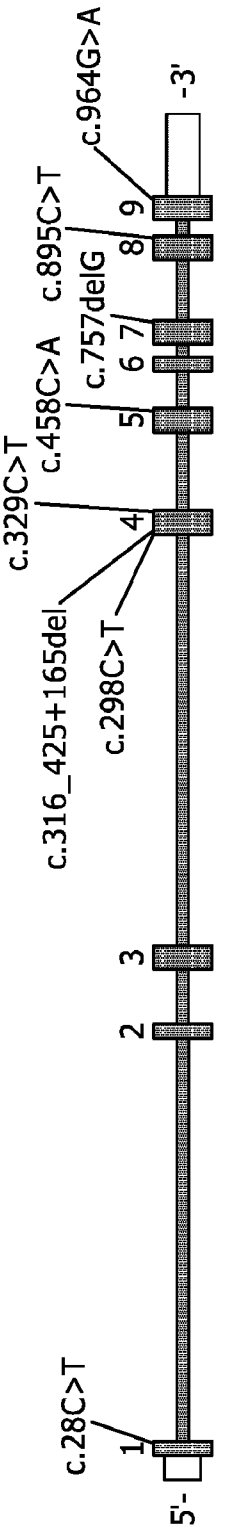

c.28C>T
1
5'-
2
3
c.316_425+165del
c.329C>T
c.298C>T
4
c.458C>A
5
c.757delG
6 7
c.895C>T
8
c.964G>A
9
-3'

FIG. 1B

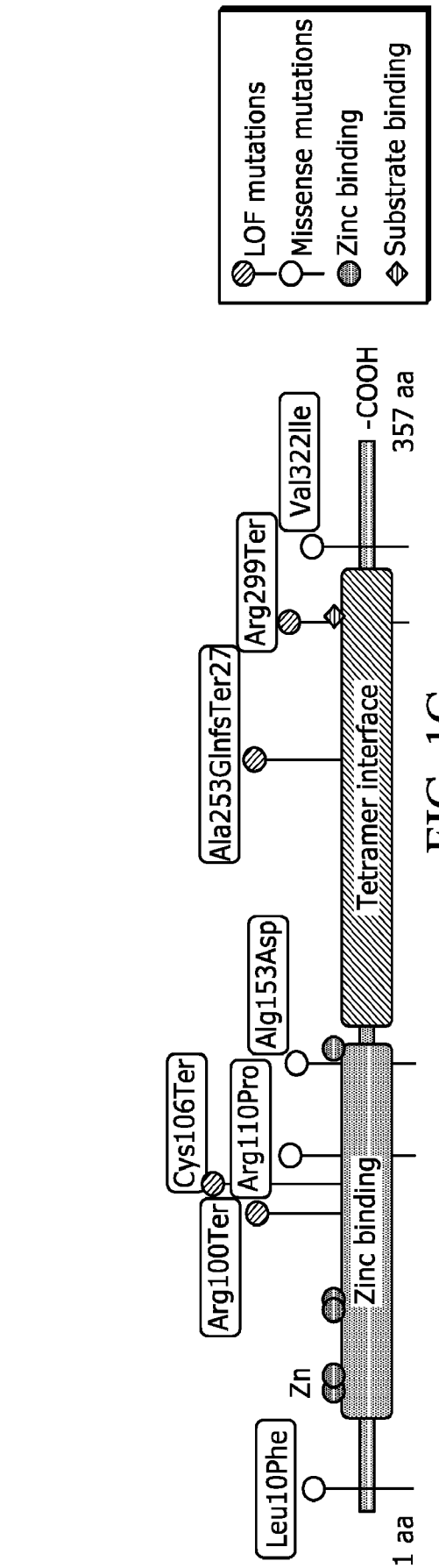

LOF mutations
Missense mutations
Zinc binding
Substrate binding
Leu10Phe
Zn
Arg100Ter
Cys106Ter
Arg110Pro
Alg153Asp
Ala253GlnfsTer27
Arg299Ter
Val322Ile
Zinc binding
Tetramer interface
1 aa
-COOH
357 aa

FIG. 1C

Humans P K N L S L V
Rhesus P K N L S L V
Mouse G E N L S L V
Dog A E N L T L V
Drosophila K D N L T A V
K M G R Y N L
K S G R Y N L
K I G R Y N L
K I G R Y N L
K Q G R Y N L
E E G A L I E
E E G A L I E
E E G A L I E
E E G A L I E
E E G A L L E
K P L V T H R
K P L V T H R
K P L V T H R
K P L V T H R
K R L V T H H
SEQ ID NO:537
SEQ ID NO:538
SEQ ID NO:539
SEQ ID NO:540
SEQ ID NO:541

FIG. 1D

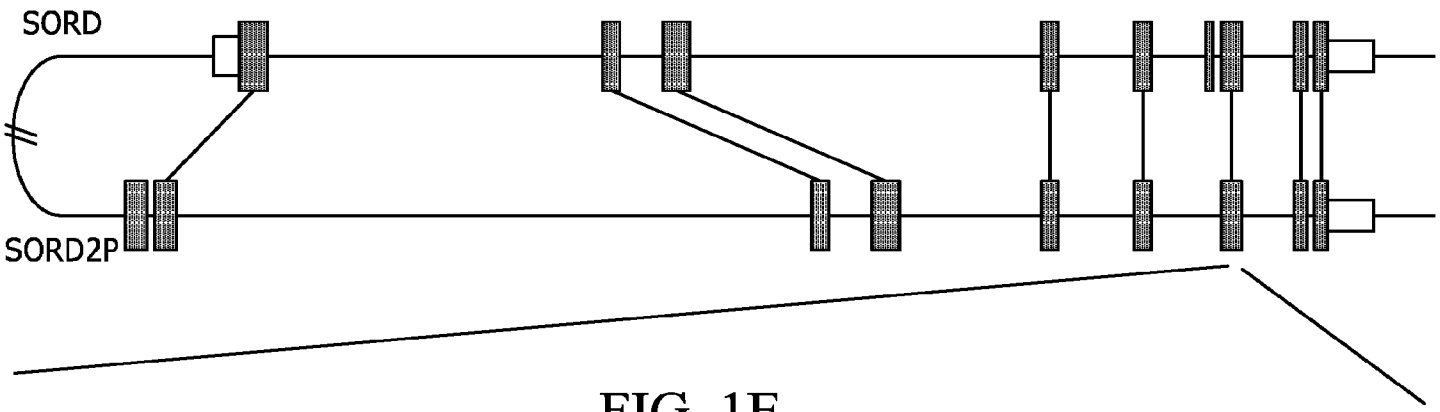


FIG. 1E

ORD exon 7 GTAGATGCCCGCCTGGATGGAGGCCTCTGCCCCCGTGCACTCGATGGTGACTTCCGGCTTGCACCCCAGCTGA
SEQ ID NO:43

_ORD2P exon 7 GTAGATGCCTGCCTGGATGGAGGCCTCTG-CCCCGTGCACTCGATGGTGACTTCCGGCTTGCACCCCAGCAGA
SEQ ID NO:44

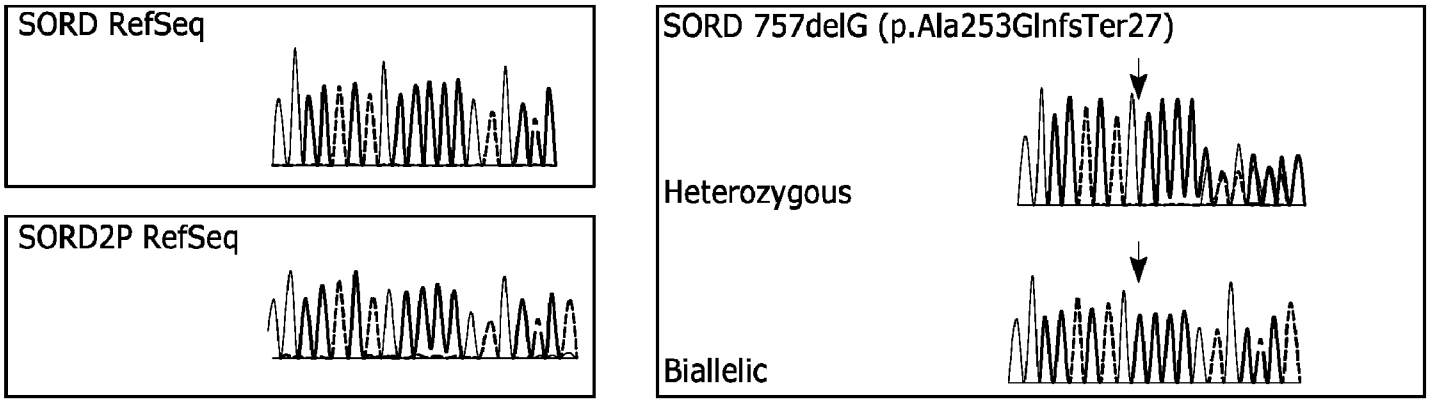


FIG. 1F

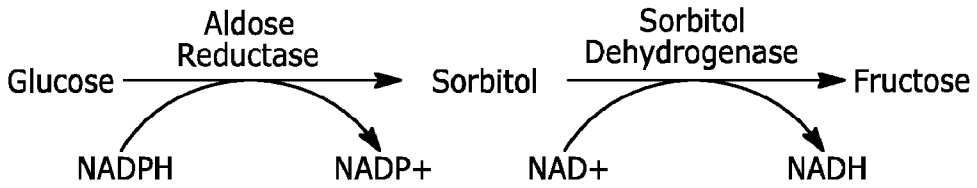


FIG. 2A

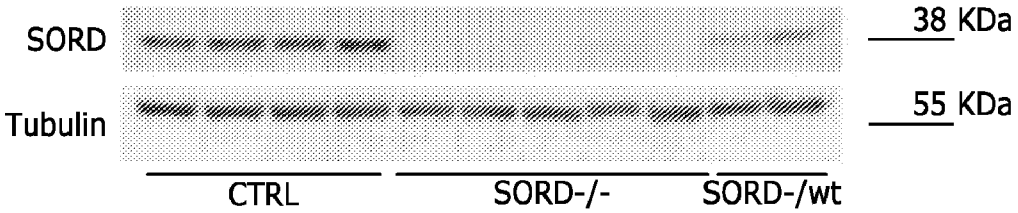
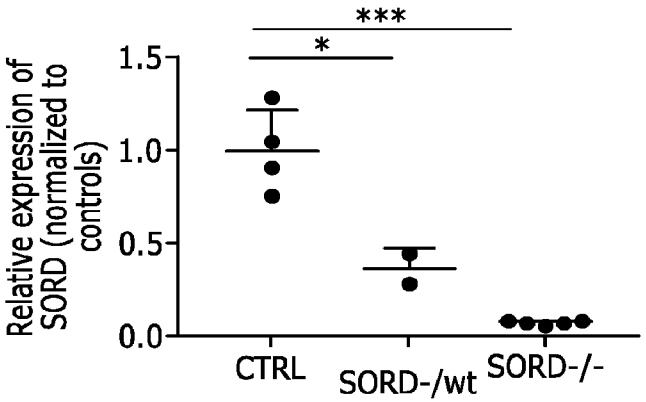


FIG. 2B



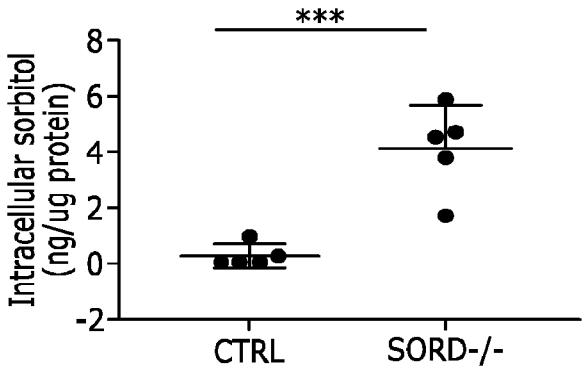


FIG. 2C

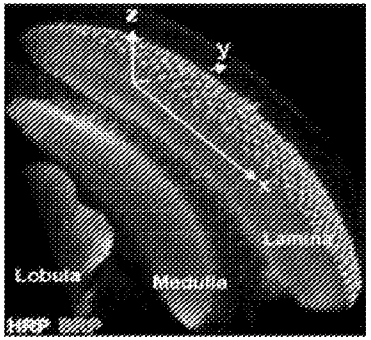
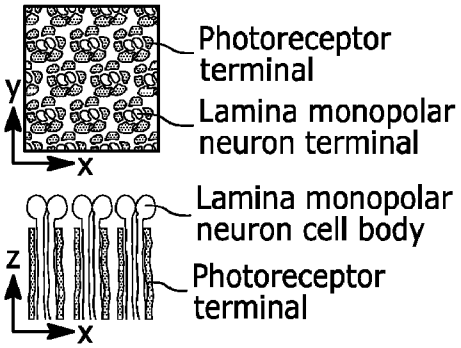


