Table 4

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Compendium of Brugada syndrome-associated SCN5A mutations

Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
Exon 2	3 G>A	M11*	Missense	N-terminal	1	1
Exon 2	53 G>A	R18Q*	Missense	N-terminal	1	3
Exon 2	191_193delTGC	L64del*	In-frame del	N-terminal	-	5
Exon 2	210 T>G	N70K*	Missense	N-terminal	-	5
Exon 2	217 C>T	Q73X*	Nonsense	N-terminal	_	2
Exon 2	250 G>A	D84N*	Missense	N-terminal	2	1
Exon 3	278 T>C	F93S*	Missense	N-terminal	1	1
Exon 3	281 T>G	194S*	Missense	N-terminal	-	7
Exon 3	310 C>T	R104W*	Missense	N-terminal	2	1, 2
Exon 3	311 G>A	R104Q	Missense	N-terminal	3	1, 7, 8
Exon 3	327 C>A	N109K*	Missense	N-terminal	-	3
Exon 3	361 C>T	R121W*	Missense	N-terminal	-	∞
Exon 3	362 G>A	R121Q*	Missense	N-terminal	2	2,6
Exon 3	376 A>G	K126E	Missense	N-terminal	1	6
Exon 3	381dupT	L128SfsX44*	Frame shift	DI-S1	-	7
Intron 3	393 –5 C>A*		Splice site	DI-S1	_	1
Exon 4	407 T>C	L136P	Missense	DI-S1	2	∞
Exon 4	410_418dupTCATGTGCA	1137_C139dup*	In-frame ins	DI-S1	1	3
Exon 4	436 G>A	V146M*	Missense	DI-S1	_	7
Exon 4	468 G>A	W156X	Nonsense	DI-S1/S2	1	3
Exon 4	477 T>A	Y159X*	Nonsense	DI-S2	-1	5
Exon 4	481 G>C	E161Q*	Missense	DI-S2	-	9
Exon 4	481 G>A	E161K	Missense	DI-S2	3	3,4
Exon 5	486delC	Y162XfsX1*	Frame shift	DI-S2	1	5
Exon 5	525 G>C	K175N*	Missense	DI-S2	_	1

Exon 5 533 C-G A178G* Missense DI-SDS3 1 9 Exon 5 534 C-T R179X* Missense DI-SDS3 1 2 Exon 5 544 T-C C182R* Missense DI-SDS3 1 4 Exon 5 544 T-C A189V* Missense DI-SDS3 1 4 Exon 5 611 C-T A294V* Missense DI-SDS3 1 4 Intron 5 611 + G-A* A294V* Missense DI-SDS3 1 4 Intron 5 611 + G-A*-G* A294V* Missense DI-SDS3 1 4 Intron 5 611 + G-A* A294V* Missense DI-SDS3 1 4 Intron 5 611 + G-A* A294V* Missense DI-SDS3 1 4 Exon 6 645 - A* 1212Q* Missense DI-SDS3 1 6 Exon 6 656 - A* 1222Q* Missense DI-SDS3 1 6 Exon 6<	Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
44 T-C R179X Nonsense DI-SDS3 1 544 T-C C182R* Missense DI-SDS3 1 544 T-C A185V* Missense DI-SDS3 1 546 C-T A185V* Missense DI-SDS3 1 611 C-T A204V* Missense DI-SDS3 1 612 C-A AC** L212Q* Missense DI-SDS3 1 640 C-T R222Q* Missense DI-SDS3 1 651 C-T A226V* Missense DI-SDS3 1 652 C-T A222Q* Missense DI-SDS3 1 653 C-T A224V* Missense DI-SDS3 1 654 C-T A224V* Missense DI-SDS3	Exon 5	533 C>G	A178G*	Missense	DI-S2	-	6
44 Th C C182R** Missense D1-52/53 1 549 C T A183V* Missense D1-52/53 1 519 C A W193X* Missense D1-53/53 1 611 C A A204V* Missense D1-53 1 611 C A A204V* Missense D1-53 1 611 C A A204V* Missense D1-53 1 611 C A A A204V* Splice site D1-53 1 611 C A A C ** A204V* Missense D1-53/54 1 656 C A A C ** A220V Missense D1-54/54 1 667 C A C ** A220V Missense D1-54/55 1 677 C A T A220V Missense D1-54/55 1 677 C A T A220V Missense D1-54/55 1 118 C A A T K150V Missense D1-54/55 1 808 C A A D T A240V Missense D1-54/55 1 817 C A D T Missense D	Exon 5	535 C>T	R179X	Nonsense	DI-S2/S3	1	2
54 C>T A185V* Missense D1-52/53 1 579 G>A W193X* Nonsense D1-53 1 611 C>T A204V* Missense D1-53 1 611 H G>A* Splice site D1-53 1 611 + J.	Exon 5	544 T>C	C182R*	Missense	DI-S2/S3	1	4
579 G>A W193X* Nonsense D1-53 1 611 C>T A2044** Missense D1-53 1 611 C>T Splice site D1-53 1 611 +1 G>A* Splice site D1-53 1 611 +1 G>A** L212Q* Splice site D1-53 1 612 -2 A>G* L212Q* Missense D1-53/54 1 656 G57inaATICA T220T Missense D1-54 1 657 C>T T220T Missense D1-54 2 658 C>T T220T Missense D1-54 2 657 C>T A225W Missense D1-54 2 657 C>T A225W Missense D1-54/55 1 657 C>T A225W Missense D1-54/55 1 657 C>T A226W Missense D1-54/55 1 657 C>T A226W Missense D1-54/55 1 658 C>A A236W Missense D1-54/55 1	Exon 5	554 C>T	A185V*	Missense	DI-S2/S3	1	2
611 C-T A2040** Missense D1-53 1 611 +1 G-A* Splice site D1-53 1 611 +3_611+4dupAA Splice site D1-53 1 612 -2 A-C** L212Q* Missense D1-53/54 1 635 T-A L212Q* Missense D1-53/54 1 645 G-S7imsATTCA T220F\$x10* Frame shift D1-53/54 1 655 G-S7imsATTCA T220F Missense D1-54 1 667 C-T R222X Nonsense D1-54 2 667 C-T R222X Missense D1-54 2 670 C-T A226V Missense D1-54/55 1 671 C-T A226V Missense D1-54/55 1 672 C-T V240M Missense D1-54/55 1 808 C-A L276Q Missense D1-54/55 1 812 C-G Missense D1-55/56 1 824 C-T R226C* Missense D1-55/56 1 <	Exon 5	579 G>A	W193X*	Nonsense	DI-S3	1	4
611+1 G>A* Splice site D1-53 1 611+3_611+4dupAA Splice site D1-53 1 612-2A>G** Splice site D1-53 1 612-2A>G** L212Q** Missense D1-53/54 1 635 G>T T220T Missense D1-54 1 646 C>T R222X Nonsense D1-54 4 656 G>A R222X Missense D1-54 4 667 G>C V221* Missense D1-54 4 670 G>C V222X* Missense D1-54 2 671 C>T V223W Missense D1-54 2 673 C>T V223W Missense D1-54/55 1 674 G>A V230W Missense D1-54/55 1 808 C>A V249W* Missense D1-54/55 1 827 C>B V230C* Missense D1-55/56 1 828 C>A V320C* Missense D1-55/56 1 838 C>A	Exon 5	611 C>T	A204V*	Missense	DI-S3	1	4
611+3_611+4dupAA Splice site D1-53 1 612-2 A>G** Splice site D1-53/54 1 635 T>A L212Q** Missense D1-53/54 1 656_657insATTCA T220I Missense D1-54 1 659 C>T T220I Missense D1-54 2 664 C>T R222X Nonsense D1-54 4 665 C>A V223L* Missense D1-54 5 670 C>T V223L* Missense D1-54 2 671 C>T A226V Missense D1-54 2 694 C>A V232I Missense D1-54/55 1 718 C>A V220W Missense D1-54/55 1 808 C>A Q270K** Missense D1-54/55 1 827 C>B L276Q Missense D1-55/56 1 844 C>T R228C** Missense D1-55/56 1 898 C>A V3301** Missense D1-55/56 1	Intron 5	611 +1 G>A*		Splice site	DI-S3	1	5
6512—2 A>G** Splice site D1-53/54 1 635 T>A L2112Q** Missense D1-53/54 1 656 G57msATTCA T220F\$X10* Frame shift D1-54 1 659 C>T T220I Missense D1-54 2 664 C>T R222X Nonsense D1-54 4 665 G>A R222Q Missense D1-54 2 667 G>C V223L* Missense D1-54 2 677 C>T A226V Missense D1-54 2 677 C>T V223L Missense D1-54/55 1 718 G>A V240M Missense D1-54/55 1 808 C>A L276Q Missense D1-54/55 1 827 T>A L276Q Missense D1-55/56 1 824 C>T H278D* Missense D1-55/56 1 828 G>A V300f* Missense D1-55/56 1 934 +1 C>A* Splice site D1-55/56 1	Intron 5	611 +3_611+4dupAA		Splice site	DI-S3	1	6
655 T>A L212Q* Missense DI-53/54 1 656_657insATTCA T220FfsX10* Frame shift DI-54 1 656_657insATTCA T220T Missense DI-54 2 664 C>T R222X Nonsense DI-54 4 665 G>A R222Q Missense DI-54 1 667 G>C V2231* Missense DI-54 2 673 C>T R225W Missense DI-54 2 674 G>A V220Y Missense DI-54/55 1 694 G>A V240M Missense DI-54/55 1 808 C>A L276Q Missense DI-53/55 1 808 C>A L276Q Missense DI-53/56 1 812 C>G H278D* Missense DI-53/56 1 898 G>A V3001* Missense DI-53/56 1 934 +1 C>T* R356 BI-55/56 1 934 +4 C>T* R46 Missense DI-55/56 1	Intron 5	612 –2 A>G*		Splice site	DI-S3	1	4
656_657insATICA T220FfsX10* Frame shift D1-54 1 659 C>T T220T Missense D1-54 4 664 C>T R222X Nonsense D1-54 4 665 G>A R222X Missense D1-54 1 667 G>C V223L* Missense D1-54 2 677 C>T A226V Missense D1-54 2 694 G>A V223L Missense D1-54/S5 1 745 A>T K249X* Nonsense D1-54/S5 1 808 C>A L276Q Missense D1-54/S5 1 827 T>A L276Q Missense D1-53/S6 1 844 C>T R282C* Missense D1-53/S6 1 898 G>A V3001* Missense D1-53/S6 1 934 +4 C>T* R282C* Splice site D1-53/S6 1 934 +4 C>T* R301c* Missense D1-53/S6 1 934 +4 C>T* R41-C>T Splice site	Exon 6	635 T>A	L212Q*	Missense	DI-S3/S4	1	5
659 C>T T720I Missense DI-54 2 664 C>T R222X Nonsense DI-54 4 665 G>A R222X Missense DI-54 1 667 G>C V223I* Missense DI-54 2 677 C>T A226V Missense DI-54 2 694 G>A V232I Missense DI-54/S 1 694 G>A V240M Missense DI-54/S 1 694 G>A V240M Missense DI-54/S 1 808 C>A Q270K* Missense DI-55/S 1 821 C>G H278D* Missense DI-55/S 1 844 C>T R282C* Missense DI-55/S 1 934+1 G>A* V300f* Missense DI-55/S 1 934+4 C>T* Splice site DI-55/S 1 944 T>C Missense DI-55/S 1	Exon 6	656_657insATTCA	T220FfsX10*	Frame shift	DI-S4	1	2
664 C>T R222X Nonsense DI-54 4 665 G>A R222Q Missense DI-54 1 667 G>C V223L* Missense DI-54 2 673 C>T R225W Missense DI-54 3 674 C>T A226V Missense DI-54 2 694 G>A V232I Missense DI-54/S5 1 745 A>T K240X* Nonsense DI-54/S5 1 808 C>A Q270K* Missense DI-55/S6 1 827 T>A L276Q Missense DI-55/S6 1 844 C>T R228C* Missense DI-55/S6 1 898 G>A V300I** Missense DI-55/S6 1 934 +1 G>A** Splice site DI-55/S6 1 944 T>C L315P* Missense DI-55/S6 1	Exon 6	659 C>T	T220I	Missense	DI-S4	2	2,3
665 G>A R222Q Missense DI-S4 1 667 G>C V223L* Missense DI-S4 2 673 C>T A226V Missense DI-S4 3 674 C>T A226V Missense DI-S4 2 694 G>A V232I Missense DI-S4/S5 1 745 A>T K249X* Nonsense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5/S6 1 821 C>G H278D* Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 934 +1 G>A* V300I* Missense DI-S5/S6 1 934 +4 C>T* Splice site DI-S5/S6 1 944 T>C Missense DI-S5/S6 1	Exon 6	664 C>T	R222X	Nonsense	DI-S4	4	2,4
667 G>C V223L* Missense DI-S4 2 673 C>T R225W Missense DI-S4 3 677 C>T A226V Missense DI-S4 2 694 G>A V232I Missense DI-S4/S5 1 718 G>A V240M Missense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5/S5 1 827 T>A L276Q Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 934 +1 G>A* V300I* Missense DI-S5/S6 1 934 +4 C>T* Splice site DI-S5/S6 1 944 T>C Missense DI-S5/S6 1	Exon 6	665 G>A	R222Q	Missense	DI-S4	1	4
673 C>T R225W Missense DI-S4 3 674 C>T A226V Missense DI-S4 2 694 G>A V232I Missense DI-S4/S5 1 718 G>A V240M Missense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5/S5 1 827 T>A L276Q Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 6	O <d <=""> 2 < > 2 < > 2 < > 3 < > 4 < 4 <</d>	V223L*	Missense	DI-S4	2	2
677 C>T A226V Missense DI-S4 2 694 G>A V232I Missense DI-S4 2 718 G>A V240M Missense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5/S5 1 827 T>A L276Q Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 6	673 C>T	R225W	Missense	DI-S4	3	1,6
694 G>A V2321 Missense DI-S4/S 2 718 G>A V240M Missense DI-S4/S 1 745 A>T K249X* Nonsense DI-S4/S 1 808 C>A Q270K* Missense DI-S5 1 827 T>A L276Q Missense DI-S5/S 1 844 C>T R282C* Missense DI-S5/S 1 934 +1 G>A* V3001* Missense DI-S5/S 1 934 +4 C>T* Splice site DI-S5/S 1 944 T>C L315P* Missense DI-S5/S 1	Exon 6	777C>T	A226V	Missense	DI-S4	2	2
718 G>A V240M Missense DI-S4/S5 1 745 A>T K249X* Nonsense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5 1 827 T>A H276Q Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 6	694 G>A	V232I	Missense	DI-S4	2	2,6
445 A>T K249X* Nonsense DI-S4/S5 1 808 C>A Q270K* Missense DI-S5 1 827 T>A L276Q Missense DI-S5/S6 1 832 C>G H278D* Missense DI-S5/S6 1 844 C>T K282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	718 G>A	V240M	Missense	DI-S4/S5	1	3
808 C>A Q270K* Missense DI-S5 1 827 T>A L276Q Missense DI-S5/S6 1 832 C>G H278D* Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 934 H G>A* V300I* Missense DI-S5/S6 1 934 + L G>A* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	745 A>T	K249X*	Nonsense	DI-S4/S5	1	9
8.27 T->A L276Q Missense DI-S5 1 8.32 C->G H278D* Missense DI-S5/S6 1 8.44 C->T R282C* Missense DI-S5/S6 1 898 G->A V300I* Missense DI-S5/S6 1 934 +1 G->A* Splice site DI-S5/S6 1 934 +4 C->T* Splice site DI-S5/S6 1 944 T->C L315P* Missense DI-S5/S6 1	Exon 7	808 C>A	Q270K*	Missense	DI-S5	1	9
832 C>G H278D* Missense DI-S5/S6 1 844 C>T R282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 934 +4 C>T* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	827 T>A	L276Q	Missense	DI-S5	1	8
844 C>T R282C* Missense DI-S5/S6 1 898 G>A V300I* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 934 +4 C>T* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	832 C>G	H278D*	Missense	DI-S5/S6	1	4
898 G>A V3001* Missense DI-S5/S6 1 934 +1 G>A* Splice site DI-S5/S6 1 934 +4 C>T* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	844 C>T	R282C*	Missense	DI-S5/S6	1	2
934+1 G>A* Splice site DI-S5/S6 1 934+4 C>T* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Exon 7	898 G>A	V300I*	Missense	DI-S5/S6	1	5
934 +4 C>T* Splice site DI-S5/S6 1 944 T>C L315P* Missense DI-S5/S6 1	Intron 7	934 +1 G>A*		Splice site	DI-S5/S6	1	3
944 T>C L315P* Missense DI-S5/86 1	Intron 7	934 +4 C>T*		Splice site	DI-S5/S6	1	5
	Exon 8	944 T>C	L315P*	Missense	DI-S5/S6	1	9

