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Development of an anitsense-mediated exon skipping therapy for Duchenne Muscular Dystrophy.

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Appendices

Appendix 1. The lengths of the different DMD exons and introns.

Exon	Length (bp)	
	Exon	Intron
1 (<i>Dp427c</i>)	351	127702
1 (<i>Dp427m</i>)	275	82853
1 (<i>Dp427p</i>)	282	107946
2	62	170318
3	93	4867
4	78	21395
5	93	6654
6	173	6856
7	119	110199
8	182	1113
9	129	52717
10	189	650
11	182	29678
12	151	18426
13	120	21910
14	102	107
15	108	7648
16	180	20367
17	176	27027
18	124	16165
19	88	10236
20	242	6177
21	181	12609
22	146	3453
23	213	3798
24	114	991
25	156	8606
26	171	6023
27	183	7141

Exon	Length (bp)	
	Exon	Intron
28	135	2789
29	150	25984
1 (<i>Dp260</i>)	95	248
30	162	21570
31	111	396
32	174	3035
33	156	5629
34	171	15310
35	180	309
36	129	1623
37	171	14259
38	123	2325
39	138	2656
40	153	851
41	183	31823
42	195	22380
43	173	70430
44	148	61403
1 (<i>Dp140</i>)	99	186859
45	176	36112
46	148	2334
47	150	54220
48	186	38355
49	102	16634
50	109	45778
51	233	44213
52	118	50048
53	212	21230

Exon	Length (bp)	
	Exon	Intron
54	155	30129
55	190	119347
1 (<i>Dp116</i>)	91	754
56	173	10336
57	157	17684
58	121	608
59	269	33478
60	147	95853
61	79	24897
62	61	56689
1 (<i>Dp71</i>)	98	5793
63	62	37833
64	75	13347
65	202	2830
66	86	2463
67	158	21030
68	167	2256
69	112	1564
70	137	698
71	39	4327
72	66	1125
73	66	2746
74	159	21924
75	244	860
76	124	12096
77	93	7428
78	32	4711
79	2307	

Appendix 2. Overview of DMD deletions (reported in the Leiden DMD mutation database) for which the reading frame can theoretically be restored by AON-mediated exon skipping