FIG. 3A



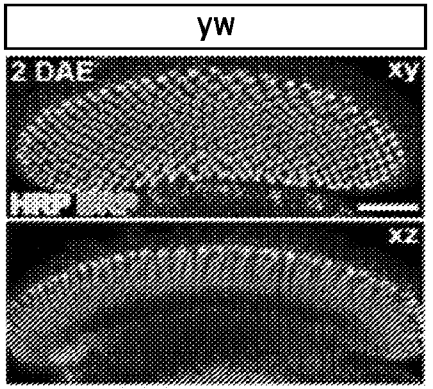


FIG. 3B

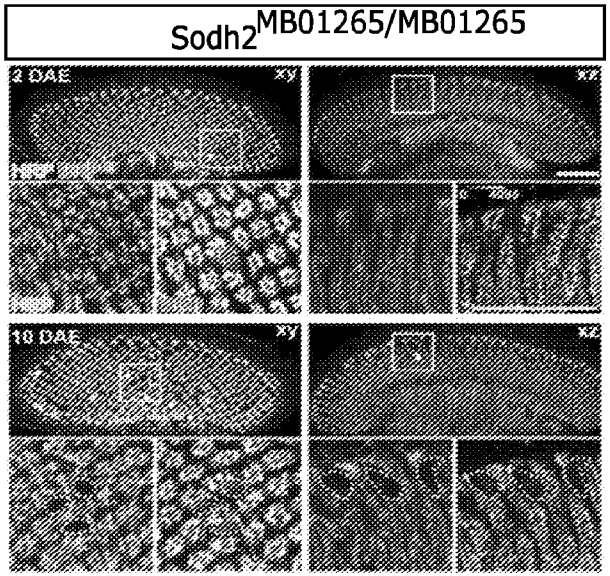


FIG. 3C

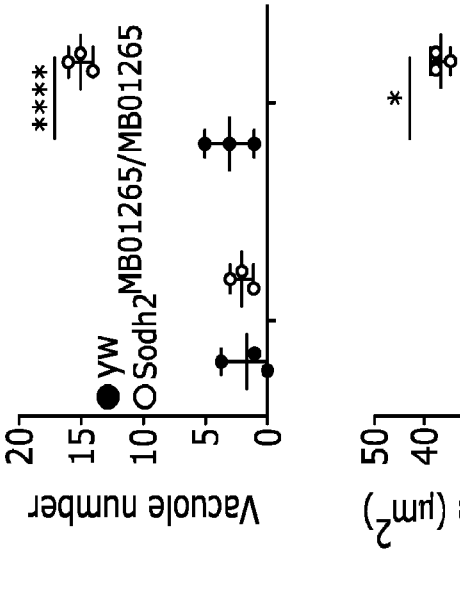


FIG. 3D

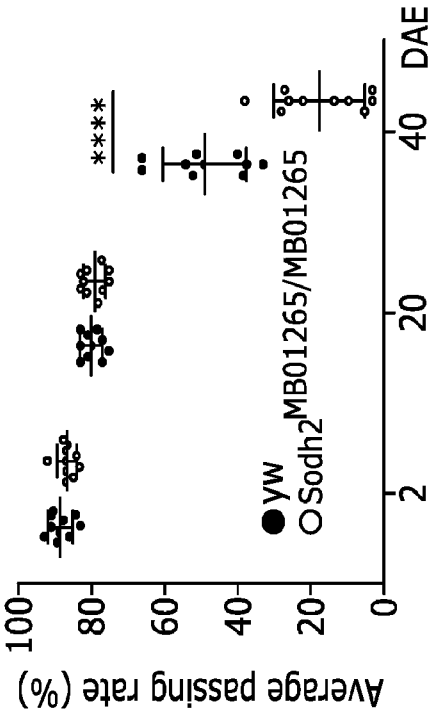


FIG. 3E

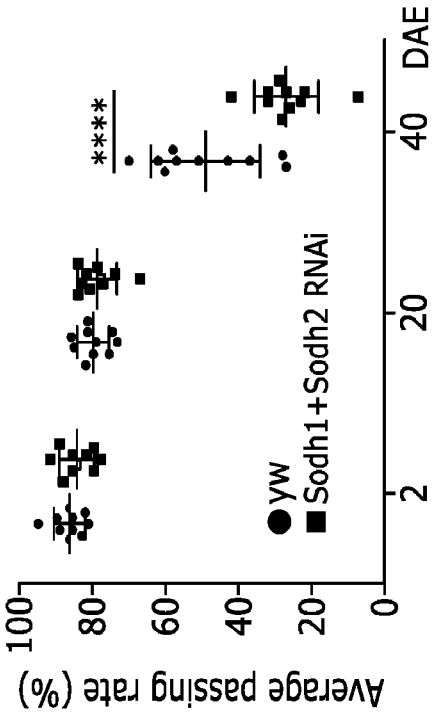


FIG. 3F

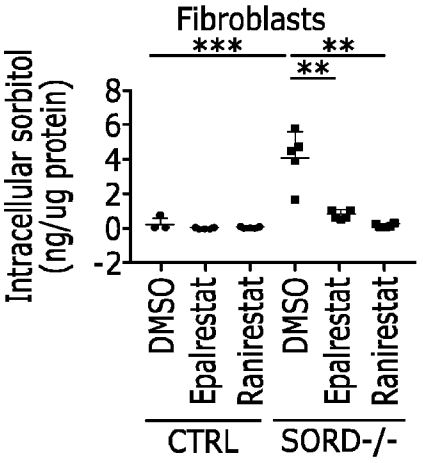


FIG. 4A

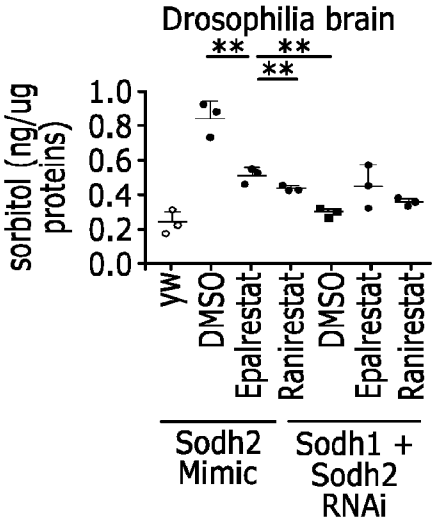


FIG. 4B

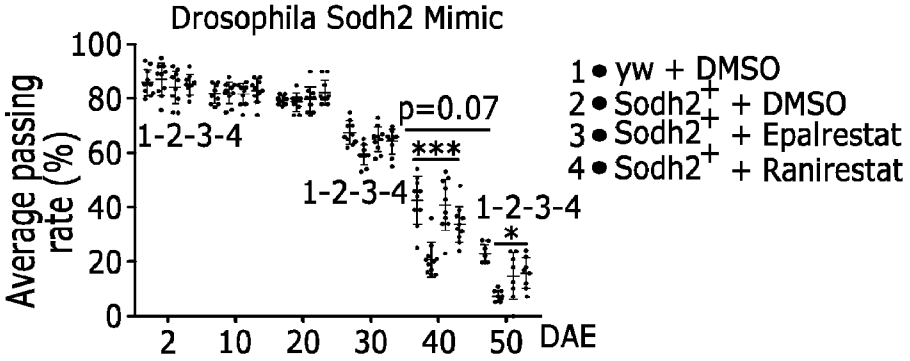


FIG. 4C

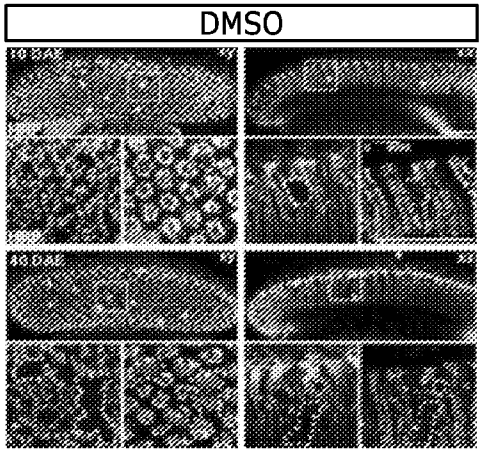


FIG. 4D

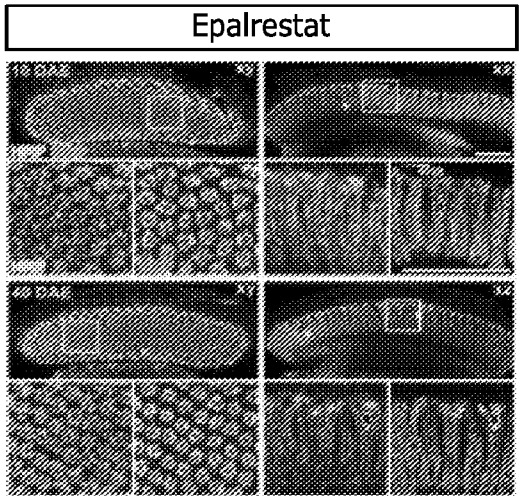


FIG. 4E

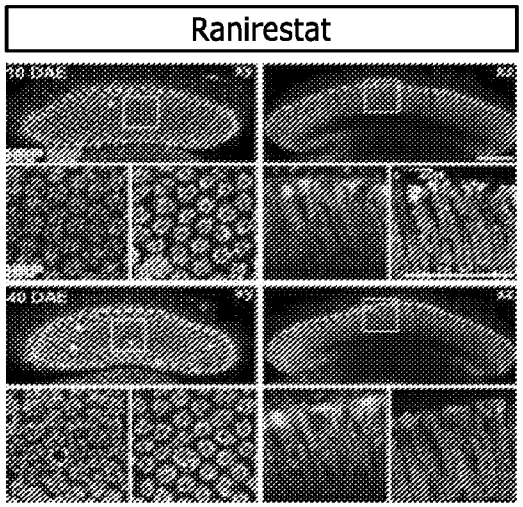


FIG. 4F

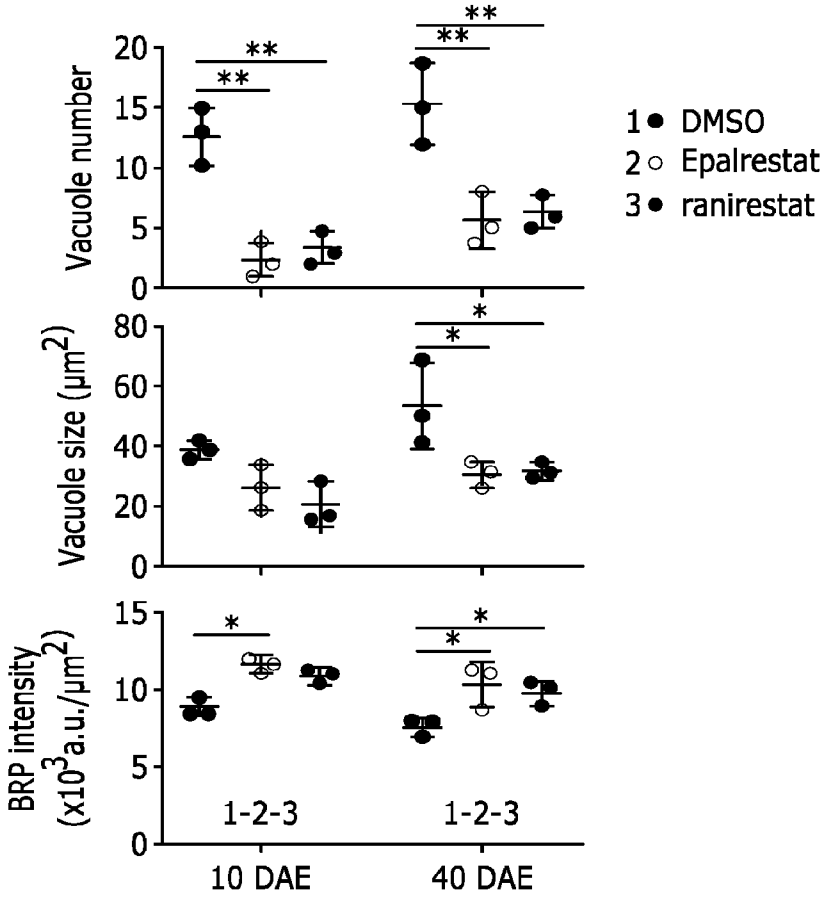


FIG. 4G

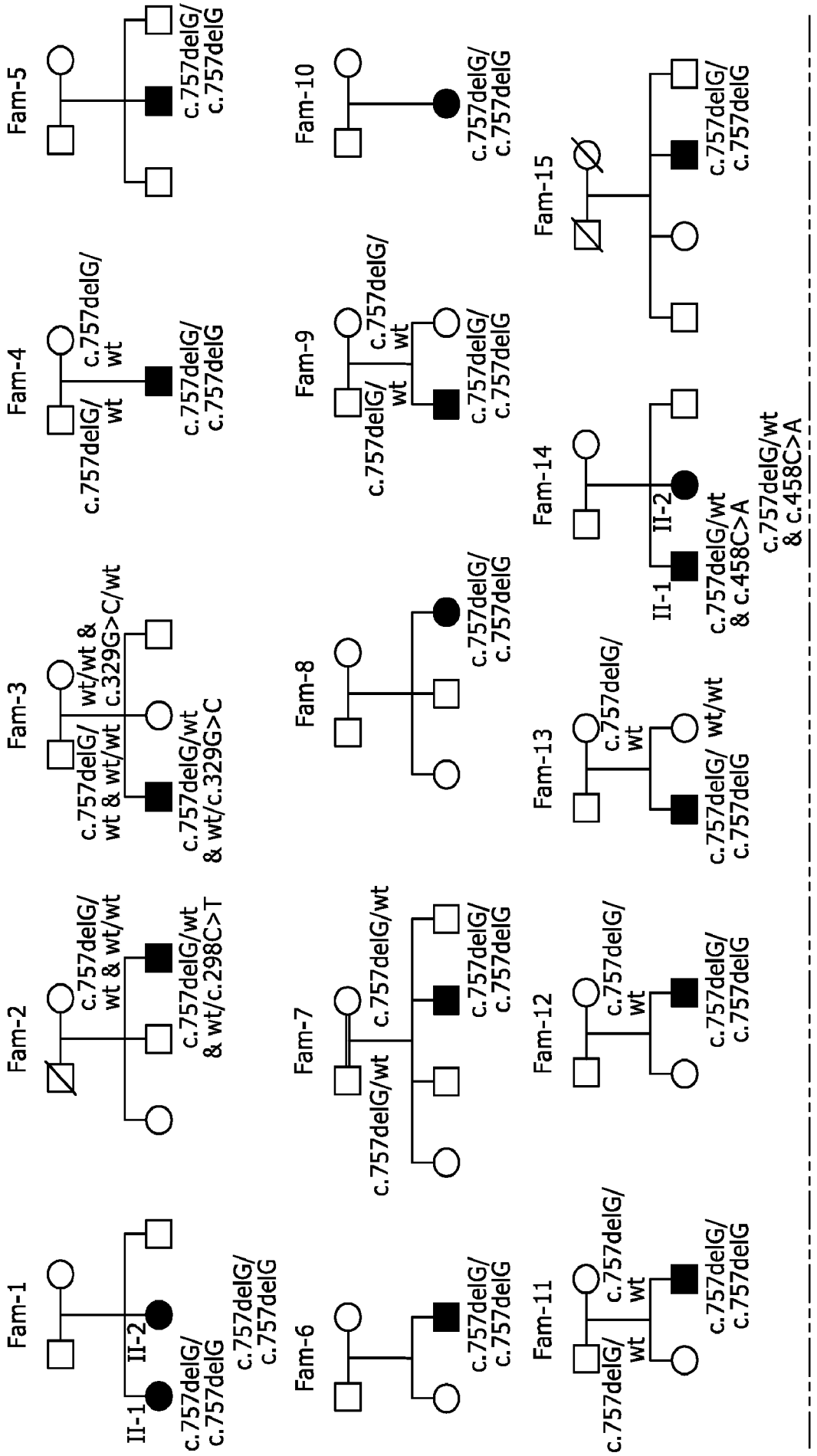

Fam-1
II-1
II-2
c.757delG/
c.757delG
c.757delG/
c.757delG
Fam-2
c.757delG/
wt & wt/wt
c.757delG/wt
& wt/c.298C>T
Fam-3
c.757delG/
wt & wt/wt
wt/wt &
c.329G>C/wt
c.757delG/wt
& wt/c.329G>C
Fam-4
c.757delG/
wt
c.757delG/
wt
c.757delG/
c.757delG
Fam-5
c.757delG/
c.757delG
Fam-6
c.757delG/
c.757delG
Fam-7
c.757delG/wt
c.757delG/wt
c.757delG/
c.757delG
Fam-8
c.757delG/
c.757delG
Fam-9
c.757delG/
wt
c.757delG/