Exon 8 959 C-A 1320N* Missense Di-SS/S6 1 Exon 8 974 T-G L323R Missense Di-SS/S6 1 Exon 9 1007 C-T P33G. Missense Di-SS/S6 1 Exon 9 1007 C-T P33G. Missense Di-SS/S6 1 Exon 9 103 G-T B346X. Missense Di-SS/S6 1 Exon 9 103 G-T B346X. Missense Di-SS/S6 1 Exon 9 103 G-T B346X. Missense Di-SS/S6 1 Exon 9 1005 G-T B35N. Missense Di-SS/S6 1 Exon 9 1100 G-A B35N. Missense Di-SS/S6 1 Exon 9 1100 G-A B35N. Missense Di-SS/S6 1 Exon 9 110 G-A Missense Di-SS/S6 1 1 Exon 10 115 G-A Missense Di-SS/S6 1 1 Exon 10 115 G-A Missense D	Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
914 T-G L325R Missense D1-535/6 1 908 + I G>A** Splice site D1-53/56 1 1007 C>T B346X Missense D1-53/56 1 1036 G>T B346X Missense D1-53/56 1 1052 G>T G331 D* Missense D1-53/56 1 1066 G>A D356N Missense D1-53/56 1 1100 G>A R367L* Missense D1-53/56 1 1100 G>A M367K Missense D1-53/56 1 1100 G>A M369K Missense D1-53/56 1 1107 G>A M369K Missense D1-53/56 1 1117 G>A M369K Missense D1-53/56 1 1117 G>A M366K Missense D1-53/56 1 1117 G>A M366K Missense D1-53/56 1 1117 G>A M366K Missense D1-53/56 1 1136 G>A M366K Missense D1-53/56	Exon 8	959 C>A	T320N*	Missense	DI-S5/S6	1	5
998 +1 G>A* Splice site DI-SS/S6 1 1007 C>T B336L Missense DI-SS/S6 2 1036 G>T E346X Nonsense DI-SS/S6 1 1032 G>T G331D* Missense DI-SS/S6 1 1052 G>A B356N Missense DI-SS/S6 1 1066 G>A B356N Missense DI-SS/S6 2 1100 G>T R367L* Missense DI-SS/S6 2 1100 G>A M369K Missense DI-SS/S6 1 1120 PA M369K* Missense DI-SS/S6 1 1120 PA R376H Missense DI-SS/S6 1 1150 PA Q386K* Missense DI-SS/S6 1 1187 P>C Q396K* Missense DI-SS/S6 1 1187 P>C Q419X* Missense DI-SS/S6 1 1187 P>A* Q419X* Missense DI-MI 1 1187 P>A* Q419X* Missense DI-MI	Exon 8	974 T>G	L325R	Missense	DI-S5/S6	1	4
1007 C>T P336L Missense DI-SS/S6 2 1036 G>T E346X Nonsense DI-SS/S6 1 1052 G>T G351V Missense DI-SS/S6 1 1056 G>A G351D* Missense DI-SS/S6 1 1066 G>A B356N Missense DI-SS/S6 2 1100 G>T R367L* Missense DI-SS/S6 1 1100 G>A M369K Missense DI-SS/S6 1 1100 G>A M374G* Missense DI-SS/S6 1 1120 T>G W374G* Missense DI-SS/S6 1 1157 G>A Missense DI-SS/S6 1 1 1157 G>A Missense DI-SS/S6 1 1 1157 G>A Missense DI-SS/S6 1 1 1187 T>C V396A* Missense DI-SS/S6 1 1187 T>C Q419X* Missense DI-MI 1 1187 T>A Q419X* Missense DI-MI	Intron 8	998 +1 G>A*		Splice site	DI-S5/S6	1	4
1936 Gy-T E346X Nonsense DI-55/56 1 1052 Gy-T G351V Missense DI-55/56 1 1066 Gy-A D356N Missense DI-55/56 1 1066 Gy-A D356N Missense DI-55/56 2 1006 Gy-A D356N Missense DI-55/56 2 1100 Gy-T R367C Missense DI-55/56 2 1100 Gy-A M369K Missense DI-55/56 1 1100 Gy-A M369K Missense DI-55/56 1 1107 Gy-A M369K* Missense DI-55/56 1 1157 Gy-A G386F* Missense DI-55/56 1 1157 Gy-A G386F* Missense DI-55/56 1 1186 Gy-C V396A* Missense DI-55/56 1 1187 Gy-A G419X* Missense DI-55/56 1 1187 Gy-A Missense DI/DII 1 1182 L431 del CAAG S476 K330* Frame shiff	Exon 9	1007 C>T	P336L	Missense	DI-S5/S6	2	2,6
1052 G>-T G351V Missense DI-S5/S6 1 1066 G>-A D356N Missense DI-S5/S6 1 1066 G>-A D356N Missense DI-S5/S6 2 1069 C>T R367C Missense DI-S5/S6 2 1100 G>-A R367L* Missense DI-S5/S6 2 1100 G>-A M369K Missense DI-S5/S6 1 110 G>-A M356R* Missense DI-S5/S6 1 112 G>-A R376H Missense DI-S5/S6 1 115 G>-A G386R* Missense DI-S5/S6 1 115 G>-A G386R* Missense DI-S5/S6 1 1186 G>-C V396A* Missense DI-S6/S6 1 1187 G>-A G419X* Missense DI-S6/S6 1 1131 G>-A B439K* Missense DI/DII 1 1132 G>-A B439K* Frame shiff DI/DII 1 123 del-C BA10A Missense <td>Exon 9</td> <td>1036 G>T</td> <td>E346X</td> <td>Nonsense</td> <td>DI-S5/S6</td> <td>1</td> <td>1</td>	Exon 9	1036 G>T	E346X	Nonsense	DI-S5/S6	1	1
1056 G>A G351D* Missense D1-55/56 1 1066 G>A D356N Missense D1-55/56 8 1100 G>A R367L* Missense D1-55/56 2 1100 G>A R367L* Missense D1-55/56 2 1100 G>A M369K Missense D1-55/56 1 110 G>A M369K Missense D1-55/56 1 112 G>A R376H Missense D1-55/56 1 115 G>A G386E* Missense D1-55/56 1 115 G>A J15 G>A Missense D1-55/56 1 115 G>A Missense D1-55/56 1 1187 T>C V396L* Missense D1-55/56 1 1187 T>C Q419X* Missense D1/DII 1 1335 4-2 T>A** S476K\$X30* Frame shift D1/DII 1 1337 delC K5213K\$X10* Frame shift D1/DII 1 1502 delA Missense D1/DII 1<	Exon 9	1052 G>T	G351V	Missense	DI-S5/S6	1	6
1066 G>A D356N Missense D1-55/56 8 1099 C>T R367L* Missense D1-55/56 2 1100 G>A R367L* Missense D1-55/56 2 1100 G>A R367H* Missense D1-55/56 1 1100 G>A M367H Missense D1-55/56 1 1110 T>G W374G* Missense D1-55/56 1 115 G>A R376H Missense D1-55/56 1 115 G>A Q38G** Missense D1-55/56 1 115 G>A Wissense D1-55/56 1 1187 T>C Q419X** Missense D1-55/56 1 1187 T>C Q419X** Missense D1/DII 1 1255 C>T Q419X** Missense D1/DII 1 1338 +2 T>A** B439K** Missense D1/DII 1 1337 delC S476R\$X310* Frame shift D1/DII 1 1502 delA K5215\$x310* Frame shift <t< td=""><td>Exon 9</td><td>1052 G>A</td><td>G351D*</td><td>Missense</td><td>DI-S5/S6</td><td>1</td><td>2</td></t<>	Exon 9	1052 G>A	G351D*	Missense	DI-S5/S6	1	2
1099 C>T R367C Missense D1-55/56 2 1100 G>T R367L* Missense D1-55/56 1 1100 G>A M369K Missense D1-55/56 1 1100 G>A W374G* Missense D1-55/56 1 1120 T>G W374G* Missense D1-55/56 1 1156 G>A G386R* Missense D1-55/56 1 1156 G>A Q386R* Missense D1-55/56 1 1157 G>A Q386R* Missense D1-55/56 1 1187 T>C V396L* Missense D1-55/56 1 1187 T>C Q419X* Missense D1/DII 1 1156 G>A E439K* Missense D1/DII 1 1157 G>A B439K* Missense D1/DII 1 1157 G>A B510G Missense D1/DII 1 1157 G>A B510G Missense D1/DII 1 1153 delC B510G Missense	Exon 9	1066 G>A	D356N	Missense	DI-S5/S6	8	1, 2, 4, 6, 7
100 G>T R36TL* Missense D1-S5/S6 1 1100 G>A R367H Missense D1-S5/S6 6 1100 G>A M369K Missense D1-S5/S6 1 1120 T>G W374G* Missense D1-S5/S6 1 1121 G>A G38G** Missense D1-S5/S6 1 1157 G>A G38G** Missense D1-S5/S6 1 1157 G>A G38G** Missense D1-S5/S6 1 1187 T>C V39G** Missense D1-S5/S6 1 1187 T>C Q419X** Missense D1/DII 1 1356 C>T Q419X** Missense D1/DII 1 1315 G>A B439K** Missense D1/DII 1 1328 L431 delCAAG S476R\$X30* Frame shiff D1/DII 1 1502 A>G B501G Missense D1/DII 1 1552 delA K5215\$x102* Frame shiff D1/DII 1 1557 C>A R526H**	Exon 9	1099 C>T	R367C	Missense	DI-S5/S6	2	3
100 G>A R367H Missense D1-S5/S6 6 1106 T>A M369K Missense D1-S5/S6 1 1120 T>G W374G* Missense D1-S5/S6 1 1120 T>A R376H Missense D1-S5/S6 1 1156 G>A G38G** Missense D1-S5/S6 1 1157 G>A G38G** Missense D1-S5/S6 1 1187 T>C V39G** Missense D1-S6/S 1 1187 T>C V39G** Missense D1/DII 1 1187 T>C Q419X** Missense D1/DII 1 1187 T>C Missense D1/DII 1 1187 G>A A Missense D1/DII 1 1187 G>A B510G Missense D1/DII 1 1502 A>G B513 V5R* Frame shift D1/DII 1 1537 del K5215ks/Y102* Frame shift D1/DII 1 1537 G Missense D1/DII 1	Exon 9	1100 G>T	R367L*	Missense	DI-S5/S6	1	1
1106 T>A M369K Missense DI-S5/S6 1 1120 T>G W374G** Missense DI-S5/S6 1 1120 T>A R376H Missense DI-S5/S6 1 115 G>A G386E** Missense DI-S5/S6 1 1157 G>A Q386E* Missense DI-S5/S6 1 1187 T>C V396A** Missense DI-S6 1 1187 T>C V396A** Missense DI-S6 1 1187 T>C Q419X** Missense DI/DII 1 1187 T>C Q419X** Missense DI/DII 1 1187 T>C Q419X** Missense DI/DII 1 1187 G>A S476K\$30** Frame shift DI/DII 1 1502 A>G B501G Missense DI/DII 1 1537 del K515KX102** Frame shift DI/DII 1 1577 G>A K526H** Missense DI/DII 1 1577 G>A K521KX102** Frame shi	Exon 9	1100 G>A	R367H	Missense	DI-S5/S6	9	1, 2, 8, 9
1120 T>G W374G* Missense DI-S5/S6 1 1127 G>A R376H Missense DI-S5/S6 4 1156 G>A G38GR* Missense DI-S5/S6 1 1157 G>A V396L* Missense DI-S5/S6 2 1187 T>C V396A* Missense DI-S6 1 1187 T>C V396A* Missense DI/DII 1 1131 G>A E439K* Missense DI/DII 1 1338 +2 T>A* A56KfsX30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1502 A>G B513VfsX8* Frame shift DI/DII 1 1502 A>G K521SfsX102* Frame shift DI/DII 1 1577 G>A K521SfsX102* Frame shift DI/DII 1 1577 G>A K526H* Missense DI/DII 4	Exon 9	1106 T>A	M369K	Missense	DI-S5/S6	1	1
1127 G>A R376H Missense DI-SS/S6 4 1156 G>A G386R* Missense DI-SS/S6 1 1157 G>A G386E* Missense DI-SS/S6 2 1186 G>C V396L* Missense DI-SS/S6 1 1187 T>C V396A* Missense DI-SG 1 1187 T>C Q419X* Nonsense DI/DII 1 1315 G>A E439K* Missense DI/DII 1 1338 +2 T>A* S476RfsX30* Frame shift DI/DII 1 1428_1431delCAAG S476RfsX30* Frame shift DI/DII 1 1502 A>G B513VfsX8* Frame shift DI/DII 1 1557delC K521SfsX102* Frame shift DI/DII 1 1557 G>A K521SfsX102* Frame shift DI/DII 2 1557 C>A K525H* Missense DI/DII 4	Exon 9	1120 T>G	W374G*	Missense	DI-S5/S6	1	1
1156 G>A G386R* Missense DI-S5/S6 1 1157 G>A G386E* Missense DI-S5/S6 2 1187 G>C V396L* Missense DI-S6 1 1187 T>C V396A* Missense DI-S6 1 1187 T>C Q419X* Missense DI/DII 1 1315 G>A E439K* Missense DI/DII 1 1338 +2 T>A* S476Rf\$X30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1537 delC K513Yf\$X8* Frame shift DI/DII 1 1577 G>A K521Sf\$X102* Frame shift DI/DII 1 1577 G>A K521Sf\$X102* Frame shift DI/DII 2 1557 G>A K525H* Missense DI/DII 4	Exon 9	1127 G>A	R376H	Missense	DI-S5/S6	4	3, 4, 8
1157 G>A G386E* Missense DI-S5/S6 2 1186 G>C V396L* Missense DI-S6 1 1187 T>C V396A* Missense DI-S6 1 1255 C>T Q419X* Nonsense DI/DII 1 1315 G>A E439K* Missense DI/DII 1 1338 +2 T>A* Splice site DI/DII 1 1428_1431delCAAG S476RfsX30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1537delC K513YfsX8* Frame shift DI/DII 1 1562delA K526H* Missense DI/DII 1 1597 C>A K526H* Missense DI/DII 1 1595 T>G Missense DI/DII 4	Exon 10	1156 G>A	G386R*	Missense	DI-S5/S6	-	1
1186 G>C V396L* Missense DI-S6 1 1187 T>C V396A* Missense DI-S6 1 1255 C>T Q419X* Nonsense DI/DII 1 1315 G>A E439K* Missense DI/DII 1 1338 +2 T>A* Splice site DI/DII 1 1428_1431delCAAG S476Rf\$X30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1537delC K513Yf\$X8* Frame shift DI/DII 1 1577 G>A K521Sf\$X102* Frame shift DI/DII 1 1577 G>A K526H* Missense DI/DII 2 1595 T>G K532C Missense DI/DII 4	Exon 10	1157 G>A	G386E*	Missense	DI-S5/S6	2	2
1187 T>C V396A* Missense DI-S6 1 1255 C>T Q419X* Nonsense DI/DII 1 1315 G>A E439K* Missense DI/DII 1 1338 +2 T>A* Splice site DI/DII 1 1428_1431 delCAAG S476KfsX30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1537 delC K513YfsX8* Frame shift DI/DII 1 1562 delA K521SfsX102* Frame shift DI/DII 1 1577 G>A K526H* Missense DI/DII 1 1595 T>G K532C Missense DI/DII 4 1603 C>T R535X Nonsense DI/DII 4	Exon 10	1186 G>C	V396L*	Missense	DI-S6	1	1
1315 G>A Q419X* Nonsense D/DII 1 1315 G>A E439K* Missense D/DII 1 1338 +2 T>A* Splice site D/DII 1 1428_1431 delCAAG S476Rf\$X30* Frame shift D/DII 1 1502 A>G D501G Missense D/DII 1 1537 delC R513 Vf\$X8* Frame shift D/DII 1 1562 delA K521Sf\$X102* Frame shift D/DII 1 1577 G>A R526H* Missense D/DII 2 1595 T>G R532C Missense D/DII 4 1603 C>T R535X Nonsense D/DII 4	Exon 10	1187 T>C	V396A*	Missense	9S-IQ	1	2
1315 G>A E439K** Missense DI/DII 1 1338 + 2 T>A* Splice site DI/DII 1 1428_1431 delCAAG \$476RfsX30* Frame shift DI/DII 1 1502 A>G D501G Missense DI/DII 1 1537 delC R513 VfsX8* Frame shift DI/DII 1 1562 delA K521 SfsX102* Frame shift DI/DII 1 1577 G>A R526H* Missense DI/DII 2 1595 T>G Missense DI/DII 4	Exon 10	1255 C>T	Q419X*	Nonsense	DI/DII	-	7
1328 + 2 T > A* Splice site DI/DII 1 1428 _ 1431delCAAG \$476RfsX30* Frame shift DI/DII 1 1502 A > G D501G Missense DI/DII 1 1537delC R513VfsX8* Frame shift DI/DII 1 1562delA K521SfsX102* Frame shift DI/DII 1 1577 G>A R526H* Missense DI/DII 2 1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 10	1315 G>A	E439K*	Missense	DI/DII	1	3
1428_1431delCAAG S476RfsX30* Frame shift DVDII 1 1502 A>G D501G Missense DVDII 1 1537delC R513VfsX8* Frame shift DVDII 1 1562delA K521SfsX102* Frame shift DVDII 1 1577 G>A R526H* Missense DVDII 2 1595 T>G K532C Missense DVDII 1 1603 C>T R535X Nonsense DI/DII 4	Intron 10	1338 +2 T>A*		Splice site	DI/DII	-	9
1502 A>G D501G Missense DI/DII 1 1537delC R513VfsX8* Frame shift DI/DII 1 1562delA K521SfsX102* Frame shift DI/DII 1 1577 G>A R526H* Missense DI/DII 2 1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 11	1428_1431delCAAG	S476RfsX30*	Frame shift	DI/DII	-	3
1537delC R513Vfs.X8* Frame shift DI/DII 1 1562delA K521Sfx.102* Frame shift DI/DII 1 1577 G>A R526H* Missense DI/DII 2 1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 11	1502 A>G	D501G	Missense	DI/DII	1	3
1562delA K521SfsX102* Frame shift DI/DII 1 1577 G>A R526H* Missense DI/DII 2 1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 12	1537delC	R513VfsX8*	Frame shift	. IId/Id	-	∞
1577 G>A R526H* Missense DI/DII 2 1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 12	1562delA	K521SfsX102*	Frame shift	DI/DII	1	2
1595 T>G F532C Missense DI/DII 1 1603 C>T R535X Nonsense DI/DII 4	Exon 12	1577 G>A	R526H*	Missense	DI/DII	2	1,5
1603 C>T R535X Nonsense DI/DII 4	Exon 12	1595 T>G	F532C	Missense	DI/DII	1	2
	Exon 12	1603 C>T	R535X	Nonsense	DI/DII	4	1, 2, 4, 5