Deletion ¹ (n) ²	Exon(s) to skip ³	Deletion ¹ (n) ²	Exon(s) to skip ³
Exon 2-11 (1)	12-19	Exon 8-27 (1)	6&7
Exon 2-13 (2)	14-19	Exon 8-29 (1)	6&7
Exon 2-18 (1)	19	Exon 8-33 (2)	6&7
Exon 2-20 (2)	21	Exon 8-39 (1)	6&7
Exon 2-25 (2)	26-50	Exon 8-41 (3)	6&7
Exon 2-27 (1)	28-50	Exon 8-42 (2)	6&7
Exon 2-30 (1)	31-50	Exon 8-43 (2)	7
Exon 2-33 (1)	34-50	Exon 8-44 (4)	6&7
Exon 2-44 (1)	45-50	Exon 8-45 (2)	7
Exon 3-7 ⁴ (24)	2 or 8	Exon 8-47 (1)	6&7
Exon 3-11 (3)	12	Exon 8-51 (1)	6&7
Exon 3-17 (5)	18	Exon 10-11 (4)	12
Exon 3-19 (4)	20	Exon 10-17 (3)	18
Exon 3-21 (1)	22	Exon 10-19 (1)	20
Exon 3-43 ⁴ (1)	44	Exon 10-21 (1)	22
Exon 4-6 (2)	7&8	Exon 10-43 ⁴ (1)	44
Exon 4-7 ⁴ (3)	8	Exon 10-52 ⁴ (1)	53
Exon 4-19 (3)	20	Exon 12 (2)	11
Exon 5-6 (2)	7&8	Exon 12-15 (2)	11
Exon 5-7 ⁴ (4)	8	Exon 12-16 (3)	11
Exon 5-11 (1)	12	Exon 12-19 (1)	11&20
Exon 5-21 (1)	22	Exon 12-20 (1)	11
Exon 5-43 ⁴ (1)	44	Exon 12-25 (1)	11
Exon 6 (2)	7&8	Exon 12-44 (3)	11
Exon 6-7 ⁴ (10)	8	Exon 12-51 (1)	11
Exon 6-17 (2)	18	Exon 13-43 ⁴ (1)	44
Exon 6-43 ⁴ (1)	44	Exon 13-50 ⁴ (1)	51
Exon 7 (2)	6&8	Exon 14-17 (3)	18
Exon 7-12 (2)	6	Exon 14-43 ⁴ (1)	44
Exon 7-13 (1)	6	Exon 16-17 (1)	18
Exon 7-18 (1)	6	Exon 16-21 (1)	22
Exon 7-33 (1)	6	Exon 17 (4)	18
Exon 7-49 (1)	6	Exon 17-21 (1)	22
Exon 8 (2)	6&7	Exon 17-43 ⁴ (1)	44
Exon 8-9 (14)	6&7	Exon 18 ⁴ (2)	17
Exon 8-11 (9)	7	Exon 18-20 ⁴ (2)	17
Exon 8-12 (2)	6&7	Exon 18-21 (1)	17&22
Exon 8-13 (1)	6&7	Exon 18-25 ⁴ (1)	17
Exon 8-15 (2)	6&7	Exon 18-27 ⁴ (2)	17
Exon 8-16 (8)	6&7	Exon 18-33 ⁴ (2)	17
Exon 8-17 (6)	7	Exon 18-41 ⁴ (1)	17
Exon 8-18 (1)	6&7	Exon 18-44 ⁴ (4)	17
Exon 8-20 (4)	6&7	Exon 19-21 (1)	22
Exon 8-22 (1)	6&7	Exon 20 ⁵ (1)	19 or 21
Exon 8-24 (1)	6&7	Exon 20-27 ⁴ (1)	19