wt
c.757delG/
c.757delG
Fam-10
c.757delG/
c.757delG
Fam-11
c.757delG/
wt
c.757delG/
wt
c.757delG/
c.757delG
Fam-12
c.757delG/
wt
c.757delG/
c.757delG
Fam-13
c.757delG/
wt
c.757delG/
c.757delG
wt/wt
Fam-14
II-1
II-2
c.757delG/wt
& c.458C>A
c.757delG/wt
& c.458C>A
Fam-15
c.757delG/
c.757delG

FIG. 5

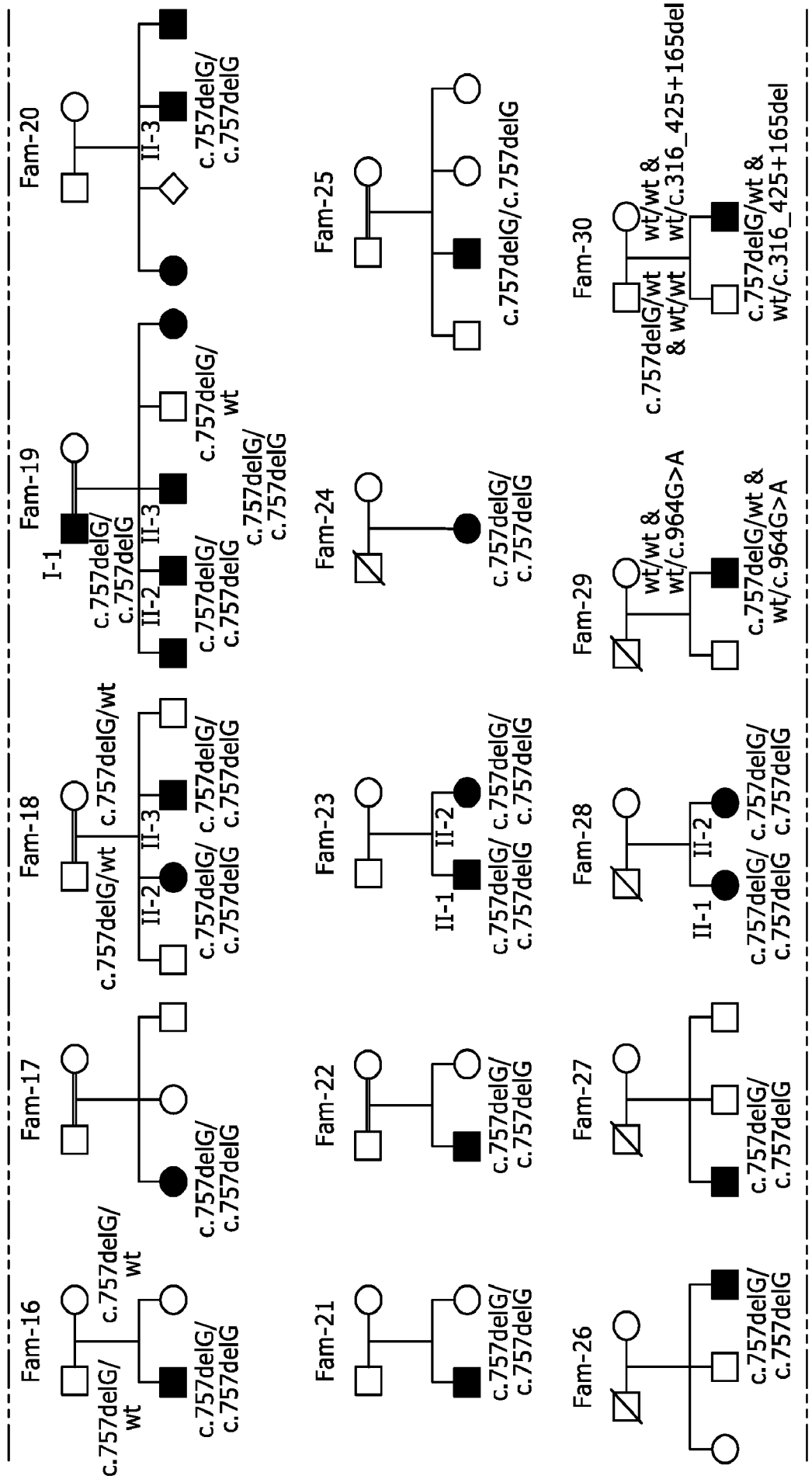

Fam-16
c.757delG/
wt
c.757delG/
wt
c.757delG/
c.757delG
Fam-17
c.757delG/
c.757delG
Fam-18
c.757delG/wt
c.757delG/wt
II-2
II-3
c.757delG/
c.757delG
c.757delG/
c.757delG
Fam-19
I-1
c.757delG/
c.757delG
II-2
II-3
c.757delG/
c.757delG
c.757delG/
wt
c.757delG/
c.757delG
Fam-20
II-3
c.757delG/
c.757delG
Fam-21
c.757delG/
c.757delG
Fam-22
c.757delG/
c.757delG
Fam-23
II-1
II-2
c.757delG/
c.757delG
c.757delG/
c.757delG
Fam-24
c.757delG/
c.757delG
Fam-25
c.757delG/c.757delG
Fam-26
c.757delG/
c.757delG
Fam-27
c.757delG/
c.757delG
Fam-28
II-1
II-2
c.757delG/
c.757delG
c.757delG/
c.757delG
Fam-29
wt/wt &
wt/c.964G>A
c.757delG/wt &
wt/c.964G>A
Fam-30
c.757delG/wt
& wt/wt
wt/wt &
wt/c.316_425+165del
c.757delG/wt &
wt/c.316_425+165del

FIG. 5CONT.