;					mulviudais	
Exon 12	1629 T>A	F543L*	Missense	DI/DII	-	2
Exon 12	1654 G>A	G552R*	Missense	DI/DII	1	6
Exon 12	1717 C>T	Q573X*	Nonsense	DI/DII	-	2
Exon 12	1721delG	G574DfsX49*	Frame shift	DI/DII	1	2
Exon 12	1844 G>A	G615E	Missense	DI/DII	1	4
Exon 12	1855 C>T	L619F	Missense	DI/DII	1	1
Exon 12	1858 C>T	R620C*	Missense	DI/DII	1	1
Exon 12	1890 G>A	T630T*	Silent/splice site	DI/DII	3	1,3
Intron 12	1890 +5 G>A*		Splice site	DI/DII	2	2,5
Exon 13	1895 C>T	T632M	Missense	DI/DII	2	2,4
Exon 13	1918 C>G	P640A*	Missense	DI/DII	-	3
Exon 13	1936delC	Q646RfsX5*	Frame shift	DI/DII	3	2, 5, 6
Exon 13	1940 C>A	A647D*	Missense	DI/DII	1	5
Exon 13	1943 C>T	P648L	Missense	DI/DII	-	7
Exon 13	1950_1953delAGAT	D651AfsX25*	Frame shift	DI/DII	_	4
Exon 13	1981 C>T	R661W*	Missense	DI/DII	_	, ,
Exon 13	1983_1993dupGGCCCTCAGCG	A665GfsX16*	Frame shift	DI/DII	1	1
Exon 14	2024_2025delAG	E675VfsX45*	Frame shift/splice	DI/DII	_	2
Exon 14	2047 T>G	C683G*	Missense	DI/DII	1	7
Exon 14	2092 G>T	E698X*	Nonsense	DI/DII	1	2
Exon 14	2102 C>T	P701L	Missense	DI/DII	1	4
Exon 14	2150 C>T	P717L*	Missense	DII-S1	-	9
Exon 14	2201dupT	M734IfsX11*	Frame shift	DII-S1	1	7
Exon 14	2204 C>T	A735V	Missense	DII-S1	4	2, 4, 8, 9
Exon 14	2236 G>A	E746K	Missense	DII-S1/S2	3	1, 2, 7
Exon 14	2254 G>A	G752R	Missense	DII-S2	5	1,5
Exon 15	2273 G>A	G758E*	Missense	DII-S2	1	2
Exon 15	277442016	*				

Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated	Testing center
					mulviuuais	
Exon 15	2291 T>G	M764R*	Missense	DII-S2	1	4
Exon 15	2314 G>A	D772N	Missense	DII-S2/S3	1	1
Exon 15	2317 C>T	P773S*	Missense	DII-S2/S3	-	9
Exon 15	2320delT	Y774TfsX28*	Frame shift	DII-S2/S3	2	3
Exon 15	2326_2328delTAC	Y776del*	In-frame del	DII-S2/S3	-	2
Exon 15	2365 G>A	*1687V	Missense	DII-S3	1	4
Exon 15	2423 G>C	R808P*	Missense	DII-S4	-	1
Exon 15	2435_24363delTGGTAinsCGCCT L812P†*	L812P†*	Indel/splice site	DII-S4	П	5
Exon 16	2465 G>A	W822X	Nonsense	DII-S4	-	4
Exon 16	2516 T>C	L839P*	Missense	DII-S4/S5	П	1
Exon 16	2533delG	V845CfsX2*	Frame shift	DII-SS	П	9
Exon 16	2549_2550insTG	F851GfsX19*	Frame shift	DII-S5	-	2
Exon 16	2550_2551dupGT	F851CfsX19*	Frame shift	DII-S5	1	5
Exon 16	2553 C>A	F851L	Missense	DII-S5	_	2
Exon 16	2582_2583delTT	F861WfsX90	Frame shift	DII-S5	11	3,7
Exon 16	2599 G>C	E867Q*	Missense	DII-S5/S6	П	2
Exon 16	2602delC	X898T	Frame shift	DII-S5/S6	2	6,7
Exon 16	2632 C>T	R878C	Missense	DII-S5/S6	1	2
Exon 16	2633 G>A	R878H*	Missense	DII-S5/S6	5	1, 2, 4, 5, 7
Exon 16	2657 A>C	H886P*	Missense	DII-S5/S6	1	2
Exon 16	2677 C>T	R893C*	Missense	DII-S5/S6	2	4
Exon 16	2678 G>A	R893H*	Missense	DII-S5/S6	3	1, 3, 4
Exon 16	2701 G>A	E901K*	Missense	DII-S5/S6	3	1,4
Exon 16	2729 C>T	Z910L	Missense	DII-S5/S6	1	1
Exon 16	2743 T>C	C915R*	Missense	9S-IIQ	-	3
Exon 16	2750 T>G	L917R*	Missense	9S-IIQ	1	2
Exon 16	2780 A>G	N927S	Missense	9S-IIQ	3	3,7
Exon 16	2783 T>C	L928P*	Missense	DII-S6	1	1