Deletion ¹ (n) ²	Exon(s) to skip ³	Deletion ¹ (n) ²	Exon(s) to skip ³
Exon 20-29 ⁴ (1)	19	Exon 46-60 ⁴ (1)	45
Exon 21 (5)	20 or 22	Exon 47-50 ⁴ (11)	51
Exon 21-45 ⁴ (1)	46	Exon 47-52 ⁴ (7)	53
Exon 22-34 (1)	21	Exon 47-54 ⁴ (6)	46 or 55
Exon 22-36 (1)	21	Exon 47-56 ⁴ (1)	46
Exon 22-43 (1)	21&44	Exon 48-50 ⁵ (100)	51
Exon 28-43 ⁴ (2)	44	Exon 48-52 ⁴ (37)	53
Exon 29-50 ⁴ (1)	51	Exon 48-54 ⁴ (6)	55
Exon 30-43 ⁴ (2)	44	Exon 48-61 (1)	46-47&62
Exon 35-43 ⁴ (1)	44	Exon 49-50 ⁴ (46)	51
Exon 36-43 ⁴ (1)	44	Exon 49-52 ⁴ (26)	53
Exon 38-43 ⁴ (1)	44	Exon 49-54 ⁴ (6)	55
Exon 40-43 ⁴ (3)	44	Exon 49-62 (1)	46-48
Exon 42-43 ⁴ (7)	44	Exon 50 ⁴ (41)	51
Exon 43 ⁴ (5)	44	Exon 50-52 ⁴ (14)	53
Exon 43-45 (5)	56	Exon 51 ⁴ (83)	50 or 52
Exon 43-50 ⁴ (6)	51	Exon 51-53 ⁴ (7)	50
Exon 43-52 ⁴ (1)	53	Exon 51-54 ⁴ (9)	50&55
Exon 44 ⁴ (57)	43 or 45	Exon 51-55 ⁵ (8)	50
Exon 44-47 ⁴ (6)	43	Exon 51-56 (1)	50&57
Exon 44-48 ⁴ (2)	43	Exon 51-57 ⁴ (1)	50 or 58
Exon 44-49 ⁴ (1)	43	Exon 52 ⁵ (25)	51 or 53
Exon 44-50 ⁴ (2)	43&51	Exon 52-54 ⁴ (1)	55
Exon 44-51 ⁴ (6)	43	Exon 52-63 ⁴ (1)	51
Exon 44-52 ⁴ (5)	43&53 or 53&54	Exon 53 ⁴ (8)	52
Exon 44-53 (1)	54	Exon 53-54 ⁴ (6)	52&55
Exon 45 ⁵ (92)	44 or 46	Exon 53-55 ⁴ (2)	52
Exon 45-50 ⁵ (78)	51	Exon 53-59 ⁴ (1)	52
Exon 45-52 ⁴ (35)	53	Exon 53-60 ⁴ (1)	52
Exon 45-54 ⁵ (17)	44 or 55	Exon 54 ⁴ (2)	55
Exon 45-68 ⁶ (1)	44 or 69	Exon 54-62 (1)	53&63
Exon 46 ⁴ (4)	45	Exon 55 (2)	54 or 56
Exon 46-47 ⁴ (42)	45	Exon 56 ⁴ (2)	55 or 57
Exon 46-48 ⁴ (17)	45	Exon 57 (2)	56
Exon 46-49 ⁴ (17)	45	Exon 57-60 (1)	56
Exon 46-50 ⁴ (26)	45&51	Exon 60-62 (1)	59&63
Exon 46-51 ⁴ (29)	45	Exon 61 (1)	59&60
Exon 46-52 ⁴ (11)	45&53 or 53&54	Exon 64-67 ⁶ (1)	63&68
Exon 46-53 ⁴ (10)	45 or 54	Exon 65-74 ⁶ (1)	75
Exon 46-55 ⁴ (3)	45 or 56		

¹Mutation data as present in the Leiden DMD mutations database on February 23rd 2004 kindly provided by Ivo Fokkema

²Absolute numbers are shown in brackets; in the Leiden DMD mutation database 1518 deletions and 2460 mutations have been reported for DMD patients (data kindly provided by Ivo Fokkema)

³Exon(s) to skip in order to convert the deletion into its nearest in frame counterpart

⁴Deletions that require skipping of exons that has been proven "skippable" in human control myotubes

⁵Deletions for which reading frame restoration has been shown feasible in patient- derived myotube cultures

⁶Since the cysteine rich region is deleted, restoring the reading frame is unlikely to result in a functional protein for these patients

Appendix 3. Overview of DMD point mutations (reported in the Leiden DMD mutation database) for which the reading frame can theoretically be restored by AON-mediated exon skipping