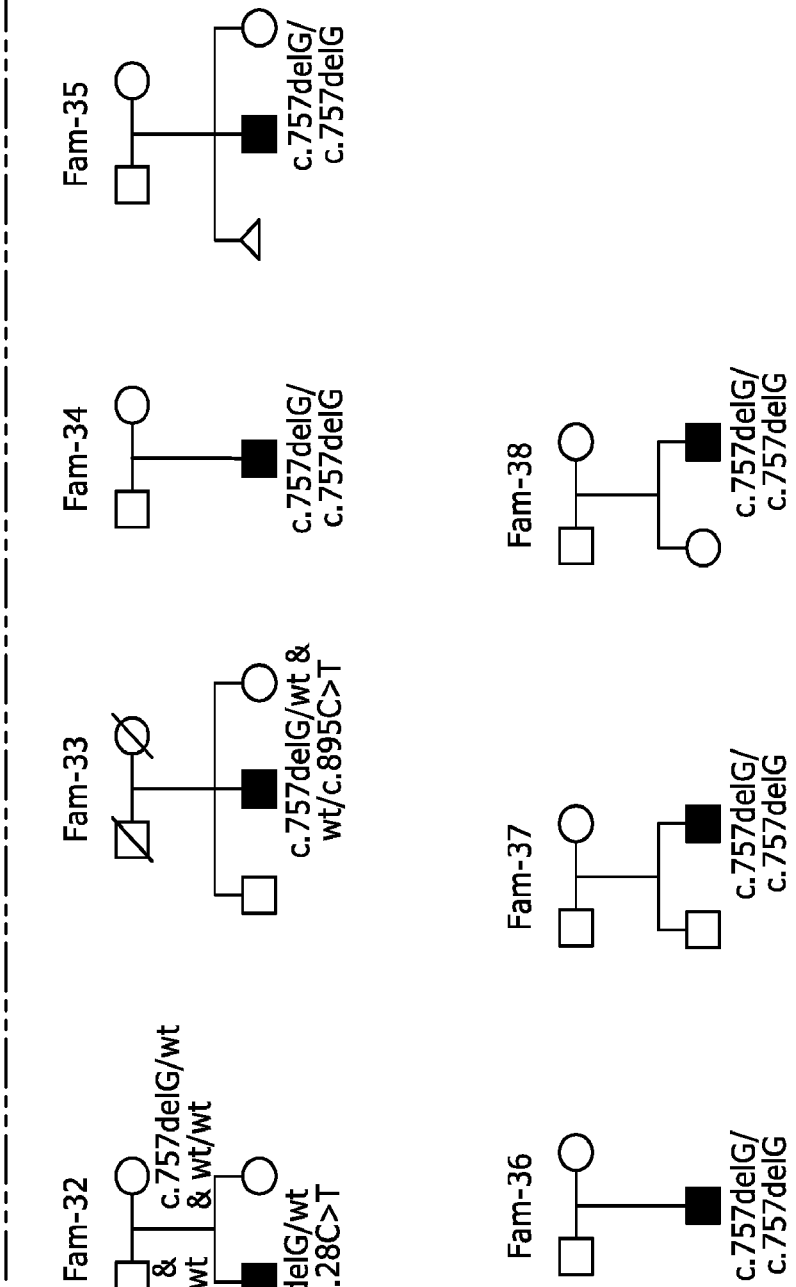

Fam-31
c.757delG/
c.757delG
Fam-32
wt/wt &
wt/wt
c.757delG/wt
& wt/wt
c.757delG/wt
& wt/c.28C>T
Fam-33
c.757delG/wt &
wt/c.895C>T
Fam-34
c.757delG/
c.757delG
Fam-35
c.757delG/
c.757delG
Fam-36
c.757delG/
c.757delG
Fam-37
c.757delG/
c.757delG
Fam-38
c.757delG/
c.757delG

FIG. 5CONT.

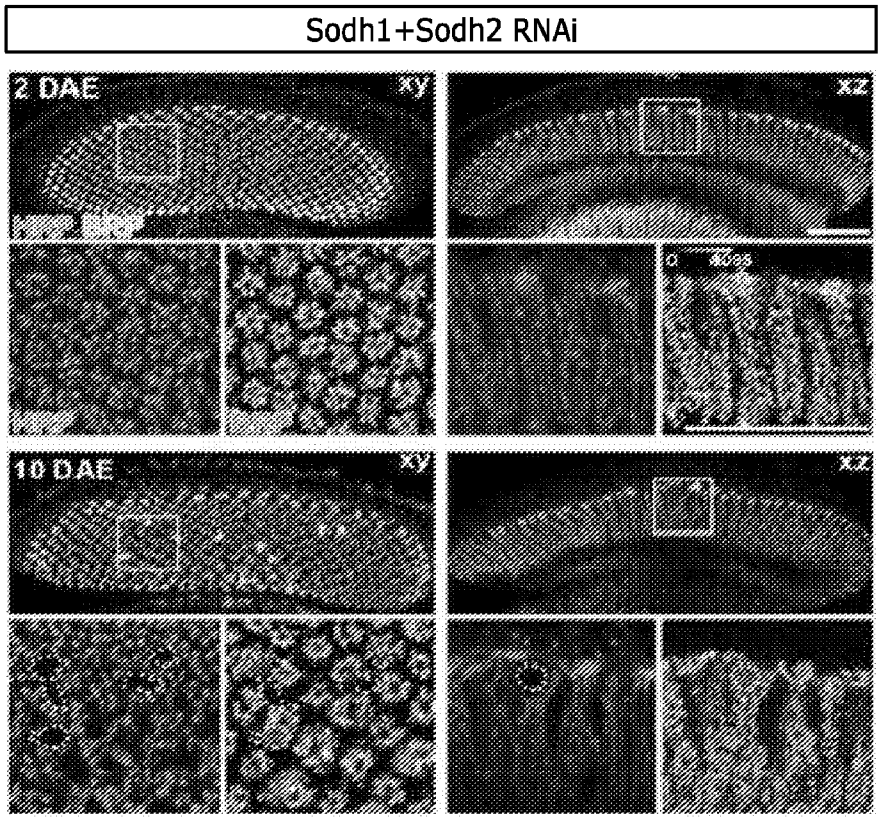

Sodh1+Sodh2 RNAi
2 DAE
xy
xz
10 DAE
xy
xz

FIG. 6A

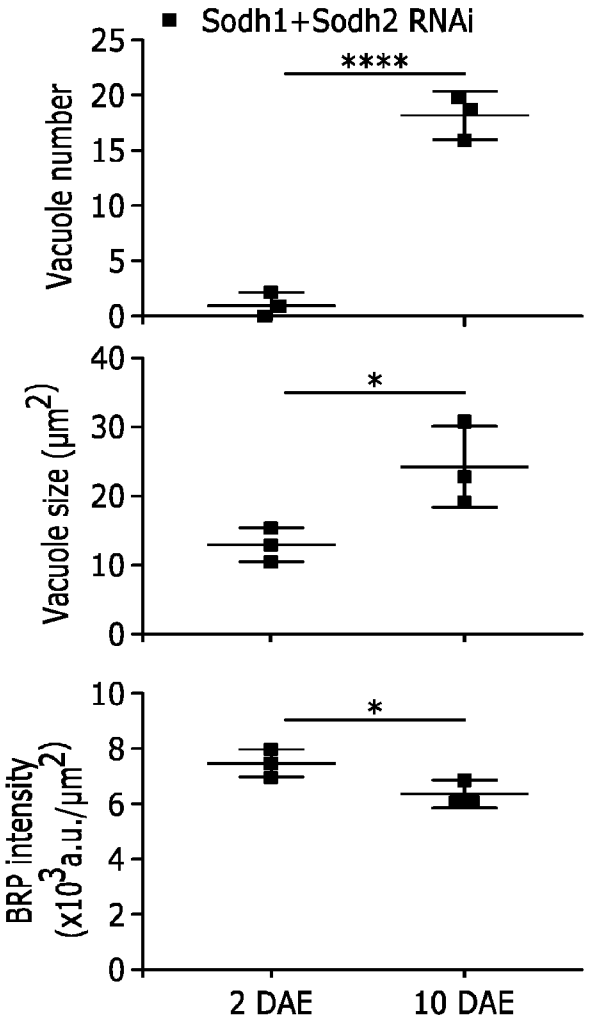

Sodh1+Sodh2 RNAi
Vacuole number
****
Vacuole size (μm2)
*
BRP intensity (x10³a.u./μm2)
*
2 DAE
10 DAE

FIG. 6B

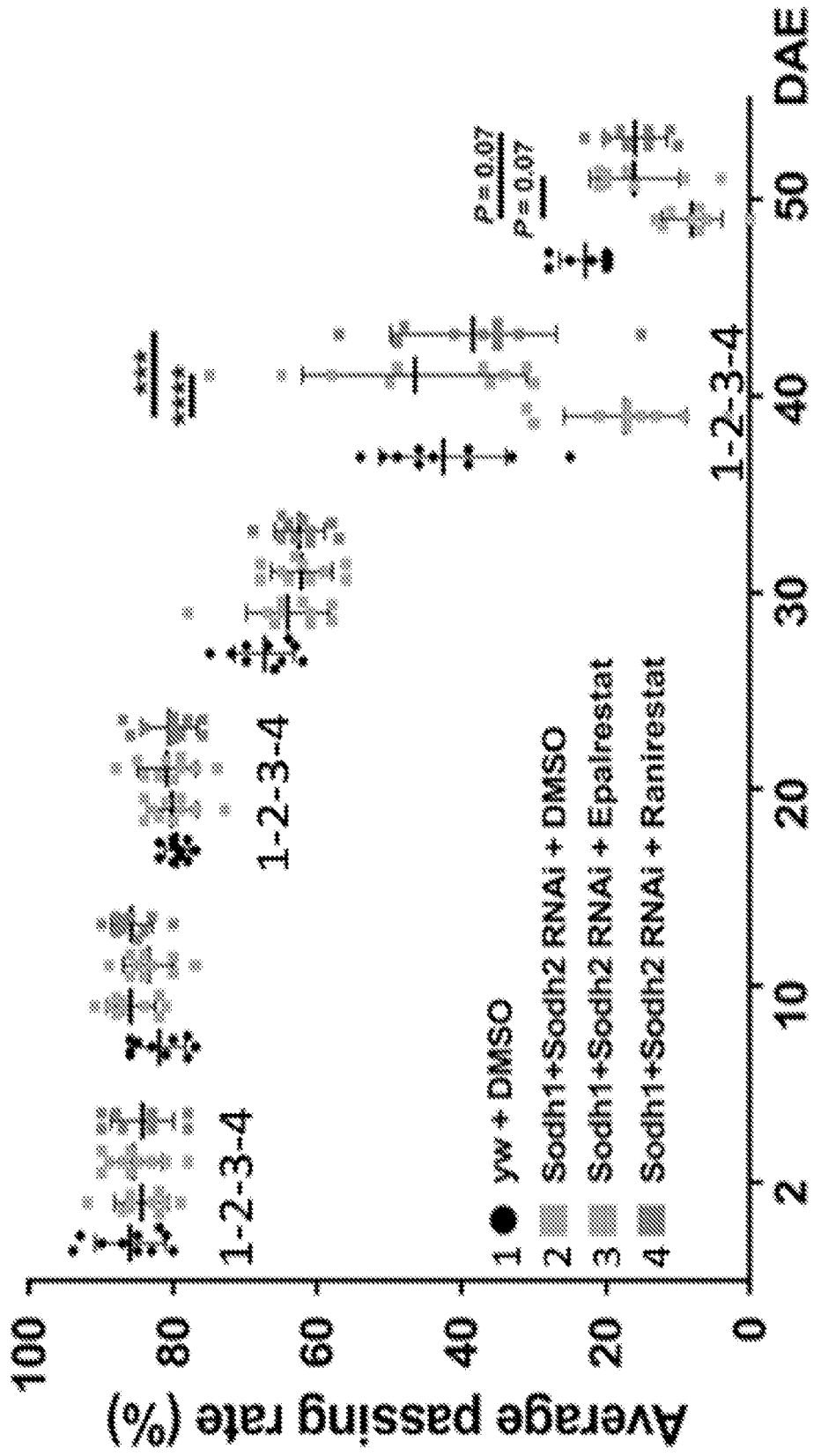

Average passing rate (%)
100
80
60
40
20
0
2
10
20
30
40
50
DAE
1-2-3-4
1-2-3-4
1-2-3-4
P = 0.07
P = 0.07
1 yw + DMSO
2 Sodh1+Sodh2 RNAi + DMSO
3 Sodh1+Sodh2 RNAi + Epalrestat
4 Sodh1+Sodh2 RNAi + Ranirestat