Bon 11 3804 P-C 1939** Missense DIL-56 1 5 Bon 11 3804 P-C Bo51M6X6* Fame shift DIDDII 3 4,4,5 Bon 11 3804 G-A R965H Missense DIDDII 3 4,4,5 Bon 12 2894 G-A R965H Missense DIDDII 3 2,4,5 Bon 11 2995 G-A A9977* Frame shift DIDDII 3 2,4,5 Bon 11 310-314dapTG P104-3745K38* Frame shift DIDDII 3 4,4,5 Bon 11 310-314dapTG P104-3745K38* Frame shift DIDDII 3 4,4,5 Bon 11 310-344-34 Missense DIDDII 3 1 1 Bon 11 310-34-44 Missense DIDDII 3 1 1 Bon 11 310-34-44 Missense DIDDII 3 1 1 1 1 1 1 1 1 1 1 1 1	Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
893 CyT R965C Miseane DIJDIII 1 894 CyA R965T Miseane DIJDIII 3 894 CyA R965H Miseane DIJDIII 3 994 CyA R965H Miseaneshift DIJDIII 1 914 2923delTTGCTCAAGC P102H6X2S Frame shift DIJDIII 1 3105_3012delCCAGCTGC P104R5X2S Frame shift DIJDIII 1 3140_314dupTG P104R5X3S Frame shift DIJDIII 1 3146 A>C D105TEiXSR Missense DIJDIII 1 3146 A>C D105TEiXSR Missense DIJDIII 1 3146 A>C MI113X* Missense DIJDIII 1 3146 C>A MI115X* Missense DIJDIII 1 3146 C>A MI115X* Missense DIJDIII 1 3146 C>A MI115X* Missense DIJDIII 1 3245 G>A MI115X* Missense DIJDIII 1 364 C>T <t< td=""><td>Exon 17</td><td>2804 T>C</td><td>L935P*</td><td>Missense</td><td>DII-S6</td><td>1</td><td>5</td></t<>	Exon 17	2804 T>C	L935P*	Missense	DII-S6	1	5
8987—T R985C Missense DII/DIII 3 2894—C>A R965H Missense DII/DIII 1 2914—2923deITTGCAAGC F972G6X170* Frame shift DII/DIII 1 3980—A A997T* Missense DII/DIII 1 3140_314ldupTG P1002HfsX25* Frame shift DII/DIII 1 3140_314ldupTG P1048CfsX98* Frame shift DII/DIII 1 3140_314ldupTG D1055G* Missense DII/DIII 1 3141_314dupTG D1055G* Missense DII/DIII 1 3171_317defTGinsA Missense DII/DIII 1 3170_AberT* Missense DII/DIII 1 3140_C-A W1113X* Missense DII/DIII 1 3140_C-A W1113X* Missense DII/DIII 1 3140_C-C W1119X* Missense DII/DIII 1 3140_C-C W1192X* Missense DII/DIII 1 3252_G-C-A W1192X* <td>Exon 17</td> <td>2850delT</td> <td>D951MfsX6*</td> <td>Frame shift</td> <td>DII/DIII</td> <td>1</td> <td>4</td>	Exon 17	2850delT	D951MfsX6*	Frame shift	DII/DIII	1	4
2894 G>A R965H Missense DILDIII 1 2914_2923delTTTGTCAAGC F972GfSXT70* Frame shift DILDIII 1 2989 G>A A997T* Missense DILDIII 1 3005_3012delCCAGCTGC P1002HfSX25* Frame shift DILDIII 1 3140_3141dupTG P1048CfSX98* Frame shift DILDIII 1 3157 G>A D1055G* Missense DILDIII 1 3140 G>C D1057GfX88* Frame shift DILDIII 1 3138 C>T A1113V* Missense DILDIII 1 3145 G>A Q11187* Missense DILDIII 1 3145 G>A W1115X* Missense DILDIII 1 3145 G>A Q1185Gfx5x5* Frame shift DILDIII 1 3156 G>A W1192X* Nonsense DILDIII 1 3654 G>A B1228K Missense DIL-SII 1 3656 G>A S1219KY* Missense DIL-SII 1	Exon 17	2893 C>T	R965C	Missense	DII/DIII	3	2, 4, 5
914_2923delTTTGTCAAGC Fy972GEXT10* Frame shift DIUDIII 1 389_G>A 4997T* Missense DIUDIII 1 3005_3012delCCAGCTGC P1002HEX25* Frame shift DIUDIII 1 3140_3141dupTG P1048CEX98* Frame shift DIUDIII 1 3157 G>A D1055G* Missense DIUDIII 3 3173 G>A D1057EEX88* Insertion/deletion DIUDIII 1 3173 G>A A1113V* Missense DIUDIII 1 3145 G>A A1113V* Missense DIUDIII 1 3145 G>A W1115X* Missense DIUDIII 1 3145 G>A W1115X* Missense DIUDIII 1 3140 G>C W1192X* Nonsense DIUDIII 1 365 G>A W1192X* Nonsense DIU-SI 1 3656 G>A S1190X* Missense DIII-SI 1 3666delG Y1228H* Missense DIII-SI 1	Exon 17	2894 G>A	R965H	Missense	DII/DIII	1	3
989 G>A A99TT* Missense DIUDIII 1 3005_3012delCCAGCTGC P1002HEX25* Frame shift DIUDIII 1 3140_3141dupTG P1048CEX308* Frame shift DIUDIII 1 3140_A>G D1055G* Missense DIUDIII 1 3171_3172delTGinsA D1057EfxX8* Insertion/deletion DIUDIII 1 3172_4A>G S1079Y* Missense DIUDIII 1 3141_6C>A A1113V* Missense DIUDIII 1 3141_6C>A W1113X* Nonsense DIUDIII 1 3141_6C>A W1113X* Missense DIUDIII 1 3553_3554delCA W1113X* Missense DIII-DIII 1 3556_A W119X* Monsense DIII-DIII 1 365_A A Missense DIII-SICS 4 365_A A Missense DIII-SICS 4 365_A A Missense DIII-SICS 1 365_A	Exon 17	2914_2923delTTTGTCAAGC	F972GfsX170*	Frame shift	DII/DIII	1	9
3005_3012deICCAGCTGC P1002HfsX25* Frame shift DIJDIII 1 3140_3141dupTG P1048CfsX98* Frame shift DIJDIII 1 3157 G>A D1055G** Missense DIJDIII 1 3164 A>G D1055G** Missense DIJDIII 1 3174 A>G D1055G** Missense DIJDIII 1 3175 G>A A1113V* Missense DIJDIII 1 3338 C>T A1113V* Missense DIJDIII 1 3419 G>C W1115X* Nonsense DIJDIII 1 3419 G>C W1192X* Nonsense DIJDIII 1 3624 G>A W1192X* Nonsense DIJDIII 1 3625 G>A W1192X* Nonsense DIJCSII 1 365 G>A A1233PfsX7* Frame shiffysplice DIJCSII 4 365 G>A A1223PfsX7* Frame shiffysplice DIJCSII 4 365 G>A A1223PfsX7* Missense DIJCSII 1 <	Exon 17	2989 G>A	A997T*	Missense	DII/DIII	1	5
3140_3141dupTG P1048CEXN98* Frame shift DIJDIII 1 3157 G>A B1053G* Missense DIJDIII 3 3164 A>G D1055G* Missense DIJDIII 1 3173 J224 +2deJT* S1079Y* Missense DIJDIII 1 3228 +2deJT* S1079Y* Missense DIJDIII 1 3338 C>A A1113V* Missense DIJDIII 1 345 G>A W1115X* Nonsense DIJDIII 1 345 G>A W1115X* Nonsense DIJDIII 1 3553 J554delCA Q1185GfsX55* Frame shift DIJDIII 1 362 G>A W1192X* Nonsense DIII-SI 1 362 G>A J60A Missense DIII-SI 1 365 G>A A1223PfsX7* Frame shift/splice DIII-SI/S2 4 365 G>A A1223PfsX7* Missense DIII-SI/S2 1 365 G>A X1223W Missense DIII-SI/S2 1 3695 G	Exon 17	3005_3012delCCAGCTGC	P1002HfsX25*	Frame shift	DII/DIII	-	7
3157 G>A E1053K Missense DIUDIII 3 3164 A>G D1057ExX88* Missense DIUDIII 1 3171_3172delTGinsA D1057ExX88* Insertion/deletion DIUDIII 1 3228 +2delT** \$1079Y** Missense DIUDIII 1 3336 C>A A1113V** Missense DIUDIII 1 3419 G>C \$1140T** Missense DIUDIII 1 345 G>A \$1140T** Missense DIUDIII 1 3553_3554delCA \$1140T** Missense DIUDIII 1 365 G>A \$11212def** In-frame del DIUDIII 1 3656 G>A \$1219N Missense DIII-SI 1 3673 G>A \$1223P Missense DIII-SI/S2 4 3674 C>T \$1223P Missense DIII-SI/S2 1 3675 G>A \$1232Q** Missense DIII-SI/S2 4 3675 G>A \$11234P* Missense DIII-SI/S2 1 367	Exon 17	3140_3141dupTG	P1048CfsX98*	Frame shift	DII/DIII	1	3
164 A>G D1055G** Missense DIVDIII I 3171_3172delTGinsA D1057EfxX88* Insertion/deletion DIVDIII I 3328 +2delT** S1079Y** Missense DIVDIII I 3336 C>A A1113V* Missense DIVDIII I 3345 G>A W1115X** Nonsense DIVDIII I 3445 G>A W1115X* Nonsense DIVDIII I 345 G>A W1115X* Nonsense DIVDIII I 3553_3554delCA Q1185GfxX55 Frame shift DII/DIII I 3556 G>A W1192X* Nonsense DIII-SI I 3654 G>A S1219N Missense DIII-SI I 3656 G>A A1223PfxX7* Frame shift/splice DIII-SI I 3654 G>A S1219N Missense DIII-SI/S2 4 3665 G>A W1223PfxX7* Missense DIII-SI/S2 4 3665 G>A R1223Q* Missense DIII-SI/S2 3	Exon 17	3157 G>A	E1053K	Missense	DII/DIII	3	1
171_3172deITGinsA DI057Ef5X88* Insertion/deletion DII/DIII I 3228 +2deIT** \$pice site DII/DIII I 3336 C>A A1113V* Missense DII/DIII I 3345 G>A W1115X** Nonsense DII/DIII I 3449 G>C \$1140T* Missense DII/DIII I 3553_3554delCA \$1140T* Missense DII/DIII I 3553_3554delCA Q1185Gf8X55* Frame shift DII/DIII I 3553_3554delCA W1192X* Nonsense DIII-S1 I 3656 G>A U1212del* In-frame del DIII-S1 I 3656 G>A A1223Pf8X7* Frame shift/splice DIII-S1 I 365 G>A HI223F Frame shift/splice DIII-S1/S2 I 365 G>A HI223F Frame shift/splice DIII-S1/S2 I 365 G>A HI223F Missense DIII-S1/S2 I 3694 C>T R1232Q* Missense DIII-S1/S2 I <td>Exon 17</td> <td>3164 A>G</td> <td>D1055G*</td> <td>Missense</td> <td>DII/DIII</td> <td>1</td> <td>1</td>	Exon 17	3164 A>G	D1055G*	Missense	DII/DIII	1	1
3336 C>A Splice site DIJDIII 1 3336 C>A A1113V* Missense DIJDIII 1 3338 C>T A1113V* Missense DIJDIII 1 3345 C>A W1115X* Nonsense DIJDIII 1 3419 G>C \$1140T* Missense DIJDIII 1 3553_3554delCA Q1185Gfx55* Frame shiff DIJDIII 1 3556 G>A W1192X* Nonsense DIII-SI 1 3656 G>A S1219N Missense DIII-SI 1 3666delG A1223Pfx7* Frame shiff/splice DIII-SI 4 3667 C>A B1225K Missense DIII-SI 1 3694 C>T R1232W Missense DIII-SI/S2 1 3695 G>A R1232Q* Missense DIII-SI/S2 1 3695 G>A R1232Q* Missense DIII-SI/S2 1 3716 T>C B1235Q* Missense DIII-SI/S2 1 3717 G>A B1243N* <td< td=""><td>Exon 17</td><td>3171_3172delTGinsA</td><td>D1057EfsX88*</td><td>Insertion/deletion</td><td>DII/DIII</td><td>-</td><td>7</td></td<>	Exon 17	3171_3172delTGinsA	D1057EfsX88*	Insertion/deletion	DII/DIII	-	7
3338 C>A Missense DII/DIII 1 3338 C>T A1113V* Missense DII/DIII 1 3345 G>A W1115X* Nonsense DII/DIII 1 3419 G>C S1140T* Missense DII/DIII 1 3553_3554delCA Q1185Gfxx53* Frame shift DII/DIII 1 3576 G>A W1192X* Nonsense DIII/DIII 1 3654_363delATC 11212del* In-frame del DIII-S1 1 3656 G>A S1219N Missense DIII-S1 1 3664 C>A Y1228H Missense DIII-S1/S2 4 3694 C>T Y1228H Missense DIII-S1/S2 1 3695 G>A R1232Q* Missense DIII-S1/S2 1 3716 T>C L1239P* Missense DIII-S1/S2 1 3777 G>A DI243N* Missense DIII-S1/S2 1	Intron 17	3228 +2delT*		Splice site	DII/DIII	-	3
3338 C>T A1113V* Missense DII/DIII 1 3345 G>A W1115X* Nonsense DII/DIII 1 3419 G>C S1140T* Missense DII/DIII 1 3553_3554delCA Q1185GfsX55* Frame shift DII/DIII 1 3566 G>A W1192X* Nonsense DIII-S1 1 3656 G>A 11212del* In-frame dele DIII-S1 1 366 delG 51219N Missense DIII-S1 1 366 delG A1223PfsX* Frame shift/splice DIII-S1 1 366 delG A1223PfsX* Frame shift/splice DIII-S1 1 366 delG A1223PfsX* Missense DIII-S1/S2 4 369 C>A Y1228H Missense DIII-S1/S2 3 3695 C>A R1232Q* Missense DIII-S1/S2 1 3716 T>C L1239P* Missense DIII-S1/S2 1 3727 G>A DII-S1 Missense DIII-S1/S2 1	Exon 18	3236 C>A	\$1079Y*	Missense	DII/DIII	1	1
345 G>A W1115X* Nonsense DII/DIII I 3419 G>C \$1140T* Missense DII/DIII I 3553_3554delCA Q1185GfsX55* Frame shift DII/DIII I 3560_BA W1192X* Nonsense DIII/SII I 3634_3636delATC L1208X Nonsense DIII-SI I 3656 G>A S1219N Missense DIII-SI I 366delG A1223PfsX7* Frame shiff/splice DIII-SI I 3662 G>A S1219N Missense DIII-SI I 3662 F>C Y1228H Missense DIII-SI/S2 4 3694 C>T K1232W Missense DIII-SI/S2 3 3695 G>A R1232Q* Missense DIII-SI/S2 1 3716 T>C L1239P* Missense DIII-SI/S2 1 3777 G>A DII-SI Missense DIII-SI/S2 1	Exon 18	3338 C>T	A1113V*	Missense	DII/DIII	1	5
3419 G>C \$1140T* Missense DII/DIII I 3553_3554delCA Q1185GfsX55* Frame shift DII/DIII I 356 G>A W1192X* Nonsense DIII/SII I 3634_3636delATC 11212del* In-frame del DIII-SI I 3656 G>A \$1219N Missense DIII-SI I 366delG A1223PfsX* Frame shiff/splice DIII-SI I 3662 G>A H1223PfsX* Aframe shiff/splice DIII-SI I 3662 G>A Y1228H Missense DIII-SI/S2 4 3694 C>T R1232W Missense DIII-SI/S2 3 3695 G>A R1233Q* Missense DIII-SI/S2 1 3716 T>C L1239P* Missense DIII-SI/S2 1 3777 G>A DII-SI Missense DIII-SI/S2 1	Exon 18	3345 G>A	W1115X*	Nonsense	DII/DIII	1	9
3553_3554delCA Q1185GfsX55* Frame shift DII/DIII 1 3576 G>A W1192X* Nonsense DIII-SI 1 3622 G>T E1208X Nonsense DIII-SI 1 3634_3636delATC 11212del* In-frame del DIII-SI 1 3656 G>A S1219N Missense DIII-SI 1 366delG A1223PfsX7* Frame shiff/splice DIII-SI 1 3662 T>C Y1228H Missense DIII-SI/S2 4 1 3694 C>T R1232W Missense DIII-SI/S2 3 3 3695 G>A R1233Q* Missense DIII-SI/S2 1 2 3716 T>C L1239P* Missense DIII-SI/S2 1 2 3777 G>A DII-SI Missense DIII-SI/S2 5 1	Exon 19	3419 G>C	S1140T*	Missense	DII/DIII	-	5
3576 G>A W1192X* Nonsense DII/DIII 1 3622 G>T E1208X Nonsense DIII-S1 1 3634_3636delATC 11212del* In-frame del DIII-S1 1 3656 G>A S1219N Missense DIII-S1 1 366delG A1223PfsX7* Frame shiff/splice DIII-S1 1 3662 T>C Y1228H Missense DIII-S1/S2 4 3694 C>T R1232W Missense DIII-S1/S2 3 3695 G>A R1233Q* Missense DIII-S1/S2 1 3716 T>C L1239P* Missense DIII-S1/S2 1 3777 G>A DII-S1 Missense DIII-S1/S2 1	Exon 20	3553_3554delCA	Q1185GfsX55*	Frame shift	DII/DIII	Ţ.	3
3634_3636delATC E1208X Nonsense DIII-S1 1 3634_3636delATC 11212del* In-frame del DIII-S1 1 3656 G>A S1219N Missense DIII-S1 1 366delG A1223PfsX7* Frame shift/splice DIII-S1 1 3673 G>A H1225K Missense DIII-S1/S2 4 1 3694 C>T R1232W Missense DIII-S1/S2 3 3695 G>A R1233Q* Missense DIII-S1/S2 1 3716 T>C L1239P* Missense DIII-S1/S2 1 3777 G>A DI243N* Missense DIII-S2 5	Exon 20	3576 G>A	W1192X*	Nonsense	DII/DIII	1	9
3634_3636delATC 11212del* In-frame del DIII-S1 1 3656 G>A S1219N Missense DIII-S1 1 3666delG A1223PfsX7* Frame shiff/splice DIII-S1 1 3673 G>A E1225K Missense DIII-S1/S2 4 3694 C>T R1232W Missense DIII-S1/S2 3 3695 G>A R1232Q* Missense DIII-S1/S2 1 3716 T>C L1239P* Missense DIII-S2 1 3777 G>A DI243N* Missense DIII-S2 5	Exon 20	3622 G>T	E1208X	Nonsense	DIII-S1	1	1
3656 G>A S1219N Missense DIII-S1 1 366 delG A1223PfsX7* Frame shiff/splice DIII-S1 1 3673 G>A H1225K Missense DIII-S1/S2 4 1 3682 T>C Y1228H Missense DIII-S1/S2 1 1 3694 C>T R1232W Missense DIII-S1/S2 3 1 3695 G>A R1232Q* Missense DIII-S1/S2 1 2 3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A DI243N* Missense DIII-S2 5 1	Exon 20	3634_3636delATC	11212del*	In-frame del	DIII-S1	1	2
366delG A1223PfsX7* Frame shiff/splice DIII-SI 1 3673 G>A E1225K Missense DIII-SI/S2 4 3682 T>C Y1228H Missense DIII-SI/S2 1 3694 C>T R1232W Missense DIII-SI/S2 3 3695 G>A R1233Q* Missense DIII-SI/S2 1 3716 T>C L1239P* Missense DIII-S2 1 3727 G>A D1243N* Missense DIII-S2 5	Exon 20	3656 G>A	S1219N	Missense	DIII-S1	1	1
3673 G>A E1225K Missense DIII-SI/S2 4 3682 T>C Y1228H Missense DIII-SI/S2 1 3694 C>T R1232W Missense DIII-SI/S2 3 1 3695 G>A R1232Q* Missense DIII-SI/S2 1 7 3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A DI243N* Missense DIII-S2 5 1	Exon 20	3666delG	A1223PfsX7*	Frame shift/splice	DIII-S1	1	1
3682 T>C Y1228H Missense DIII-SI/S2 1 1 3694 C>T R1232W Missense DIII-SI/S2 3 1, 2, 2 3695 G>A R1232Q* Missense DIII-SI/S2 1 7 3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A DI243N* Missense DIII-S2 5 1, 2,	Exon 21	3673 G>A	E1225K	Missense	DIII-S1/S2	4	1, 5, 6, 7
3694 C>T R1232W Missense DIII-SI/S2 3 1, 2, 3695 G>A R1232Q* Missense DIII-SI/S2 1 7 3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A DI243N* Missense DIII-S2 5 1, 2,	Exon 21	3682 T>C	Y1228H	Missense	DIII-S1/S2	1	1
3695 G>A R1232Q* Missense DIII-S1/S2 1 7 3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A D1243N* Missense DIII-S2 5 1, 2,	Exon 21	3694 C>T	R1232W	Missense	DIII-S1/S2	8	1, 2, 9
3716 T>C L1239P* Missense DIII-S2 1 2 3727 G>A D1243N* Missense DIII-S2 5 1, 2,	Exon 21	3695 G>A	R1232Q*	Missense	DIII-S1/S2	1	7
3727 G>A DI243N* Missense DIII-S2 5 1, 2,	Exon 21	3716 T>C	L1239P*	Missense	DIII-S2	1	2
	Exon 21	3727 G>A	D1243N*	Missense	DIII-S2	5	1, 2, 5