Mutation in exon ¹	Exon(s) to skip ²	Mutation in exon ¹	Exon(s) to skip ²
2 (2)	2-7	39 (9)	39
3 (9)	3	40 ⁴ (3)	40
4 (4)	4	41 ⁴ (8)	41
5 (5)	5	42 ⁴ (1)	42
6 (12)	6-8	43 ⁵ (12)	43&44
7 (10)	6-8	44 ⁴ (12)	43&44 or 44&45
8 (18)	6-8	45 ⁴ (8)	44&45 or 45&46
9 (4)	9	46 ⁴ (3)	45&46
10 (7)	10	47 (7)	47
11 (4)	11&12	48 ⁴ (10)	48
12 (10)	11&12	49 ⁵ (1)	49
13 (9)	13	50 ⁴ (4)	50&51
14 (7)	14	51 ⁴ (7)	50&51 or 51&52
15 (2)	15	52 ⁴ (6)	51&52 or 52&53
16 (10)	16	53 ⁴ (4)	52&53
17 (9)	17&18	54 ⁴ (4)	54&55
18 (12)	17&18	55 ⁴ (6)	54&55 or 55&56
19 (21)	19&20	56 (6)	55&56 or 56&57
20 (10)	19&20 or 20&21	57 (3)	56&57
21 (12)	20&21 or 21&22	58 (6)	58&59
22 (5)	21&22	59 (17)	58&59
23 (12)	23	60 (6)	60
24 (10)	24	61 (4)	59-61
25 (6)	25	62 (10)	62&63
26 (11)	26	63 (1)	62&63
27 (3)	27	64 ⁵ (6)	64
28 (1)	28	65 ⁵ (13)	65&66
29 ⁴ (5)	29	66 ⁵ (18)	65&66
30 (6)	30	67 ⁵ (5)	66-68
31 (2)	31	68 ⁵ (8)	68&69
32 (8)	32	69 ⁵ (11)	68&69 or 69&70
33 (6)	33	70 (39)	69&70
34 (14)	34	72 (1)	72
35 (16)	35	74 (9)	74
36 (4)	36	75 (4)	75&76
37 (4)	37	76 (2)	75&76
38 (3)	38	77 (1)	77

¹Mutation data as present in the Leiden DMD mutation database on February 23rd 2004 kindly provided by Ivo Fokkema

²Exon(s) to skip in order to convert the deletion into its nearest in frame counterpart

³Absolute numbers are shown in brackets; in the Leiden DMD mutation database 570 point mutations and 2460 mutations have been reported for DMD patients (data kindly provided by Ivo Fokkema)

⁴Mutations that require skipping of exons that has been proven "skippable" in human control myotubes

⁵Mutations for which reading frame restoration has been shown feasible *in vitro*

⁶Since this exon is located in the cysteine rich region, restoring the reading frame may not result in a functional protein for these patients

Appendix 4. Overview of all duplications (reported in the Leiden DMD mutation database) for which the reading frame can theoretically be restored by AON-mediated exon skipping