FIG. 7

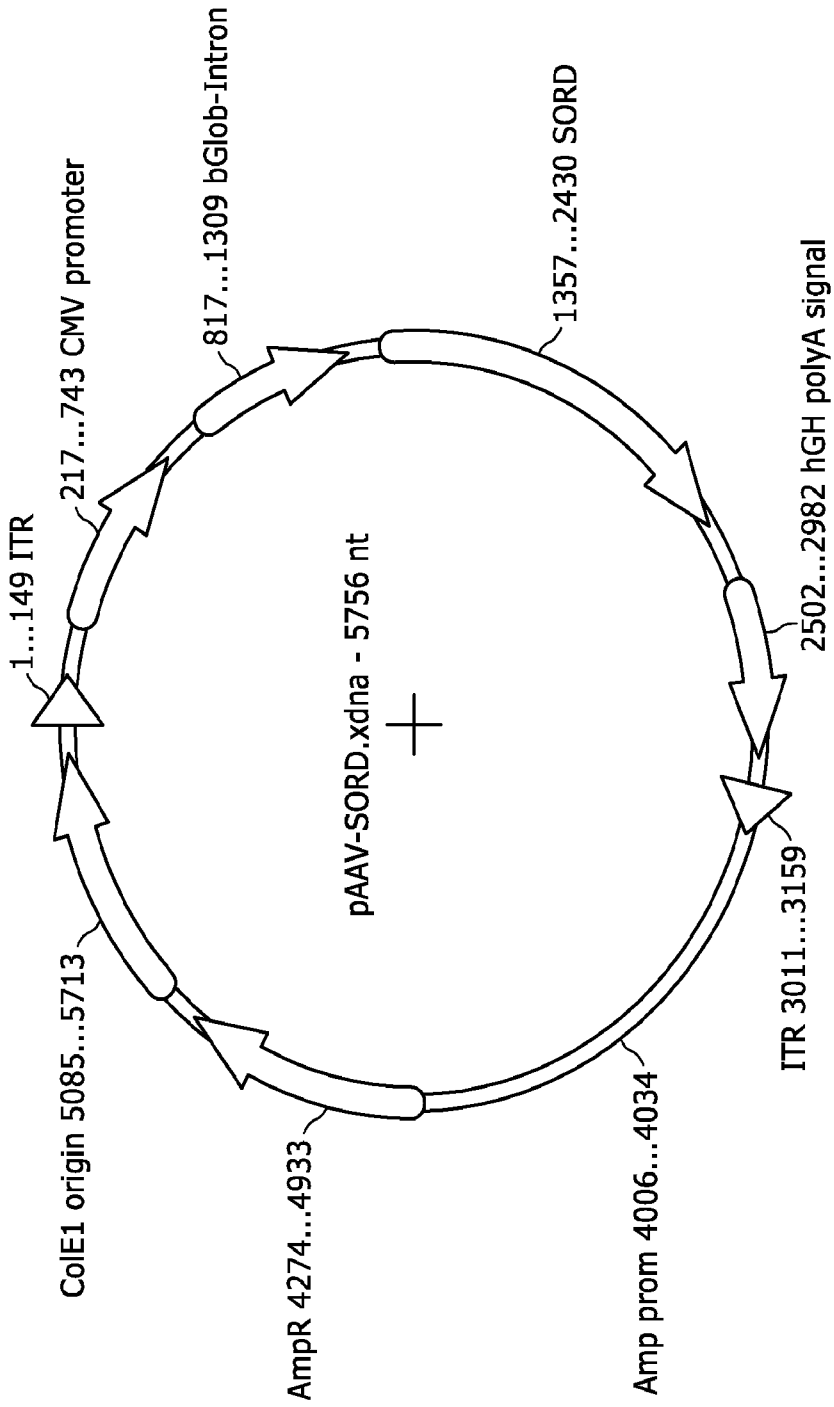

1...149 ITR
217...743 CMV promoter
817...1309 bGlob-Intron
1357...2430 SORD
2502...2982 hGH polyA signal
ITR 3011...3159
Amp prom 4006...4034
AmpR 4274...4933
ColE1 origin 5085...5713
pAAV-SORD.xdna - 5756 nt

FIG. 8

> [pAAV-SORD.xdna] - 5756 bp SEQ ID NO: 48

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCG
GCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGCGGCCGCAACCGTCTAGT
TATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGG
CCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGA
CTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGT
ACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTAC
TTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGC
GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGAC
TTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAG
AGCTCGTTTAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGAT
CCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTAC
CGCCTATAGAGTCTATAGGCCCACAAAAAATGCTTTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTT
CCCTAATCTCTTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGATAA
TTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATTTCTGCATATAAATTGTAACTGATGTAAGAGGTTTCAT
ATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCA
AGCTAGGCCCTTTTGCTAATCATGTTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCT
GGCCCATCACTTTGGCAAAGAATTGGGATTCGAACATCGATCCGAGGAGATCTGCCGCCGCGATCGCCGGCGCGCCATGG
CGGCGGCGGCCAAGCCCAACAACCTTTCCCTGGTGGTGCACGGACCGGGGGACTTGCGCCTGGAGAACTATCCTATCCCT
GAACCAGGCCCAAATGAGGTCTTGCTGAGGATGCATTCTGTTGGAATCTGTGGCTCAGATGTCCACTACTGGGAGTATGG
TCGAATTGGGAATTTTATTGTGAAAAAGCCCATGGTGCTGGGACATGAAGCTTCGGGAACAGTCGAAAAAGTGGGATCAT
CGGTAAAGCACCTAAAACCAGGTGATCGTGTTGCCATCGAGCCTGGTGCTCCCCGAGAAAATGATGAATTCTGCAAGATG
GGCCGATACAATCTGTCACCTTCCATCTTCTTCTGTGCCACGCCCCCCGATGACGGGAACCTCTGCCGGTTCTATAAGCA
CAATGCAGCCTTTTGTTACAAGCTTCCTGACAATGTCACCTTTGAGGAAGGCGCCCTGATCGAGCCACTTTCTGTGGGGA
TCCATGCCTGCAGGAGAGGCGGAGTTACCCTGGGACACAAGGTCCTTGTGTGTGGAGCTGGGCCAATCGGGATGGTCACT
TTGCTCGTGGCCAAAGCAATGGGAGCAGCTCAAGTAGTGGTGACTGATCTGTCTGCTACCCGATTGTCCAAAGCCAAGGA
GATTGGGGCTGATTTAGTCCTCCAGATCTCCAAGGAGAGCCCTCAGGAAATCGCCAGGAAAGTAGAAGGTCAGCTGGGGT
GCAAGCCGGAAGTCACCATCGAGTGCACGGGGGCAGAGGCCTCCATCCAGGCGGGCATCTACGCCACTCGCTCTGGTGGG
AACCTCGTGCTTGTGGGGCTGGGCTCTGAGATGACCACCGTACCCCTACTGCATGCAGCCATCCGGGAGGTGGATATCAA
GGGCGTGTTTCGATACTGCAACACGTGGCCAGTGGCGATTTCGATGCTTGCGTCCAAGTCTGTGAATGTAAAACCCCTCG
TCACCCATAGGTTTCCTCTGGAGAAAGCTCTGGAGGCCTTTGAAACATTTAAAAAGGGATTGGGGTTGAAAATCATGCTC
AAGTGTGACCCCAGTGACCAGAATCCCTGAAGATCTCAAGCTTAACTAGCTAGCGGACCGACGCGTACGCGGCCGCTCGT
TTAAACGGCCGGCCGGATCTACGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTC
CAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATGGGG
TGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTG
GAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGT
TGTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCC
AGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCAC
TGCTCCCTTCCCTGTCCTTCTGATTTTGTAGGTAACCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTT
GGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG
CGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGT
ATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACG
CGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGC
CGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAA
AACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACG
TTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACTCTATCTCGGGCTATTCTTTTGATTTATAAGGGAT
TTTGCCGATTTCGGTCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGT
TTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCC
GCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTG
TCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCA
TGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAA
ATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAG
TATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGG
TGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTT
GAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTAT
TGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAA
AGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTA
CTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCG
TTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGC
GCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCA
GGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGG
TATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGG
ATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATAT
ATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAA
AATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTT
TTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCA
ACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCA
CCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATA
AGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGC
ACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCC
CGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAA
ACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGG
CGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT

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 3	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
SORD Exon 2	Fw/sequencing: AGCGTGCCATTTAGCGTATC Rv: GCAGTAGACTCTGTTCTCAGCCTAAC	4 5		
SORD Exon 3	Fw ACCTTTTCTCATAAATAGATACGAATCC Rv/sequencing TCTTGTTCCCTGCTGTACCC	6 7		
SORD Exon 4	Fw and sequencing GCATGCAAGCCTTCATAACA Rv CGAGGTCATTGTTGTTATGACG	8 9		
SORD Exon 5	Fw/sequencing CGTGGCCATGTTAACTCCTT Rv GTTCCCTGAATTCCCAGTCA	10 11		
SORD Exon 6	Fw/sequencing ATGTTTAATATTTCACGAACATATTCC Rv GCTGTTTCCCAGTCAAGGAG	12 13		
SORD exon 7	Fw TGAGTCATCAGATTTCTCTTGTTTG Rv AGCCTGGGCGACTGAGTGAG 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	
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)	c.298C>T; p.(Arg100Ter) (absent in the mother, father deceased)
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	
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)	c.458C>A; p.(Ala153Asp) (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	scoliosis	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** **dHMN** **CMT intermediate**	 23 (51%) 18 (40%) 4 (9%)
Foot deformities	31 (69%)
Upper limb weakness **Proximal muscle groups** **Distal muscle groups**	 0/44 (0%) 26/44 (59%)
Lower limb weakness **Proximal muscle groups** **Distal muscle groups** **Prominent involvement of foot plantar flexion**	 2/44 (5%) 43/44 (98%) 15/37 (41%)
Reduced vibratory sensation	17/40 (42%)
Reduced pinprick superficial sensation	13/39 (33%)
Disease severity **Mild** **Moderate** **Severe**	 30 (67%) 14 (31%) 1 (2%)
Use of ankle-foot orthoses (AFOs) **Other walking aids**	19 (42%) 2 (4%)
Nerve conduction study **Reduced motor conduction velocity** **Reduced sensory action potentials**	 11/42 (26%) 26/40 (65%)