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Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated	Testing center
	0	0	;		individuals	
Exon 21	3746 T>A	V1249D*	Missense	DIII-S2	1	9
Exon 21	3758 A>G	E1253G*	Missense	DIII-S2	1	1
Exon 21	3784 G>A	G1262S	Missense	DIII-S2	1	1
Exon 21	3813 G>C	W1271C*	Missense	DIII-S3	1	1
Exon 21	3823 G>A	D1275N	Missense	DIII-S3	3	1,5
Intron 21	3840 +1 G>A		Splice site	DIII-S3	9	1, 3, 4
Exon 22	3863 C>G	A1288G*	Missense	DIII-S3	1	4
Exon 22	3894delC	11299SfsX13*	Frame shift	DIII-S4	1	5
Exon 22	3932 T>C	L1311P*	Missense	DIII-S4	1	7
Exon 22	3956 G>T	G1319V	Missense	DIII-S4/S5	5	2, 3, 7
Intron 22	3963 +4 A>G*		Splice site	DIII-S4/S5	1	5
Intron 22	3963 +2 T>C		Splice site	DIII-S4/S5	1	1
Exon 23	3968 T>G	V1323G*	Missense	DIII-S4/S5	1	7
Exon 23	3995 C>T	P1332L	Missense	DIII-S4/S5	1	2
Exon 23	4018 G>A	V1340I*	Missense	DIII-S5	1	6
Exon 23	4030 T>C	F1344L*	Missense	DIII-S5	1	1
Exon 23	4036 C>A	L13461*	Missense	DIII-S5	1	4
Exon 23	4037 T>C	L1346P*	Missense	DIII-S5	1	3
Exon 23	4052 T>G	MI351R*	Missense	DIII-S5	1	2
Exon 23	4057 G>A	V1353M*	Missense	DIII-S5	7	2
Exon 23	4072 G>T	G1358W*	Missense	DIII-S5	1	4
Exon 23	4077 G>T	K1359N*	Missense	DIII-S5	-	4
Exon 23	4079 T>G	F1360C	Missense	DIII-S5/S6	1	
Exon 23	4088 G>A	C1363Y	Missense	DIII-S5/S6	1	3
Exon 23	4118 T>A	L1373X*	Nonsense	DIII-S5/S6	1	2
Exon 23	4145 G>T	S1382I	Missense	DIII-S5/S6	1	1
Exon 23	4147 C>T	Q1383X*	Nonsense	DIII-S5/S6	1	1
Exon 23	4178 T>A	L1393X	Nonsense	DIII-S5/S6	3	1, 3, 9