Mutation ¹	Phenotype	Exon to skip ²	Mutation ¹	Phenotype	Exon to skip ²
Exon 2 (9) ³⁴	DMD	2	Exon 16-34 (2)	BMD	16-34
Exon 2-6 (1)	BMD	2-6	Exon 17 (1)	DMD	17
Exon 2-7 (4)	1 DMD,3 BMD	2-7	Exon 17-28 (1)	BMD	17-28
Exon 2-9 (1)	DMD	2-9	Exon 17-39 (1)	BMD	17-39
Exon 2-11 (1)	DMD	2-11	Exon 18 (1)	DMD	18
Exon 2-21 (1)	DMD	2-21	Exon 18-19 (1)	BMD	18-19
Exon 3 (1)	DMD	3	Exon 18-23 (1)	DMD	18-23
Exon 3-4 (3)	2 DMD,1 IMD	3-4	Exon 18-32 (1)	DMD	18-32
Exon 3-5 (1)	DMD	3-5	Exon 18-52 (1)	BMD	18-52
Exon 3-7 (6)	DMD	3-7	Exon 20 (1)	DMD	20
Exon 3-8 (2)	1 DMD,1 BMD	3-8	Exon 20-27 (1)	DMD	20-27
Exon 3-11 (1)	DMD	3-11	Exon 20-41 (2)	1 IDB,1 BMD	20-41
Exon 3-12 (1)	BMD	3-12	Exon 22-25 (2)	DMD	22-25
Exon 3-13 (1)	DMD	3-13	Exon 22-27 (1)	BMD	22-27
Exon 3-17 (1)	DMD	3-17	Exon 37-43 (1)	DMD	37-43
Exon 3-30 (1)	DMD	3-30	Exon 37-44 (1)	DMD	37-44
Exon 4-8 (1)	DMD	4-8	Exon 38-43 (1)	DMD	38-43
Exon 4-10 (1)	DMD	4-10	Exon 38-44 (1)	DMD	38-44
Exon 5 (1)	BMD	5	Exon 42-43 ⁴ (1)	DMD	42-43
Exon 5-6 (1)	DMD	5-6	Exon 42-52 (1)	DMD	42-52
Exon 5-7 (2)	DMD	5-7	Exon 43 ⁴ (2)	DMD	43
Exon 6 (6)	DMD	6	Exon 44 ⁴ (3)	DMD	44
Exon 6-7 (2)	DMD	6-7	Exon 44-56 (1)	DMD	44-56
Exon 6-8 (1)	DMD	6-8	Exon 44-57 (1)	DMD	44-57
Exon 7-8 (1)	DMD	7-8	Exon 45 ⁴ (1)	DMD	45
Exon 7-9 (1)	DMD	7-9	Exon 45-50 (1)	DMD	45-50
Exon 7-20 (1)	DMD	7-20	Exon 45-51 ⁴ (1)	DMD	45-51
Exon 8 (1)	DMD	8	Exon 45-52 (1)	DMD	45-52
Exon 8-9 (5)	DMD	8-9	Exon 46-47 (1)	DMD	46-47
Exon 8-13 (2)	DMD	8-13	Exon 46-60 (1)	DMD	46-60
Exon 8-29 (1)	DMD	8-29	Exon 47 (1)	DMD	47
Exon 9-12 (1)	DMD	9-12	Exon 48 ⁴ (1)	DMD	48
Exon 9-14 (1)	DMD	9-14	Exon 48-52 (1)	DMD	48-52
Exon 9-16 (1)	DMD	9-16	Exon 48-60 (1)	DMD	48-60
Exon 10-11 (1)	DMD	10-11	Exon 49-60 (1)	DMD	49-60
Exon 12 (1)	DMD	12	Exon 50 ⁴ (2)	1 DMD,1 BMD	50
Exon 12-13 (2)	DMD	12-13	Exon 50-52 (2)	DMD	50-52
Exon 13-19 (1)	DMD	13-19	Exon 50-55 (1)	DMD	50-55
Exon 13-20 (1)	DMD	13-20	Exon 51 ⁴ (6)	DMD	51
Exon 13-42 (1)	BMD	13-42	Exon 51-55 (2)	DMD	51-55
Exon 14-18 (1)	BMD	14-18	Exon 51-57 (1)	DMD	51-57
Exon 14-21 (1)	DMD	14-21	Exon 52 ⁴ (1)	DMD	52
Exon 14-26 (1)	BMD	14-26	Exon 52-55 (1)	DMD	52-55
Exon 14-36 (1)	BMD	14-36	Exon 53 ⁴ (1)	DMD	53
Exon 14-42 (1)	BMD	14-42	Exon 53-55 (1)	DMD	53-55
Exon 15-18 (1)	DMD	15-18	Exon 54 (1)	DMD	54

Mutation ¹	Phenotype	Exon to skip ²	Mutation ¹	Phenotype	Exon to skip ²
Exon 15-28 (1)	BMD	15-28	Exon 56 (1)	DMD	56
Exon 56-61 (1)	DMD	56-61	Exon 61 (1)	DMD	61
Exon 58-59 (1)	DMD	58-59	Exon 61-64 (1)	DMD	61-64
Exon 58-63 (1)	DMD	58-63			

¹Mutation data as present in the Leiden DMD mutation database on February 23rd 2004 kindly provided by Ivo Fokkema

²Exon(s) to skip in order to convert the deletion into its nearest in frame counterpart

³Absolute numbers are shown in brackets; in the Leiden DMD mutation database 157 duplications and 2460 mutations have been reported for DMD patients (data kindly provided by Ivo Fokkema)

⁴Duplications that require skipping of exons that has been proven "skippable" in human control myotubes