FIG. 12

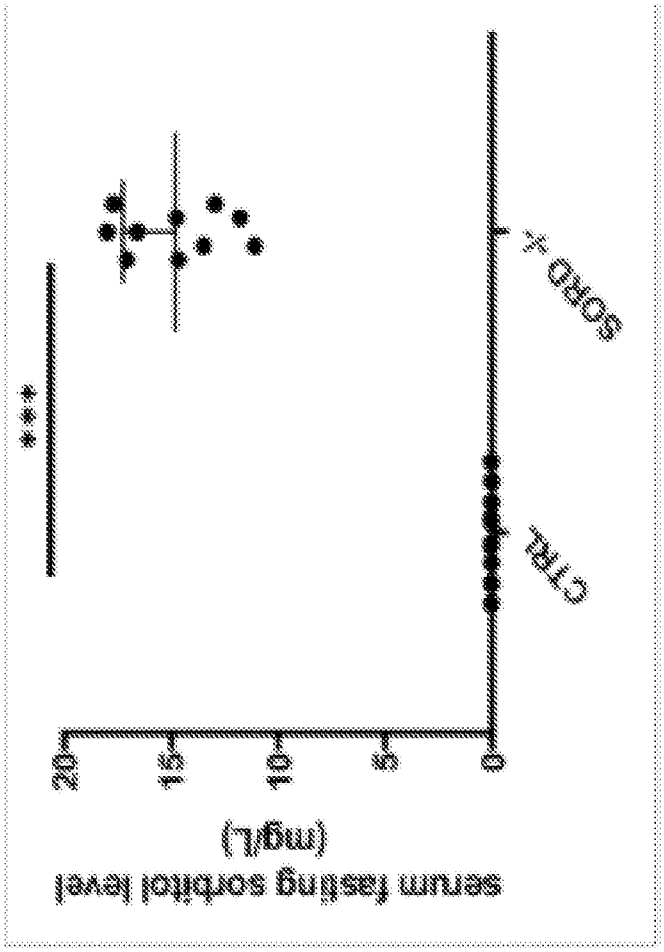


FIG. 13

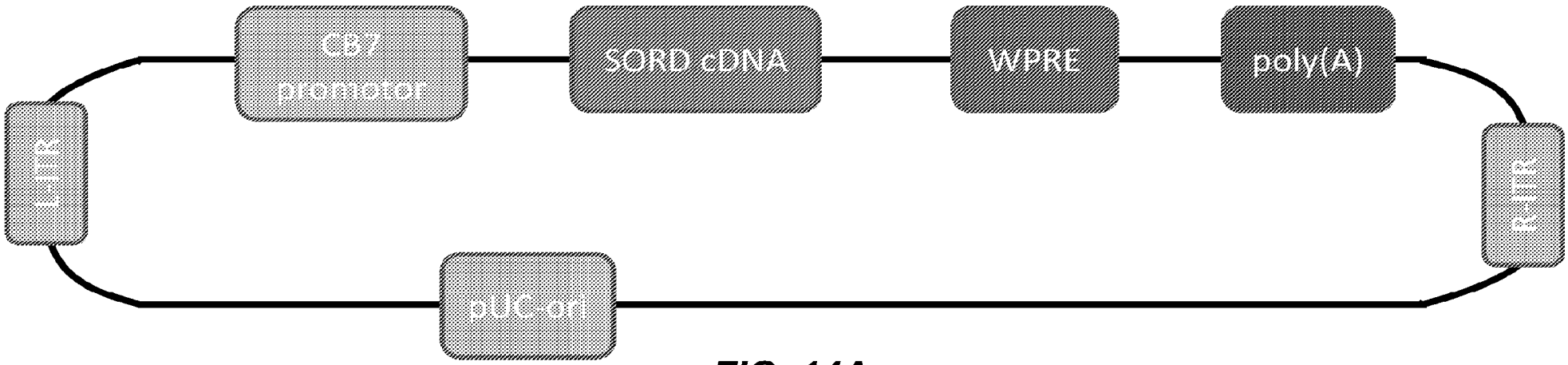


FIG. 14A

atggcggcggcggccaagcccaacaacctttccctggtggtgcacggaccgggggacttgcgcctggagaactatcctatccctgaaccaggcccaaatgaggtcttgctgaggatgcattctgttggaatctgtggctcag
atgtccactactgggagtatggtcgaattgggaattttattgtgaaaaagcccatggtgctgggacatgaagcttcgggaacagtcgaaaaagtgggatcatcggtaaagcacctaaaaccaggtgatcgtgttgccatcga
gcctggtgctccccgagaaaatgatgaattctgcaagatgggccgatacaatctgtcaccttccatcttcttctgtgccacgcccccgatgacgggaacctctgccggttctataagcacaatgcagccttttgttacaagctt
cctgacaatgtcacctttgaggaaggcgccctgatcgagccactttctgtggggatccatgcctgcaggagaggcggagttaccctgggacacaaggtccttgtgtgtggagctgggccaatcgggatggtcactttgctcgt
ggccaaagcaatgggagcagctcaagtagtggtgactgatctgtctgctacccgattgtccaaagccaaggagattggggctgatttagtcctccagatctccaaggagagccctcaggaaatcgccaggaaagtagaag
gtcagctggggtgcaagccggaagtcaccatcgagtgcacgggggcagaggcctccatccaggcgggcatctacgccactcgctctggtgggaacctcgtgcttgtggggctgggctctgagatgaccaccgtacccctact
gcatgcagccatccgggaggtggatatcaagggcgtgtttcgatactgcaacacgtggccagtggcgatttcgatgcttgcgtccaagtctgtgaatgtaaaaccccctcgtcacccataggtttcctctggagaaagctctgg
aggcctttgaaacatttaaaaagggattggggttgaaaatcatgctcaagtgtgaccccagtgaccagaatccctga

FIG. 14B (SEQ ID NO: 45)

MAAAAKPNNLSLVVHGPGDLRLENYPIPEPGPNEVLLRMHSVGICGSDVHYWEYGRIGNFIVKKPMVLGHEASGTVEKVGSSVKHLKPGDRVAIEPGAPRENDEFCKMGRYN
LSPSIFFCATPPDDGNLCRFYKHNAAFCYKLPDNVTFEEGALIEPLSVGIHACRRGGVTLGHKVLVCGAGPIGMVTLLVAKAMGAAQVVVTDLSATRLSKAKEIGADLVLQISKES
PQEIARKVEGQLGCKPEVTIECTGAEASIQAGIYATRSGGNLVLVGLGSEMTTVPLLHAAIREVDIKGVFRYCNTWPVAISMLASKSVNVKPLVTHRFPLEKALEAFETFKKGLGLKI
MLKCDPSDQNP

FIG. 14C (SEQ ID NO: 46)

AR 1A

G*T*T*T*A*A*G#*A*T*C*A*T*C*T*C*C*A*C*C*T

[SEQ ID NO: 22]

AR-S 1A

T*A*T*T*A*C*A#*G*C*T*A*C*A*T*C*C*T*G*T*C

[SEQ ID NO: 47]

FIG. 15A

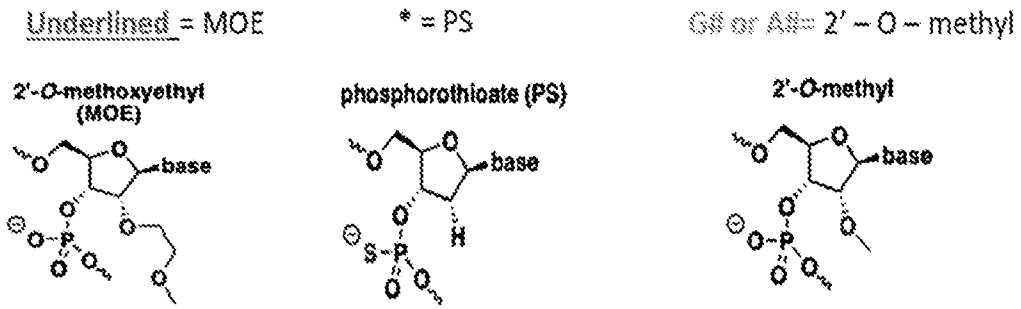


FIG. 15B

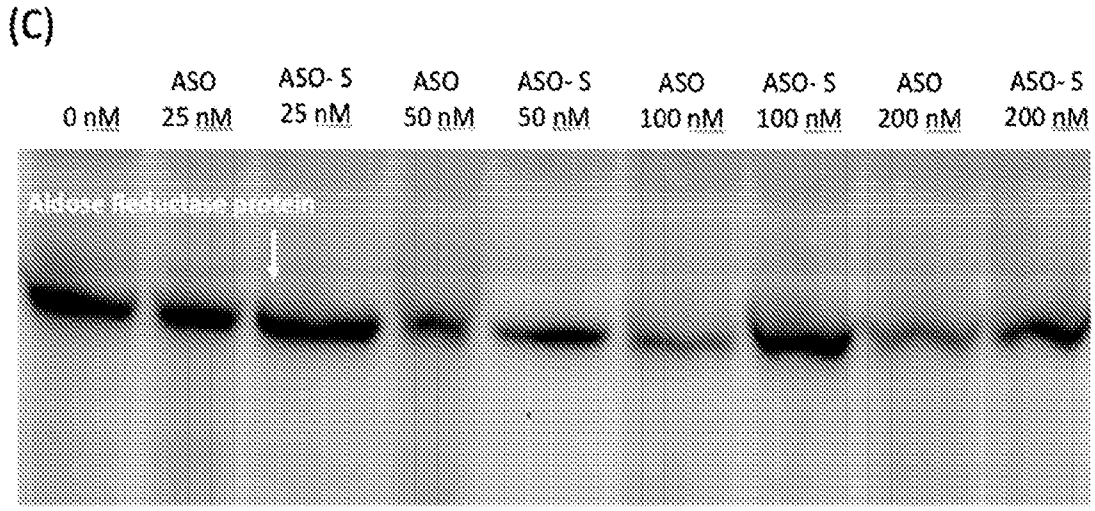


FIG. 15C

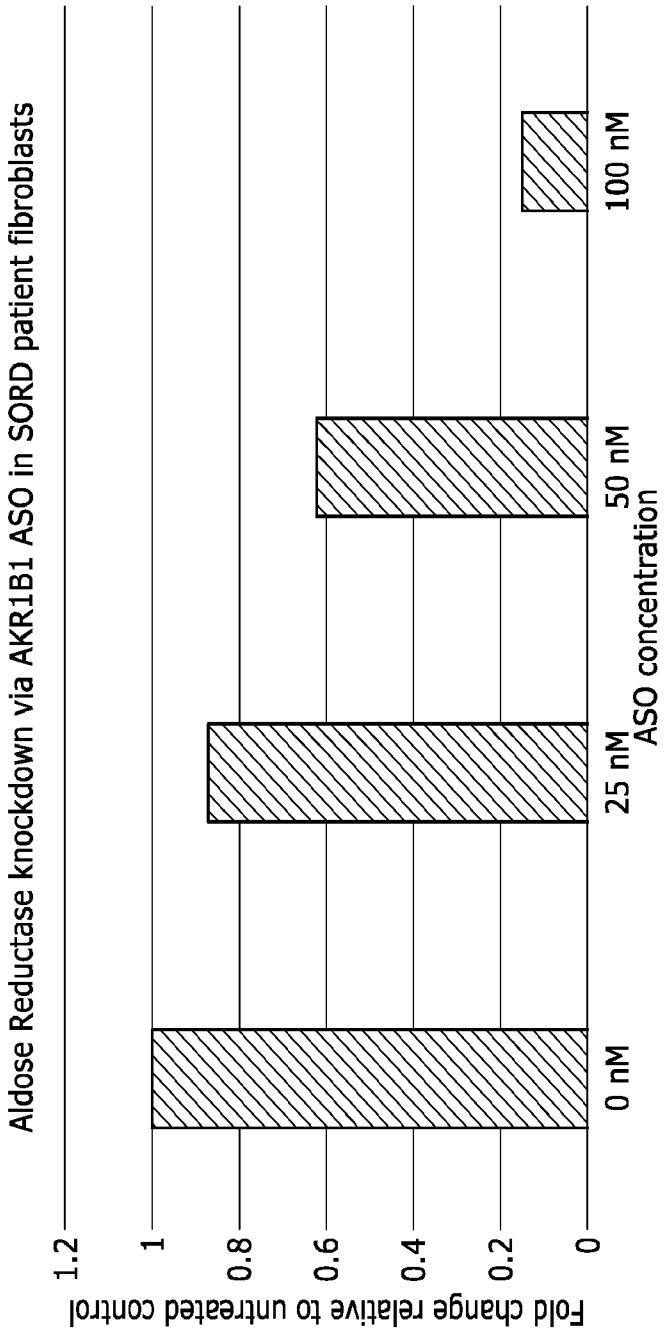

Aldose Reductase knockdown via AKR1B1 ASO in SORD patient fibroblasts
Fold change relative to untreated control
1.2
1
0.8
0.6
0.4
0.2
0
0 nM
25 nM
50 nM
100 nM
ASO concentration

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	UCGCAGCCAAGCACAAUAAA	TTTATTGTGCTTGGCTGCGA	50	45.00%	-16.3
2	51	GCAGCCAAGCACAAUAAAAC	GTTTTATTGTGCTTGGCTGC	52	45.00%	-16.3
3	53	GAUCGCAGCCAAGCACAAUA	TATTGTGCTTGGCTGCGATC	54	50.00%	-16.2
4	55	AUCGCAGCCAAGCACAAUAA	TTATTGTGCTTGGCTGCGAT	56	45.00%	-16.1
5	57	CGCAGCCAAGCACAAUAAAA	TTTTATTGTGCTTGGCTGCG	58	45.00%	-15.9
6	59	GCCAAGCACAAUAAAACUAC	GTAGTTTTATTGTGCTTGGC	60	40.00%	-15.7
7	61	CGAUCGCAGCCAAGCACAAU	ATTGTGCTTGGCTGCGATCG	62	55.00%	-15.6
8	63	AGCACAAUAAAACUACAGCC	GGCTGTAGTTTTATTGTGCT	64	40.00%	-15.2
9	65	CAGCCAAGCACAAUAAAACU	AGTTTTATTGTGCTTGGCTG	66	40.00%	-14.8
10	67	GCGAUCGCAGCCAAGCACAA	TTGTGCTTGGCTGCGATCGC	68	60.00%	-14.7
11	69	GCACAAUAAAACUACAGCCC	GGGCTGTAGTTTTATTGTGC	70	45.00%	-13.6
12	71	AACCAGAUUGAGUGCCACCC	GGGTGGCACTCAATCTGGTT	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	ACAACCUGAAUACCCUUUUC	GAAAAGGGTATTCAGGTTGT	80	40.00%	-12.3
17	81	CUCCCACAAGGAUUACCCCU	AGGGGTAATCCTTGTGGGAG	82	55.00%	-12.2
18	83	CCAGAUUGAGUGCCACCCAU	ATGGGTGGCACTCAATCTGG	84	55.00%	-12.1
19	85	CAACCUGAAUACCCUUUUCU	AGAAAAGGGTATTCAGGTTG	86	40.00%	-12.1
20	87	AGUACAACCUGAAUACCCUU	AAGGGTATTCAGGTTGTACT	88	40.00%	-11.9
21	89	GUACAACCUGAAUACCCUUU	AAAGGGTATTCAGGTTGTAC	90	40.00%	-11.9
22	91	AAGGCGAUCGCAGCCAAGCA	TGCTTGGCTGCGATCGCCTT	92	60.00%	-11.8
23	93	UCCCACAAGGAUUACCCCUU	AAGGGGTAATCCTTGTGGGA	94	50.00%	-11.8