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Exon 23 4182 C-G Y1394X* Nonsense DIII-SSSG 1 5 Exon 23 4190delA K1397R\$X2 Fame shift DIII-SSSG 1 7 Exon 23 4213 C>-A V1405A* Mrisense DIII-SSSG 2 1,7 Exon 23 4213 C>-C V1405L Mrisense DIII-SSSG 2 1,7 Exon 24 4213 C>-C V1405C Mrisense DIII-SSSG 1 3 Exon 25 4213 C>-C C1406E Mrisense DIII-SSSG 1 1,4,5,7 Exon 24 4227 C>-C V1405C* Mrisense DIII-SSSG 1 1,4,5,7 Exon 24 4225 C>-C V1405C* Mrisense DIII-SSSG 1 2 Exon 24 4225 C>-C V1405C* Mrisense DIII-SSSG 1 4 Exon 25 422 C>-C A1427S* Mrisense DIII-SSSG 1 4 Exon 26 422 C>-C A1427S* Mrisense DIII-SSSG 1	Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
41304ddA K1397R£X2 Fnme shift DIII-58586 1 4213 G>A V1405M* Missense DIII-58586 2 4213 G>C G1406R* Missense DIII-58586 2 4215 G>C G1406R* Missense DIII-58586 2 4217 G>A G1408R* Missense DIII-58586 2 4222 G>A Y1409C** Missense DIII-58586 1 4224 C>C Y1409C** Missense DIII-58586 1 4225 A>C G1420R* Missense DIII-58586 1 4224 C>C A1428** Missense DIII-58586 1 4224 C>C A1428** Missense DIII-58586 1 4229 C>C A1428** Missense DIII-58586 1 4229 C>C A1428** Missense DIII-58586 1 4229 C>C A1432** Missense DIII-58586 1 4229 C>C A1433** Missense DIII-58586 1 4229 C>C	Exon 23	4182 C>G	Y1394X*	Nonsense	DIII-S5/S6	-	5
413 G>A V1405M* Missense DIII-SS/86 2 4213 G>C V1405L Missense DIII-SS/86 2 4216 G>C G1406R Missense DIII-SS/86 1 4217 G>A G1406R* Missense DIII-SS/86 1 4222 G>A Y1409C** Missense DIII-SS/86 1 4224 C>T X1419E** Missense DIII-SS/86 1 4225 A>G A14278* Missense DIII-SS/86 1 4224 C>T A14278* Missense DIII-SS/86 1 4228 G>C A14278* Missense DIII-SS/86 1 4229 G>C R1432G* Missense DIII-SS/86 1 4229 G>C R1433G* Missense DIII-SS/86 1 4229 G>C	Exon 23	4190delA	K1397RfsX2	Frame shift	DIII-S5/S6	1	6
413 G>C V1405L Missense DIII-55/56 2 4216 G>C G1406R Missense DIII-55/56 1 4217 G>A G1406R Missense DIII-55/56 2 4222 G>A G1408R Missense DIII-55/56 1 4224 C>G Y1409Q* Missense DIII-55/56 1 4227 C>G K1419E* Missense DIII-55/56 1 4227 C>G G1420R* Missense DIII-55/56 1 4228 C>C G1420R* Missense DIII-55/56 1 4229 G>T A1422R* Missense DIII-55/56 1 4229 G>C A1432R* Missense DIII-55/56 1 4229 G>C A1433R* Missense DIII-55/56 1 4229 G>C	Exon 23	4213 G>A	V1405M*	Missense	DIII-S5/S6	2	1,7
4116 G>C G1406R* Missense DIII-S5/S6 1 4217 G>A G1406E* Missense DIII-S5/S6 2 4222 G>A G1408R Missense DIII-S5/S6 7 4226 A>G Y1409C* Missense DIII-S5/S6 1 4227 C>G Y1409C* Missense DIII-S5/S6 1 4227 C>G K1419E* Missense DIII-S5/S6 1 4228 C>C G1420R* Missense DIII-S5/S6 1 4229 G>C R1422R* Missense DIII-S5/S6 1 4229 G>C R1432R* Missense DIII-S5/S6 1 4229 G>C R1432R* Missense DIII-S5/S6 1 4229 G>C G1433G* Splice site DIII-S5/S6 1 4229 G>C Y1434X* Nonsense DIII-S5/S6 1 4320 C>C Y1434X* Nonsense DIII-S5/S6 1 4331 C>C P1438L Missense DIII-S5/S6 1 4332 C>C	Exon 23	4213 G>C	V1405L	Missense	DIII-S5/S6	2	3
417 G>A G140GE* Missense DIII-55/56 2 422 G>A G140RR Missense DIII-55/56 7 422 G>A>G Y1409C* Missense DIII-55/56 1 4227 C>G Y1409C* Missense DIII-55/56 1 4227 C>G K1419E* Missense DIII-55/56 1 4258 G>C G1420R* Missense DIII-55/56 1 4279 G>T A1427S* Missense DIII-55/56 1 4294 A>G R1432G* Missense DIII-55/56 1 4296 G>C R1432S* Missense DIII-55/56 1 4299 G>A G1433Q* Nisense DIII-55/56 1 4299 H1GelG* Y1434X* Nonsense DIII-55/56 1 4300 C>A	Exon 23	4216 G>C	G1406R	Missense	DIII-S5/S6	1	3
4222 G>A G1408R Missense DIII-55/56 7 4226 A>G Y1409C* Missense DIII-55/56 1 4227 C>G Y1409X* Nonsense DIII-55/56 1 4227 C>G X1419E* Missense DIII-55/56 1 4255 A>G G1420R* Missense DIII-55/56 1 4258 G>C G1420R* Missense DIII-55/56 1 4299 G>C A1427S* Missense DIII-55/56 1 4294 A>G R1432G* Missense DIII-55/56 1 4299 G>C G1433G* Splice site DIII-55/56 1 4299 H G>T Splice site DIII-55/56 1 4299 H Golf* Splice site DIII-55/56 1 4299 H Golf* Nonsense DIII-55/56 1 4300 L G>A* Y1444X* Nonsense DIII-55/56 1 4313 C-T B1441Q* Missense DIII-55/56 1 4331 C-C B1448I* Missense <t< td=""><td>Exon 23</td><td>4217 G>A</td><td>G1406E*</td><td>Missense</td><td>DIII-S5/S6</td><td>2</td><td>5</td></t<>	Exon 23	4217 G>A	G1406E*	Missense	DIII-S5/S6	2	5
4226 A>G Y1409C** Missense DIII-S5/86 1 4227 C>G Y1409X** Nonsense DIII-S5/86 1 4234 C>T L1412F* Missense DIII-S5/86 1 4234 C>T G1420R* Missense DIII-S5/86 1 4235 A>G G1420R* Missense DIII-S5/86 1 4239 G>T A1428V* Missense DIII-S5/86 1 4294 A>G R1432G* Missense DIII-S5/86 1 4299 G>C G1433G* Missense DIII-S5/86 1 4299 G>A G1433G* Splice site DIII-S5/86 1 4299 HdelG* A299 HdelG* Splice site DIII-S5/86 1 4299 HdelG* A300 -1 G>A* Splice site DIII-S5/86 1 4302 P>G Y1434X* Nonsense DIII-S5/86 1 4313 C>T B14410* Missense DIII-S5/86 1 4320 G>A B1448I* Missense DIII-S5/86 1	Exon 23	4222 G>A	G1408R	Missense	DIII-S5/S6	7	1, 4, 5, 7
4227 C~G Y1409X* Nonsense DIII-55/56 1 4234 C~J L1412F* Missense DIII-55/56 1 4234 C~J K1419E* Missense DIII-55/56 1 4256 A~G G1420R* Missense DIII-55/56 1 4279 G~J A14278* Missense DIII-55/56 1 4294 A~G R1432G Missense DIII-55/56 1 4296 G~C R1432G Missense DIII-55/56 1 4296 G~C R1432G Missense DIII-55/56 1 4299 G~C G1433G* Splice site DIII-55/56 1 4299 HdelG* A190 Hdelg* Splice site DIII-55/56 1 4299 HdelG* Y1434X* Nonsense DIII-55/56 1 4300 -1 G~A* Y1434X* Nonsense DIII-55/56 1 4320 G~A W1440X Nonsense DIII-55/56 1 4321 G~C B1441Q* Missense DIII-55/56 1 4343	Exon 23	4226 A>G	Y1409C*	Missense	DIII-S5/S6	1	1
4234 C>T L1412F* Missense DIII-55/56 1 4255 A>G K1419E* Missense DIII-55/56 1 4258 G>C G1420R* Missense DIII-55/56 1 4279 G>T A1427S* Missense DIII-55/56 1 4294 A>G R1432S* Missense DIII-55/56 1 4296 G>C R1432S* Missense DIII-55/56 1 4299 G>C G1433V* Missense DIII-55/56 1 4299 G>C G1433V* Splice site DIII-55/56 1 4299 G>A Splice site DIII-55/56 1 4299 H G>T* Splice site DIII-55/56 1 4300 – I G>A* V1434X* Nonsense DIII-55/56 1 4300 – I G>A* W1440X* Nonsense DIII-55/56 1 4321 G>C E1441Q* Missense DIII-55/56 1 4343 T>C BII-48BT* Missense DIII-55/56 1 4343 T>C BII-44BT*	Exon 23	4227 C>G	Y1409X*	Nonsense	DIII-S5/S6	1	8
4255 A>G K1419E* Missense DIII-55/56 1 4258 G>C G1420R* Missense DIII-55/56 1 4279 G>T A14278* Missense DIII-55/56 1 4283 C>T A1428V* Missense DIII-55/56 1 4294 A>G R1432S* Missense DIII-55/56 1 4298 G>C R1432S* Missense DIII-55/56 1 4299 G>A G1433V* Missense DIII-55/56 1 4299 G>A G1433V* Splice site DIII-55/56 1 4299 H G>T* Splice site DIII-55/56 1 4299 + 1 del G** Splice site DIII-55/56 1 4300 - 1 G>A* Splice site DIII-55/56 1 4313 C>F P1434L* Missense DIII-55/56 1 4320 G>A W1440X Nonsense DIII-55/56 1 4321 G>C E1441Q** Missense DIII-55/56 1 4342 A>C I1448L** Missense DIII-55/56 1 4343 T>C I1448T* Missense	Exon 23	4234 C>T	L1412F*	Missense	DIII-S5/S6	1	5
4258 G>C G1420R* Missense DIII-S5/S6 1 4279 G>T A1427S* Missense DIII-S5/S6 1 4284 C>C R1432G Missense DIII-S5/S6 1 4294 A>G R1432S* Missense DIII-S5/S6 1 4296 G>C R1432S* Missense DIII-S5/S6 1 4299 G>A G1433V* Missense DIII-S5/S6 1 4299 H G>T* G1433G* Splice site DIII-S5/S6 1 4299 +1 G>T* Splice site DIII-S5/S6 1 4300 -1 G>A* Y1434X* Nonsense DIII-S5/S6 1 4313 C>T P1438L Missense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4342 A>C B1441Q* Missense DIII-S5/S6 1 4342 A>C B1448T* Missense DIII-S6/S6 1	Exon 24	4255 A>G	K1419E*	Missense	DIII-S5/S6	1	1
4279 G>T A1427S** Missense DIII-55/56 1 4283 C>T R1428V** Missense DIII-55/56 1 4294 A>G R1432G* Missense DIII-55/56 1 4296 G>C R1432S* Missense DIII-55/56 1 4299 G>A G1433Q** Missense DIII-55/56 1 4299 H G>T** Splice site DIII-55/56 1 4299 +1 G>T** Splice site DIII-55/56 1 4300 -1 G>A** Y1434X* Nonsense DIII-55/56 1 4313 C>T P1438L Missense DIII-55/56 1 4320 G>A W1440X Nonsense DIII-55/56 1 4342 A>C B1441Q* Missense DIII-55/56 1 4342 A>C B1448I* Missense DIII-55/56 1 4343 T>C B1448I* Missense DIII-55/56 1	Exon 24	4258 G>C	G1420R*	Missense	DIII-S5/S6	1	3
4284 C>T A1428V* Missense DIII-S5/S6 1 4294 A>G R1432G* Missense DIII-S5/S6 1 4296 G>C R1432S* Missense DIII-S5/S6 1 4298 G>T G1433Q* Missense DIII-S5/S6 1 4299 G>A G1433G* Silent/splice site DIII-S5/S6 1 4299 +1 G>T* Splice site DIII-S5/S6 1 4300 -1 G>A* Y1434X* Nonsense DIII-S5/S6 1 4302 T>G Y1434X* Nonsense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4342 A>C H1448L* Missense DIII-S5/S6 1 4342 A>C H1448T* Missense DIII-S5/S6 1 4342 A>C H1448T* Missense DIII-S6/S6 1	Exon 24	4279 G>T	A1427S*	Missense	DIII-S5/S6	1	2
4294 A>G R1432G Missense DIII-SS/S6 1 4296 G>C R1432S* Missense DIII-SS/S6 1 4298 G>T G1433V* Missense DIII-SS/S6 1 4299 G>A G1433G* Silent/splice site DIII-SS/S6 1 4299 +1 G>T* Splice site DIII-SS/S6 1 4299 +1 delG* X1434X* Nonsense DIII-SS/S6 1 4300 -1 G>A* Y1434X* Nonsense DIII-SS/S6 1 4313 C>T W1440X Nonsense DIII-SS/S6 1 4320 G>A W1440X Nonsense DIII-SS/S6 1 4342 A>C E1441Q* Missense DIII-SS/S6 1 4342 A>C I1448T* Missense DIII-SS/S6 1	Exon 24	4283 C>T	A1428V*	Missense	DIII-S5/S6	1	2
4296 G>C R1432S* Missense DIII-SS/S6 1 4298 G>T G1433Q* Missense DIII-SS/S6 1 4299 G>A G1433G* Silent/splice site DIII-SS/S6 1 4299 +1 G>T* Splice site DIII-SS/S6 1 4299 +1 delg* Splice site DIII-SS/S6 1 4300 -1 G>A* Y1434X* Nonsense DIII-SS/S6 1 4302 T>G W1440X Missense DIII-SS/S6 1 4320 G>A W1440X Missense DIII-SS/S6 1 4342 A>C H1448L* Missense DIII-SS/S6 1 4343 T>C H1448T* Missense DIII-SS/S6 1	Exon 24	4294 A>G	R1432G	Missense	DIII-S5/S6	1	4
4298 G>T G1433Q* Missense DIII-55/56 1 4299 G>A G1433G* Silent/splice site DIII-55/56 1 4299 +1 G>T* Splice site DIII-55/56 1 4299 +1 delG* Splice site DIII-55/56 1 4300 -1 G>A* Y1434X* Nonsense DIII-55/56 1 4312 C>T P1438L Missense DIII-55/56 1 4320 G>A W1440X Nonsense DIII-55/56 1 4321 G>C E1441Q* Missense DIII-55/56 1 4342 A>C I1448L* Missense DIII-56/56 1 4343 T>C I1448T* Missense DIII-56/56 1	Exon 24	4296 G>C	R1432S*	Missense	DIII-S5/S6	1	2
4299 G>A G1433G* SilenvSplice site DIII-S5/S6 1 4299 +1 G>T* Splice site DIII-S5/S6 1 4299 +1 delG* Splice site DIII-S5/S6 1 4300 -1 G>A* Y1434X* Nonsense DIII-S5/S6 1 4302 T>G Y1434X* Nonsense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4324 A>C L1448L* Missense DIII-S5/S6 1 4342 A>C L1448T* Missense DIII-S6 1	Exon 24	4298 G>T	G1433V*	Missense	DIII-S5/S6	-	3
4299 +1 G>T* Splice site DIII-SS/S6 1 4299 +1 delG* Splice site DIII-SS/S6 1 4300 -1 G>A* Splice site DIII-SS/S6 1 4302 T>G Y1434X* Nonsense DIII-SS/S6 1 4313 C>T P1438L Missense DIII-SS/S6 1 4320 G>A W1440X Nonsense DIII-SS/S6 1 4321 G>C E1441Q* Missense DIII-SS/S6 1 4342 A>C I1448I** Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	Exon 24	4299 G>A	G1433G*	Silent/splice site	DIII-S5/S6	-	4
4300 –1 G>A* Splice site DIII-SS/S6 1 4300 –1 G>A* Splice site DIII-SS/S6 1 4302 T>G Y1434X* Nonsense DIII-SS/S6 1 4313 C>T P1438L Missense DIII-SS/S6 1 4320 G>A W1440X Nonsense DIII-SS/S6 1 4321 G>C E1441Q* Missense DIII-SS/S6 1 4342 A>C 11448T* Missense DIII-SS 1	ntron 24	4299 +1 G>T*		Splice site	DIII-S5/S6	-	5
4300 - 1 G>A* Splice site DIII-S5/S6 1 4302 T>G Y1434X* Nonsense DIII-S5/S6 1 4313 C>T P1438L Missense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4321 G>C E1441Q* Missense DIII-S5/S6 1 4342 A>C I1448I** Missense DIII-S6 1 4343 T>C I1448I** Missense DIII-S6 1	ntron 24	4299 +1 delG*		Splice site	DIII-S5/S6	1	1
4302 T>G Y1434X* Nonsense DIII-S5/S6 1 4313 C>T P1438L Missense DIII-S5/S6 1 4320 G>A W1440X Nonsense DIII-S5/S6 1 4321 G>C E1441Q* Missense DIII-S5/S6 1 4342 A>C I1448L* Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	ntron 24	4300 –1 G>A*		Splice site	DIII-S5/S6	1	2
4313 C>T P1438L Missense DIII-SS/S6 1 4320 G>A W1440X Nonsense DIII-SS/S6 1 4321 G>C E1441Q* Missense DIII-SS/S6 1 4342 A>C I1448L* Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	3xon 25	4302 T>G	Y1434X*	Nonsense	DIII-S5/S6	1	5
4320 G>A W1440X Nonsense DIII-S5/S6 1 4321 G>C E1441Q* Missense DIII-S5/S6 1 4342 A>C I1448L* Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	3xon 25	4313 C>T	P1438L	Missense	DIII-S5/S6	1	4
4321 G>C E1441Q* Missense DIII-S5/S6 1 4342 A>C I1448L* Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	exon 25	4320 G>A	W1440X	Nonsense	DIII-S5/S6	1	2
4342 A>C I1448L* Missense DIII-S6 1 4343 T>C I1448T* Missense DIII-S6 1	exon 25	4321 G>C	E1441Q*	Missense	DIII-S5/S6	1	7
4343 T>C II448T* Missense DIII-S6 1	3xon 25	4342 A>C	11448L*	Missense	9S-IIIQ	-	4
	3xon 25	4343 T>C	I1448T*	Missense	DIII-S6	1	2