FIG. 16

24	95	AAGUACAACCUGAAUACCCU	AGGGTATTCAGGTTGTACTT	96	40.00%	-11.8
25	97	AACCUGAAUACCCUUUUCUG	CAGAAAAGGGTATTCAGGTT	98	40.00%	-11.8
26	99	ACCUGAAUACCCUUUUCUGA	TCAGAAAAGGGTATTCAGGT	100	40.00%	-11.7
27	101	UACCUCCCACAAGGAUUACC	GGTAATCCTTGTGGGAGGTA	102	50.00%	-11.5
28	103	AAAGUACAACCUGAAUACCC	GGGTATTCAGGTTGTACTTT	104	40.00%	-11.5
29	105	CCUGAAUACCCUUUUCUGAC	GTCAGAAAAGGGTATTCAGG	106	45.00%	-11.5
30	107	UAACCAGAUUGAGUGCCACC	GGTGGCACTCAATCTGGTTA	108	50.00%	-11.2
31	109	AUUGAGUGCCACCCAUAUCU	AGATATGGGTGGCACTCAAT	110	45.00%	-11.2
32	111	GUGCCACCCAUAUCUCACUC	GAGTGAGATATGGGTGGCAC	112	55.00%	-11.2
33	113	UGCCACCCAUAUCUCACUCA	TGAGTGAGATATGGGTGGCA	114	50.00%	-11.2
34	115	CACAAUAAAACUACAGCCCA	TGGGCTGTAGTTTTATTGTG	116	40.00%	-11.2
35	117	CCCACAAGGAUUACCCCUUC	GAAGGGGTAATCCTTGTGGG	118	55.00%	-11.2
36	119	CUGAAUACCCUUUUCUGACC	GGTCAGAAAAGGGTATTCAG	120	45.00%	-11.2
37	121	GAUUGAGUGCCACCCAUAUC	GATATGGGTGGCACTCAATC	122	50.00%	-11.1
38	123	AGUGCCACCCAUAUCUCACU	AGTGAGATATGGGTGGCACT	124	50.00%	-11.1
39	125	GCCACCCAUAUCUCACUCAG	CTGAGTGAGATATGGGTGGC	126	55.00%	-11.1
40	127	GAGUGCCACCCAUAUCUCAC	GTGAGATATGGGTGGCACTC	128	55.00%	-11
41	129	UGAAUACCCUUUUCUGACCA	TGGTCAGAAAAGGGTATTCA	130	40.00%	-11
42	131	UUGAGUGCCACCCAUAUCUC	GAGATATGGGTGGCACTCAA	132	50.00%	-10.9
43	133	UGAGUGCCACCCAUAUCUCA	TGAGATATGGGTGGCACTCA	134	50.00%	-10.9
44	135	AGAUUGAGUGCCACCCAUAU	ATATGGGTGGCACTCAATCT	136	45.00%	-10.8
45	137	CCACCCAUAUCUCACUCAGG	CCTGAGTGAGATATGGGTGG	138	55.00%	-10.8
46	139	CAGAUUGAGUGCCACCCAUA	TATGGGTGGCACTCAATCTG	140	50.00%	-10.7
47	141	CCACAAGGAUUACCCCUUCC	GGAAGGGGTAATCCTTGTGG	142	55.00%	-10.6
48	143	GAAAGUACAACCUGAAUACC	GGTATTCAGGTTGTACTTTC	144	40.00%	-10.6
49	145	GAAUACCCUUUUCUGACCAA	TTGGTCAGAAAAGGGTATTC	146	40.00%	-10.5
50	147	ACAAUAAAACUACAGCCCAG	CTGGGCTGTAGTTTTATTGT	148	40.00%	-10.4
51	149	GUACCUCCCACAAGGAUUAC	GTAATCCTTGTGGGAGGTAC	150	50.00%	-10.3
52	151	AAACAAACCUGGCUUGAAGU	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	GAUCUUAAACAAACCUGGCU	AGCCAGGTTTGTTTAAGATC	158	40.00%	-10
56	159	UGAUCUUAAACAAACCUGGC	GCCAGGTTTGTTTAAGATCA	160	40.00%	-9.9
57	161	UAAACAAACCUGGCUUGAAG	CTTCAAGCCAGGTTTGTTTA	162	40.00%	-9.8
58	163	AACAAACCUGGCUUGAAGUA	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	UGUACCUCCCACAAGGAUUA	TAATCCTTGTGGGAGGTACA	180	45.00%	-9.6
67	181	AAGUGACCUAUACCUGUGUU	AACACAGGTATAGGTCACTT	182	40.00%	-9.6
68	183	GUGGGACAGCAACCUGUAGA	TCTACAGGTTGCTGTCCCAC	184	55.00%	-9.6
69	185	UAGUGCCACUAACGGUUGAG	CTCAACCGTTAGTGGCACTA	186	50.00%	-9.6
70	187	AGUGCCACUAACGGUUGAGU	ACTCAACCGTTAGTGGCACT	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	TCAACCGTTAGTGGCACTAT	194	45.00%	-9.5
74	195	CAAGUGACCUAUACCUGUGU	ACACAGGTATAGGTCACTTG	196	45.00%	-9.4
75	197	AGUGACCUAUACCUGUGUUU	AAACACAGGTATAGGTCACT	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	AAGCCGUCUCCUGCUCAACA	TGTTGAGCAGGAGACGGCTT	204	55.00%	-9.3
79	205	UCUUAAACAAACCUGGCUUG	CAAGCCAGGTTTGTTTAAGA	206	40.00%	-9.3
80	207	UCUGUGACACCAGAACGCAU	ATGCGTTCTGGTGTCACAGA	208	50.00%	-9.3
81	209	CUGUGACACCAGAACGCAUU	AATGCGTTCTGGTGTCACAG	210	50.00%	-9.3

FIG. 16 CONT.

82	211	UGUGACACCAGAACGCAUUG	CAATGCGTTCTGGTGTCACA	212	50.00%	-9.3
83	213	AACUUCAACCAUCUCCAGGU	ACCTGGAGATGGTTGAAGTT	214	45.00%	-9.2
84	215	ACAAACCUGGCUUGAAGUAU	ATACTTCAAGCCAGGTTTGT	216	40.00%	-9.2
85	217	UUAACCAGAUUGAGUGCCAC	GTGGCACTCAATCTGGTTAA	218	45.00%	-9.2
86	219	GUGACACCAGAACGCAUUGC	GCAATGCGTTCTGGTGTCAC	220	55.00%	-9.2
87	221	UGACACCAGAACGCAUUGCU	AGCAATGCGTTCTGGTGTCA	222	50.00%	-9.1
88	223	AUUACCCCUUCCAUGAAGAG	CTCTTCATGGAAGGGGTAAT	224	45.00%	-9.1
89	225	GGGACAGCAACCUGUAGAGU	ACTCTACAGGTTGCTGTCCC	226	55.00%	-9.1
90	227	AUACCCUUUUCUGACCAAAG	CTTTGGTCAGAAAAGGGTAT	228	40.00%	-9.1
91	229	AUCAAGGCGAUCGCAGCCAA	TTGGCTGCGATCGCCTTGAT	230	55.00%	-9
92	231	AGUCUGUGACACCAGAACGC	GCGTTCTGGTGTCACAGACT	232	55.00%	-9
93	233	CUGUACCUCCCACAAGGAUU	AATCCTTGTGGGAGGTACAG	234	50.00%	-9
94	235	CACAAGGAUUACCCCUUCCA	TGGAAGGGGTAATCCTTGTG	236	50.00%	-9
95	237	GAUUACCCCUUCCAUGAAGA	TCTTCATGGAAGGGGTAATC	238	45.00%	-9
96	239	UUACCCCUUCCAUGAAGAGU	ACTCTTCATGGAAGGGGTAA	240	45.00%	-9
97	241	UACCCCUUCCAUGAAGAGUU	AACTCTTCATGGAAGGGGTA	242	45.00%	-9
98	243	CACCCAUAUCUCACUCAGGA	TCCTGAGTGAGATATGGGTG	244	50.00%	-8.9
99	245	GGAUUACCCCUUCCAUGAAG	CTTCATGGAAGGGGTAATCC	246	50.00%	-8.9
100	247	ACUCAGCAGUGGGACAGCAA	TTGCTGTCCCACTGCTGAGT	248	55.00%	-8.9
101	249	AAGCCUGCAGUUAACCAGAU	ATCTGGTTAACTGCAGGCTT	250	45.00%	-8.8
102	251	GUCUGUGACACCAGAACGCA	TGCGTTCTGGTGTCACAGAC	252	55.00%	-8.8
103	253	GCUGUACCUCCCACAAGGAU	ATCCTTGTGGGAGGTACAGC	254	55.00%	-8.8
104	255	AGGAUUACCCCUUCCAUGAA	TTCATGGAAGGGGTAATCCT	256	45.00%	-8.8
105	257	AGCCUGCAGUUAACCAGAUU	AATCTGGTTAACTGCAGGCT	258	45.00%	-8.7
106	259	CCAAGUGACCUAUACCUGUG	CACAGGTATAGGTCACTTGG	260	50.00%	-8.7
107	261	ACUUCAACCAUCUCCAGGUG	CACCTGGAGATGGTTGAAGT	262	50.00%	-8.6
108	263	UUGAGCUGUACCUCCCACAA	TTGTGGGAGGTACAGCTCAA	264	50.00%	-8.6
109	265	UGAGCUGUACCUCCCACAAG	CTTGTGGGAGGTACAGCTCA	266	55.00%	-8.6
110	267	GAGCUGUACCUCCCACAAGG	CCTTGTGGGAGGTACAGCTC	268	60.00%	-8.6

FIG. 16 CONT.

111	269	AGCUGUACCUCCCACAAGGA	TCCTTGTGGGAGGTACAGCT	270	55.00%	-8.6
112	271	ACCCCUUCCAUGAAGAGUUU	AAACTCTTCATGGAAGGGGT	272	45.00%	-8.6
113	273	GGAAAGUACAACCUGAAUAC	GTATTCAGGTTGTACTTTCC	274	40.00%	-8.6
114	275	GGAAUUUUUCCCAUUGGAUG	CATCCAATGGGAAAAATTCC	276	40.00%	-8.5
115	277	GGUGGAGAUGAUCUUAAACA	TGTTTAAGATCATCTCCACC	278	40.00%	-8.5
116	279	GCCUGCAGUUAACCAGAUUG	CAATCTGGTTAACTGCAGGC	280	50.00%	-8.5
117	281	ACAAGGAUUACCCCUUCCAU	ATGGAAGGGGTAATCCTTGT	282	45.00%	-8.5
118	283	AGCCGUCUCCUGCUCAACAA	TTGTTGAGCAGGAGACGGCT	284	55.00%	-8.4
119	285	AUUGGAUGAGUCGGGCAAUG	CATTGCCCGACTCATCCAAT	286	50.00%	-8.4
120	287	UAAGCCUGCAGUUAACCAGA	TCTGGTTAACTGCAGGCTTA	288	45.00%	-8.4
121	289	CCCCAAGUCUGUGACACCAG	CTGGTGTCACAGACTTGGGG	290	60.00%	-8.4
122	291	GUGACCUAUACCUGUGUUUC	GAAACACAGGTATAGGTCAC	292	45.00%	-8.4
123	293	GGACAGCAACCUGUAGAGUG	CACTCTACAGGTTGCTGTCC	294	55.00%	-8.4
124	295	CUUAAACAAACCUGGCUUGA	TCAAGCCAGGTTTGTTTAAG	296	40.00%	-8.3
125	297	CAAUAAAACUACAGCCCAGG	CCTGGGCTGTAGTTTTATTG	298	45.00%	-8.3
126	299	AAGUCUGUGACACCAGAACG	CGTTCTGGTGTCACAGACTT	300	50.00%	-8.3
127	301	GUUGAGCUGUACCUCCCACA	TGTGGGAGGTACAGCTCAAC	302	55.00%	-8.3
128	303	UACCCUUUUCUGACCAAAGA	TCTTTGGTCAGAAAAGGGTA	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	TGGTGTCACAGACTTGGGGA	310	55.00%	-8.2
132	311	CAAGGAUUACCCCUUCCAUG	CATGGAAGGGGTAATCCTTG	312	50.00%	-8.2
133	313	AAGGAUUACCCCUUCCAUGA	TCATGGAAGGGGTAATCCTT	314	45.00%	-8.2
134	315	AAUAGUGCCACUAACGGUUG	CAACCGTTAGTGGCACTATT	316	45.00%	-8.2
135	317	UUGGAUGAGUCGGGCAAUGU	ACATTGCCCGACTCATCCAA	318	50.00%	-8.1
136	319	CAACUUCAACCAUCUCCAGG	CCTGGAGATGGTTGAAGTTG	320	50.00%	-8.1
137	321	AUAAGCCUGCAGUUAACCAG	CTGGTTAACTGCAGGCTTAT	322	45.00%	-8.1
138	323	CCUGCAGUUAACCAGAUUGA	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	UGGAUGAGUCGGGCAAUGUG	CACATTGCCCGACTCATCCA	332	55.00%	-8
143	333	AAUGUGGUUCCCAGUGACAC	GTGTCACTGGGAACCACATT	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 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	337	UCGCAGCCAAGCACAAUAAA	TTTATTGTGCTTGGCTGCGA	338	45.00%	0.819	8.6
2	339	CGCAGCCAAGCACAAUAAAA	TTTTATTGTGCTTGGCTGCG	340	45.00%	0.818	9
3	341	GCCCUUCUUUCUACCCUGCU	AGCAGGGTAGAAAGAAGGGC	342	55.00%	0.735	9.9
4	343	GACCUCACGGGCUAUUUAAA	TTTAAATAGCCCGTGAGGTC	344	45.00%	0.698	7.8
5	345	UACCUCCCACAAGGAUUACC	GGTAATCCTTGTGGGAGGTA	346	50.00%	0.694	7.3
6	347	CCCUUCUUUCUACCCUGCUG	CAGCAGGGTAGAAAGAAGGG	348	55.00%	0.693	9.9
7	349	ACCUCCCACAAGGAUUACCC	GGGTAATCCTTGTGGGAGGT	350	55.00%	0.69	7.4
8	351	ACCUCACGGGCUAUUUAAAG	CTTTAAATAGCCCGTGAGGT	352	45.00%	0.684	9.9
9	353	AUUGAGUGCCACCCAUAUCU	AGATATGGGTGGCACTCAAT	354	45.00%	0.668	6.7
10	355	GAUCUUAAACAAACCUGGCU	AGCCAGGTTTGTTTAAGATC	356	40.00%	0.666	12
11	357	UGAUCUUAAACAAACCUGGC	GCCAGGTTTGTTTAAGATCA	358	40.00%	0.664	12.7
12	359	AAGGCGAUCGCAGCCAAGCA	TGCTTGGCTGCGATCGCCTT	360	60.00%	0.663	9.4
13	361	GAUUGAGUGCCACCCAUAUC	GATATGGGTGGCACTCAATC	362	50.00%	0.649	6.2
14	363	CAGAUUGAGUGCCACCCAUA	TATGGGTGGCACTCAATCTG	364	50.00%	0.644	5.8
15	365	CCAGAUUGAGUGCCACCCAU	ATGGGTGGCACTCAATCTGG	366	55.00%	0.643	5.6
16	367	UCAAGGCGAUCGCAGCCAAG	CTTGGCTGCGATCGCCTTGA	368	60.00%	0.639	10.1
17	369	UAAACAAACCUGGCUUGAAG	CTTCAAGCCAGGTTTGTTTA	370	40.00%	0.636	9.3
18	371	UUACCCCUUCCAUGAAGAGU	ACTCTTCATGGAAGGGGTAA	372	45.00%	0.633	8.6
19	373	AAACAAACCUGGCUUGAAGU	ACTTCAAGCCAGGTTTGTTT	374	40.00%	0.631	8.5
20	375	UACCCCUUCCAUGAAGAGUU	AACTCTTCATGGAAGGGGTA	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	AAUACAAAAAUUAGCCCGGC	GCCGGGCTAATTTTTGTATT	378	40.00%	0.859	7.5
2	379	AAUACCAUCUCCUCUUCGGC	GCCGAAGAGGAGATGGTATT	380	50.00%	0.818	3.8
3	381	AAAUACCAUCUCCUCUUCGG	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	AUACAAAAAUUAGCCCGGCA	TGCCGGGCTAATTTTTGTAT	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	AAAATGACTGAATGGGTGTC	396	40.00%	0.787	1.9
11	397	UCAUGAUAAUCUCCCAGAAC	GTTCTGGGAGATTATCATGA	398	40.00%	0.783	4
12	399	CAGUUUAUCUUAUCGCUCCU	AGGAGCGATAAGATAAACTG	400	40.00%	0.783	10
13	401	AGUUUAUCUUAUCGCUCCUC	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	CAUGAGGUCAGAAGAUAGAG	CTCTATCTTCTGACCTCATG	408	45.00%	0.761	7.5
17	409	CUUCAUGAUAAUCUCCCAGA	TCTGGGAGATTATCATGAAG	410	40.00%	0.759	1.6
18	411	AUGAGGUCAGAAGAUAGAGA	TCTCTATCTTCTGACCTCAT	412	40.00%	0.757	8
19	413	ACUGUUUUCUCCUUUCUCCU	AGGAGAAAGGAGAAAACAGT	414	40.00%	0.755	7.2
20	415	UUCUCCUUUCUCCUGACAGC	GCTGTCAGGAGAAAGGAGAA	416	50.00%	0.753	7.2
21	417	AGACCCAGCCUCCUUUCCCU	AGGGAAAGGAGGCTGGGTCT	418	60.00%	0.751	10.9
22	419	CCCUUAUUCUUGUCUGAGCU	AGCTCAGACAAGAATAAGGG	420	45.00%	0.75	3.4

FIG. 18

23	421	CUCUCCCAUUCAUCCGUCUU	AAGACGGATGAATGGGAGAG	422	50.00%	0.749	5
24	423	CAUGAUAAUCUCCCAGAACC	GGTTCTGGGAGATTATCATG	424	45.00%	0.747	8.5
25	425	UCUCUCCCAUUCAUCCGUCU	AGACGGATGAATGGGAGAGA	426	50.00%	0.747	4.3
26	427	CCUUAUUCUUGUCUGAGCUC	GAGCTCAGACAAGAATAAGG	428	45.00%	0.744	3.4
27	429	UCUCUCACUACCCUUAUUCU	AGAATAAGGGTAGTGAGAGA	430	40.00%	0.734	4.8
28	431	CCUUUCUUGCCCUCUCUGUC	GACAGAGAGGGCAAGAAAGG	432	55.00%	0.718	-0.1
29	433	CCAAUCUGUCCAUUCCAUUU	AAATGGAATGGACAGATTGG	434	40.00%	0.716	3.8
30	435	CUCUCUCCUUUAGUACUUCC	GGAAGTACTAAAGGAGAGAG	436	45.00%	0.716	5.6
31	437	UCUCUCCUUUAGUACUUCCU	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	AUUGACUUCCCCAAACAACA	TGTTGTTTGGGGAAGTCAAT	454	40.00%	0.691	13
40	455	CUAGAAAAACCUCUCACAAC	GTTGTGAGAGGTTTTTCTAG	456	40.00%	0.688	5.3
41	457	UUGACUUCCCCAAACAACAG	CTGTTGTTTGGGGAAGTCAA	458	45.00%	0.688	13.1
42	459	UAGCCUGAGCCUGAUUAUCU	AGATAATCAGGCTCAGGCTA	460	45.00%	0.686	2.9
43	461	AACGUAUCACCCACGGCCAU	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	GUAACUAGCAAGACCUGUAA	TTACAGGTCTTGCTAGTTAC	470	40.00%	0.676	5.3
48	471	AUAAGCAUCUCAAGCCGGUA	TACCGGCTTGAGATGCTTAT	472	45.00%	0.672	4.2
49	473	AAACGUAUCACCCACGGCCA	TGGCCGTGGGTGATACGTTT	474	55.00%	0.672	8.7
50	475	CCGUAGCUAGUUGAUAAUUC	GAATTATCAACTAGCTACGG	476	40.00%	0.67	6.8
51	477	AUUUGUUUCUACCCCAGCUC	GAGCTGGGGTAGAAACAAAT	478	45.00%	0.67	7.5

FIG. 18 CONT.

52	479	AAUAAGCAUCUCAAGCCGGU	ACCGGCTTGAGATGCTTATT	480	45.00%	0.669	4.2
53	481	UUUGUUUCUACCCCAGCUCU	AGAGCTGGGGTAGAAACAAA	482	45.00%	0.669	7.6
54	483	ACGUAUCACCCACGGCCAUA	TATGGCCGTGGGTGATACGT	484	55.00%	0.669	9.4
55	485	UAAAACCUCAACACCACACA	TGTGTGGTGTTGAGGTTTTA	486	40.00%	0.668	6.7
56	487	GUCCCCUCUUAACCCACACC	GGTGTGGGTTAAGAGGGGAC	488	60.00%	0.667	11.1
57	489	GUCUCAGCUCCAGCCCGUUU	AAACGGGCTGGAGCTGAGAC	490	60.00%	0.663	8.3
58	491	AGUCUCAGCUCCAGCCCGUU	AACGGGCTGGAGCTGAGACT	492	60.00%	0.656	5.3
59	493	AAAACCUCAACACCACACAG	CTGTGTGGTGTTGAGGTTTT	494	45.00%	0.65	8.6
60	495	CCCGUAGCUAGUUGAUAAUU	AATTATCAACTAGCTACGGG	496	40.00%	0.644	8.9
61	497	UAGUGUCCAUGUCUCCGUCU	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	GCAUUUUGUUAUUCUGUCCC	GGGACAGAATAACAAAATGC	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	GUUUUAUUGCACCACAGCAU	ATGCTGTGGTGCAATAAAAC	512	40.00%	0.626	6.1
69	513	UAAGCAUCUCAAGCCGGUAG	CTACCGGCTTGAGATGCTTA	514	50.00%	0.624	6.5
70	515	UGCCCUCACAACCAUUCACA	TGTGAATGGTTGTGAGGGCA	516	50.00%	0.623	11.9
71	517	UAUCACCCACGGCCAUACAG	CTGTATGGCCGTGGGTGATA	518	55.00%	0.621	14.3
72	519	AUGACACCAAGCUAAUUUCC	GGAAATTAGCTTGGTGTCAT	520	40.00%	0.618	9
73	521	UUAUUGCACCACAGCAUAUC	GATATGCTGTGGTGCAATAA	522	40.00%	0.616	6.4
74	523	GCAUGGGCUCUUAGAUUAAU	ATTAATCTAAGAGCCCATGC	524	40.00%	0.616	9.9
75	525	AUUCCAUUUUGUGUCCUCUG	CAGAGGACACAAAATGGAAT	526	40.00%	0.613	11.3
76	527	GGCUAAUCUUUUUUCUUCCC	GGGAAGAAAAAAGATTAGCC	528	40.00%	0.601	14.3
77	528	ACAGAUGCUCGACAGAAGAU	ATCTTCTGTCGAGCATCTGT	530	45.00%	0.6	7.2
78	531	GAUGCUCGACAGAAGAUGUG	CACATCTTCTGTCGAGCATC	532	50.00%	0.599	8.6
79	533	UUGUUUCCUCCAAAAACUCC	GGAGTTTTTGGAGGAAACAA	534	40.00%	0.597	9.6
80	535	GUACUUAACCUAUGUAGGCU	AGCCTACATAGGTTAAGTAC	536	40.00%	0.594	6.6

FIG. 18 CONT.