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Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center	
Exon 25	4346 A>G	Y1449C*	Missense	9S-IIIQ	1	1	
Exon 25	4352 T>A	V1451D*	Missense	9S-IIIQ	1	5	
Exon 25	4376_4379delTCTT	F1459SfsX3*	Frame shift	DIII-S6	1	9	
Exon 25	4387 A>T	N1463Y*	Missense	9S-IIIQ	1	2	
Exon 25	4389_4396delCCTCTTTA	L1464WfsX5*	Frame shift	DIII-S6	-	8	
Exon 25	4402 G>T	V1468F*	Missense	DIII-S6	1	2	
Exon 25	4426 C>T	Q1476X*	Nonsense	DIII/DIV	1	4	
Intron 25	4437 +5 G>A*		Splice site	DIII/DIV	2	3,5	
Exon 26	4477_4479delAAG	K1493del*	In-frame del	DIII/DIV	2	1,7	
Exon 26	4477 A>T	K1493X*	Nonsense	DIII/DIV	1	2	
Exon 26	4501 C>G	L1501V	Missense	DIII/DIV	1	1	
Exon 27	4562 T>A	11521K*	Missense	DIII/DIV	П	5	
Exon 27	4573 G>A	V1525M*	Missense	DIV-S1	1	4	
Exon 27	4642 G>A	E1548K*	Missense	DIV-S1/S2	3	1, 4	
Exon 27	4708_4710dupATC	11570dup*	In-frame ins	DIV-S2	1	3	
Exon 27	4712 T>G	F1571C*	Missense	DIV-S2	1	4	
Exon 27	4720 G>A	E1574K	Missense	DIV-S2	4	2, 6, 7	
Exon 27	4745 T>C	L1582P*	Missense	DIV-S2	1	3	
Exon 27	4747 C>T	R1583C*	Missense	DIV-S2/S3	2	1, 2	
Exon 27	4748 G>A	R1583H*	Missense	DIV-S2/S3	-	1	
Exon 27	4773 G>A	W1591X*	Nonsense	DIV-S3	-	2	
Exon 27	4810 G>A	V1604M*	Missense	DIV-S3	1	1	
Exon 27	4813 +2_4813+5dupTGGG		Splice site	DIV-S3	-	2	
Exon 28	4838 A>T	Q1613L*	Missense	DIV-S3/S4	1	1	
Exon 28	4845 C>A	Y1615X*	Nonsense	DIV-S3/S4	1	2	
Exon 28	4856delC	P1619RfsX12*	Frame shift	DIV-S3/S4	1	2	
Exon 28	4859 C>T	T1620M	Missense	DIV-S3/S4	2	2,9	_

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Exon 28 4867 C>T R1623Q Missense DIV-54 2 2.3 Exon 28 4886 C>A R1623Q* Missense DIV-54 1 5 Exon 28 4886 C>A R1623Q* Missense DIV-54 1 5 Exon 28 4986 C>A R1623Q* Missense DIV-54 1 3 Exon 28 4912 C>T R1638X Nonsense DIV-54 1 3,3,3 Exon 28 4931 C>T R1638X Missense DIV-54 1 3,3,3 Exon 28 4931 C>T G1661R* Missense DIV-54 1 4 Exon 28 4931 C>T G1661R* Missense DIV-55 1 4 Exon 29 4931 C>T G1661R* Missense DIV-55 1 4 Exon 29 5015 C>A A1660T Missense DIV-55 1 4 Exon 29 502 C>A A1660T Missense DIV-55 1 4 Exon 2	Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center	
4886 G>A R1629Q* Missense DIV-34 1 4886 G>A R1629Q* Missense DIV-34 1 4886 G>A R1629Q* Missense DIV-34 1 4912 C>T R1638X Nonsense DIV-34 1 4912 C>T R1638X Missense DIV-34 1 4925 G>A G1642E* Missense DIV-34 1 4981 G>A G1661R* Missense DIV-35 1 4981 G>A G1661R* Missense DIV-35 2 5015 C>A A1661R* Missense DIV-35 2 5038 G>A A1661R* Missense DIV-35 2 5002 G>A A1661R* Missense DIV-35 2 5002 G>A A1698T* Missense DIV-35 1 5002 G>A A1698T* Missense DIV-35 1 512 G>A T1709M* Missense DIV-35 1 5124 G>A T1709K* Missense DIV	Exon 28	4867 C>T	R1623X	Nonsense	DIV-S4	2	2,3	
488 Cy-T R1629X* nonsense DIV-54 1 488 G>A R1629Q** Missense DIV-54 1 4912 Cy-T R1638X Nonsense DIV-54 1 4912 Cy-T R1638X Nonsense DIV-54 1 4925 G>A G164D** Missense DIV-54 1 4981 G>A G1661R** Missense DIV-55 1 4981 G>A C1661R** Missense DIV-55 1 5015 C>A V1667T Missense DIV-55 1 5038 G>A A1680T Missense DIV-55 1 5032 C>A A1680T Missense DIV-55 1 5032 C>A A1698T* Frame shift DIV-55 1 5032 C>A T1709M* Missense DIV-55 1 5032 C>A T1709M* Missense DIV-55/56 1 5112 C>C T1709M* Missense DIV-55/56 1 5114 A>G D1735** Missense	Exon 28	4868 G>A	R1623Q	Missense	DIV-S4	1		
4886 G>A R1629Q* Missense DIV-54 1 4912 C>T R1638X Nonsense DIV-54 3 4912 C>T G1642E* Missense DIV-54 3 4925 G>A 11660V Missense DIV-55 1 4981 G>C G1661R* Missense DIV-55 1 5015 C>A A1680T Missense DIV-55/56 1 5015 C>A A1680T Missense DIV-55/56 1 5012 C>A T1709M* Missense DIV-55/56 1 5124 G>C T1709M* Missense DIV-55/56 1 5124 G>C T1709M* Missense DIV-55/56 1 5124 G>C T1709M* Missense DIV-55/56 1 514 G>C T1709M* Missense	Exon 28	4885 C>T	R1629X*	nonsense	DIV-S4	-	3	
4912 C>T R1638X Nonsense DIV-54 3 4925 G>A G1642E* Missense DIV-54 1 4978 A>G 11660V Missense DIV-55 5 4981 G>A G1661R* Missense DIV-55 5 4981 G>A G1661R* Missense DIV-55 5 4981 G>A V1667T Missense DIV-55 1 5015 C>A A1680T Missense DIV-55 2 5082 SO70delGA A1680T Missense DIV-55/56 1 5082 C>A A1680T* Missense DIV-55/56 1 5124 C>C T1709M* Missense DIV-55/56 1 5124 C>A T1709M* Missense DIV-55/56 1 5144 A>G D1714G Missense DIV-55/56 1 5154 A>G D1730S Missense DIV-55/56 1 5164 A>G C1728R* Missense DIV-55/56 1 5184 C>G C1728R* Missen	Exon 28	4886 G>A	R1629Q*	Missense	DIV-S4	1	3	
4925 G>A G1642E* Missense DIV-54 1 4978 A>G 11660V Missense DIV-55 5 4981 G>A G1661R** Missense DIV-55 5 4981 G>C G1661R** Missense DIV-55 1 4981 G>C V16671 Missense DIV-55 1 5015 C>A A1680T Missense DIV-55 1 5082 G>A A1680T Missense DIV-55/56 1 5092 G>A A1698T** Missense DIV-55/56 1 5126 C>T T1709M** Missense DIV-55/56 1 5124 G>A T1709K** Missense DIV-55/56 1 514 A>G D1714G** Missense DIV-55/56 1 516 A>G D1714G** Missense DIV-55/56 1 518 C>G C1728K** Missense DIV-55/56 1 518 C>G C1728K** Missense DIV-55/56 1 5227 C>A G1740R Mi	Exon 28	4912 C>T	R1638X	Nonsense	DIV-S4	3		
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4981 G>A G1661R** Missense DIV-S5 2 4981 G>C G1661R** Missense DIV-S5 1 4999 G>A V16671 Missense DIV-S5 1 5015 C>A A1680T Missense DIV-S5 2 5083 G>A A1680T Missense DIV-S5/S6 1 5083 C>T Q1695X Missense DIV-S5/S6 1 5092 G>A A1698T* Missense DIV-S5/S6 1 5124 5126delCAC T1709del* Missense DIV-S5/S6 1 5126 C>T T1709del* Missense DIV-S5/S6 1 5144 G>A Q1712S* Missense DIV-S5/S6 1 5144 A>G D1714G Missense DIV-S5/S6 1 5184 C>G Q1728R* Missense DIV-S5/S6 1 5184 C>G Q1743R Missense DIV-S5/S6 1 5222 G>A Q1743R Missense DIV-S5/S6 5 5228 G>A Q1743R	Exon 28	4978 A>G	11660V	Missense	DIV-S5	5	2, 3, 5, 6	
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5092 G>A A1698T* Missense DIV-S5/S6 1 5124_512delcAC T1709del* In-frame del DIV-S5/S6 1 5126 C>T T1709M Missense DIV-S5/S6 2 5136 C>C T1709R* Missense DIV-S5/S6 1 5134 G>A G1712S* Missense DIV-S5/S6 1 5141 A>G D1714G Missense DIV-S5/S6 1 5157 delC N172D* Missense DIV-S5/S6 1 5182 T>C C1728R* Missense DIV-S5/S6 1 518 C>A G1740R Missense DIV-S5/S6 1 5227 G>A G1743R Missense DIV-S5/S6 5 5228 G>A G1743R Missense DIV-S5/S6 5 52290delG V1764SfxX23* Frame shift DIV-S6/S6 6	exon 28	5083 C>T	Q1695X	Nonsense	DIV-S5/S6	2	1,4	
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5126 C>T T1709M Missense DIV-S5/S6 2 5126 C>G T1709R* Missense DIV-S5/S6 1 5134 G>A G1712S* Missense DIV-S5/S6 1 5141 A>G D1714G Missense DIV-S5/S6 1 5157delC N172D* Frame shift DIV-S5/S6 1 5164 A>G N172D* Missense DIV-S5/S6 1 5182 T>C C1728W* Missense DIV-S5/S6 1 5218 G>A G1740R Missense DIV-S5/S6 1 5227 G>A G1743R Missense DIV-S5/S6 5 52290delG V1764SfxX23* Frame shift DIV-S5/S6 6	exon 28	5124_5126delCAC	$T1709$ del *	In-frame del	DIV-S5/S6	1	4	
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\$134 G>A G1712S* Missense DIV-S5/S6 1 \$141 A>G D1714G Missense DIV-S5/S6 1 \$157 delC 1172 0SfsX67* Frame shift DIV-S5/S6 1 \$164 A>G N1722D* Missense DIV-S5/S6 1 \$182 T>C C1728W* Missense DIV-S5/S6 1 \$218 G>A G1740R Missense DIV-S5/S6 1 \$2227 G>A G1743R Missense DIV-S5/S6 5 \$222 G>A G1743E Missense DIV-S5/S6 5 \$222 G>A G1743E Missense DIV-S5/S6 5 \$229 GelG V1764SfsX23* Frame shift DIV-S6/S6 1	exon 28	5126 C>G	T1709R*	Missense	DIV-S5/S6	-	4	
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\$164 A>G N1722D* Missense DIV-S5/S6 1 \$182 T>C C1728R* Missense DIV-S5/S6 1 \$184 C>G C1728W* Missense DIV-S5/S6 1 \$218 G>A G1740R Missense DIV-S5/S6 1 \$227 G>A G1743R Missense DIV-S5/S6 5 \$2290delG V1764SfxX23* Frame shift DIV-S6/S 1	exon 28	5157delC	11720SfsX67*	Frame shift	DIV-S5/S6	1	8	
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5218 G>A G1740R Missense DIV-S5/S6 1 5227 G>A G1743R Missense DIV-S5/S6 5 5228 G>A G1743E Missense DIV-S5/S6 6 52290delG V1764Sf5X23* Frame shift DIV-S6 1	xon 28	5184 C>G	C1728W*	Missense	DIV-S5/S6	1	2	
5227 G>A G1743R Missense DIV-S5/S6 5 5228 G>A G1743E Missense DIV-S5/S6 6 5290delG V1764Sf\$X23* Frame shift DIV-S6 1	xon 28	5218 G>A	G1740R	Missense	DIV-S5/S6	1	3	
5228 G>A G1743E Missense DIV-S5/S6 6 2, 5290delG V1764SfsX23* Frame shift DIV-S6 1 8	xon 28	5227 G>A	G1743R	Missense	DIV-S5/S6	5	4, 5, 7, 9	
5290delG V1764SfsX23* Frame shift DIV-S6 1	xon 28	5228 G>A	G1743E	Missense	DIV-S5/S6	9		
	Sxon 28	5290delG	V1764SfsX23*	Frame shift	DIV-S6	1	8	

Region	Nucleotide change	Coding effect	Mutation type	Location	No. of unrelated individuals	Testing center
Exon 28	5290 G>T	V1764F	Missense	DIV-S6	1	7
Exon 28	5336 C>T	T1779M	Missense	C-terminal	1	2
Exon 28	5350 G>A	E1784K	Missense	C-terminal	14	1, 2, 5, 6, 7
Exon 28	5356_5357delCT	L1786EfsX2*	Frame shift	C-terminal	2	1
Exon 28	5387_5388insTGA	1795_1796insD	In-frame ins	C-terminal	1	3
Exon 28	5420dupA	F1808IfsX3*	Frame shift	C-terminal	1	7
Exon 28	5435 C>A	S1812X	Nonsense	C-terminal	1	7
Exon 28	5464_5467delTCTG	E1823HfsX10*	Frame shift	C-terminal	-	2
Exon 28	5494 C>G	Q1832E*	Missense	C-terminal	1	9
Exon 28	5577_5578dupAA	R1860KfsX13*	Frame shift	C-terminal	1	2
Exon 28	5581 G>A	V18611*	Missense	C-terminal	1	2
Exon 28	5616 G>C	K1872N*	Missense	C-terminal	1	5
Exon 28	5707 G>C	S1904L	Missense	C-terminal	1	2
Exon 28	5770 G>A	A1924T	Missense	C-terminal	1	3
Exon 28	5803 G>A	G1935S	Missense	C-terminal	1	2
Exon 28	5812 G>A	E1938K*	Missense	C-terminal	_	2
Exon 28	6010_6012dupTTC	F2004dup*	In-frame ins	C-terminal	-	7
Exon 28	9<10109	F2004V*	Missense	C-terminal	-	5

 $del = deletion; \ dup = duplication; \ ins = insertion; \ indel = insertion/deletion; \ ins = insertion$

Testing Center: 1 = Nantes; 2 = Brugada; 3 = AMC; 4 = Paris; 5 = PGxHealth; 6 = MMRL; 7 = UKM; 8 = NCVC; 9 = BCM.

*
novel mutation

Heart Rhythm Disorders

Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome

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Objectives

The goal of this study was to evaluate the prevalence and the clinical significance of ST-segment elevation

during recovery from exercise testing.

Background

During recovery from exercise testing, ST-segment elevation is reported in some patients with Brugada

syndrome (BrS).

Methods

Treadmill exercise testing was conducted for 93 patients (91 men), 46 ± 14 years of age, with BrS (22 documented ventricular fibrillation, 35 syncope alone, and 36 asymptomatic); and for 102 healthy control subjects (97 men), 46 ± 17 years of age. Patients were routinely followed up. The clinical end point was defined as the

occurrence of sudden cardiac death, ventricular fibrillation, or sustained ventricular tachyarrhythmia.

Results

Augmentation of ST-segment elevation ≥ 0.05 mV in V₁ to V₃ leads compared with baseline was observed at early recovery (1 to 4 min at recovery) in 34 BrS patients (37% [group 1]), but was not observed in the remaining 59 BrS patients (63% [group 2]) or in the 102 control subjects. During 76 \pm 38 months of follow-up, ventricular fibrillation occurred more frequently in group 1 (15 of 34, 44%) than in group 2 (10 of 59, 17%; p = 0.004). Multivariate Cox regression analysis showed that in addition to previous episodes of ventricular fibrillation (p = 0.005), augmentation of ST-segment elevation at early recovery was a significant and independent predictor for cardiac events (p = 0.007), especially among patients with history of syncope alone (6 of 12 [50%] in group 1 vs. 3 of 23 [13%] in group 2) and among asymptomatic patients (3 of 15 [20%] in group 1 vs. 0 of 21 [0%] in group 2).

Conclusions

Augmentation of ST-segment elevation during recovery from exercise testing was specific in patients with BrS, and can be a predictor of poor prognosis, especially for patients with syncope alone and for asymptomatic patients. (J Am Coll Cardiol 2010;56:1576–84) © 2010 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is recognized as a clinical syndrome that leads to sudden cardiac death (SCD) in middle-aged persons due to ventricular fibrillation (VF) (1). Brugada syndrome is defined by a distinct 12-lead electrocardiogram (ECG) pattern in precordial leads (V₁ to V₃) presenting coved-type ST-segment elevation. Both depolar-

the pathogenesis of phenotype in BrS (2–5). Although several indexes have been reported as predictive factors of VF occurrence (6), the recent largest series of BrS patients suggested that there were no reliable predictors of cardiac events except for prior symptoms and spontaneous type 1 ECG (7). However, risk stratification remains disputable, especially for BrS patients without documented VF episodes.

ization and repolarization hypotheses have been reported for

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Autonomic function has been suggested to relate to the occurrence of VF in BrS. It has also been shown that ST-segment elevation in patients with BrS was augmented

Abbreviations

and Acronyms

AF = atrial fibrillation

BrS = Brugada syndrome

ECG = electrocardiogram

by selective stimulation of muscarinic receptors but mitigated by beta-adrenergic stimulation (8). Heart rate during exercise testing is considered as 1 parameter to evaluate cardiac autonomic function (9). Sympathetic withdrawal and parasympathetic activation occur at early recovery after exercise (10), which are expected to augment ST-segment elevation directly by inhibition of calcium-channel current or by decreasing heart rate (5,11). Two cases of BrS were reported in which ST-segment was augmented during and after exercise (12). Amin et al. (13) recently assessed the ECG responses to exercise in BrS patients with and without SCN5A mutations and control subjects. They reported that exercise resulted in an increase of peak J-point amplitude in all groups, including control subjects, and more QRS widening in BrS patients with SCN5A mutation. The peak J-point amplitude measured by Amin et al. (13) is thought to represent the depolarization parameter as QRS duration, or at least the combined parameter of both depolarization and repolarization. Therefore, in the present study, we measured several points of ST-segment as a repolarization parameter rather than a depolarization parameter, and tried to investigate the relationship between augmented STsegment elevation during recovery from exercise testing and prognosis of BrS patients. We also evaluated parasympathetic reactivation by using heart rate recovery (HRR), which is defined as heart rate decay in the first minute after exercise cessation, and its relation with ST-segment change.

Methods

Study population. The study population consisted of 93 consecutive Japanese patients with BrS (91 males; mean age 46 ± 14 years) admitted to the National Cerebral and Cardiovascular Center in Suita, Japan, between 1994 and 2006. Ventricular fibrillation was documented in 22 BrS patients, syncope alone in 35 patients, and the remaining 36 patients were asymptomatic. As control subjects, 102 age-, sex-, and QRS duration-matched healthy subjects were randomly selected from persons who underwent treadmill exercise testing between 2002 and 2007 (97 males; mean age 46 ± 17 years). They included 55 normal subjects with normal QRS duration (<100 ms), 21 with incomplete right bundle branch block (RBBB) (100 ms ≤QRS duration <120 ms), and 26 with complete RBBB (120 ms ≤QRS duration) but without structural heart disease or any ventricular arrhythmias.

Brugada syndrome was diagnosed when a coved STsegment elevation (≥0.2 mV at J-point) was observed in >1 of the right precordial leads $(V_1 \text{ to } V_3)$ in the presence or absence of a sodium-channel-blocking agent, and in conjugation with 1 of the following: documented VF, polymorphic ventricular tachycardia, family history of SCD <45 years of age, family history of BrS, inducibility of VF with programmed electrical stimulation, syncope, or an nocturnal agonal respiration (6). Structural heart diseases were carefully excluded by history

taking, physical examinations, chest roentgenogram, ECG, and echocardiogram.

Clinical, laboratory, electrocardiographic, and electrophysiologic study. The following clinical data were collected: family history of SCD (<45 years of age) or BrS, documented atrial fibrillation (AF), documented VF, syncope, age at the first cardiac event, and implantation of implantable cardioverter-defibrillator (ICD).

A 12-lead ECG was recorded in all 93 BrS patients, and RR interval, PR interval (lead II), QRS duration (lead V₅), corrected QT interval (lead V2), QRS axis, J-point amplitude

EPS = electrophysiologic study HRR = heart rate recovery ICD = implantable cardioverter-defibrillator

branch block RVOT = right ventricular outflow tract

SCD = sudden cardlac

RBBB = right bundle

VF = ventricular fibrillation

(leads V₂), and amplitude of several points of ST-segment (leads V₁, V₂, V₃) were measured.

Signal-averaged ECG was recorded and analyzed in 91 patients by using a signal-averaged ECG system (1200EPX, Arrhythmia Research Technology, Milwaukee, Wisconsin). Three parameters were assessed using a computer algorithm: 1) total filtered QRS duration; 2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes (V₄₀); and 3) duration of low-amplitude signals $<40 \mu V$ of the filtered QRS complexes (T_{40}). Late potential was considered present when the 2 criteria (V₄₀ $<18 \mu V$ and $T_{40} >38 \text{ ms}$) were fulfilled.

Electrophysiologic study (EPS) was performed in 79 BrS patients (21 documented VF patients, 30 syncope alone patients, and 28 asymptomatic patients). A maximum of 3 programmed ventricular extrastimuli were delivered from the right ventricular apex and RVOT, unless VF was induced. No patients received antiarrhythmic drugs before EPS. The atrio-His and His-ventricular intervals were measured during sinus rhythm. The EPS was conducted after all subjects gave written informed consent.

Genetic testing for the presence of an SCN5A mutation was also conducted.

Exercise testing. Treadmill exercise testing was conducted in all 93 patients with BrS and 102 control subjects. Neither BrS patients nor control subjects used antiarrhythmic agents. A symptom-limited or submaximal (up to 90% of the age-predicted maximum heart rate) graded treadmill exercise testing similar to modified Bruce protocol was used. All 93 BrS patients and 102 control subjects were in normal sinus rhythm, and none had atrioventricular block at the exercise testing. The standard 12-lead ECGs were recorded at rest, at the end of each exercise stage, at peak exercise, and at every minute during recovery. The amplitude of STsegment from the isoelectric line at the right precordial leads (V₁ to V₃ leads) and QRS width at V₅ lead were manually measured. The ST-segment point was defined as the point

where the vertical line from the end point of QRS at V_5 lead intersected the precordial leads. We also measured peak J-point amplitude in lead V_2 as a depolarization parameter, and amplitude of the point, which was 40 and 80 ms later than the peak J-points (ST40, ST80) in lead V_2 as a repolarization parameter. Measurements of ECG parameters were performed as the mean of 3 beats by single electrocardiologist who knew nothing about the patients. Significant augmentation of ST-segment elevation was defined as ST-segment amplitude increase ≥ 0.05 mV in at least 1 of V_1 to V_3 leads at early recovery (1 to 4 min at recovery) compared with the ST-segment amplitude at baseline (pre-exercise). We also recorded heart rate and blood pressure during exercise testing.

The HRR was defined as decay of heart rate from peak exercise to 1 min at recovery.

Follow-up. Follow-up was started after undergoing treadmill exercise testing. All patients with BrS were routinely followed up at the outpatient clinic of our hospital. The ICD implantation was performed in 63 BrS patients (20 documented VF patients, 25 syncope alone patients, and 18 asymptomatic patients). Antiarrhythmic drugs were prescribed for 7 patients; 2 patients who had episodes of VF but refused implantation of ICD (disopyramide 300 mg daily for 1 patient, and amiodarone 200 mg daily for another patient), 2 patients who had AF (quinidine 300 mg daily), and 3 patients who had previous history of both VF and AF and implanted ICD (quinidine 300 mg daily for 1 patient, amiodarone 200 mg daily for 2 patients).

Cardiac events were defined as SCD or aborted cardiac arrest, and VF or sustained ventricular tachyarrhythmia documented by ICD or ECG recordings.

Statistical analysis. Data were analyzed with Dr. SPSS II for Windows software package (SPSS Inc., Chicago, Illinois). Numeric values are expressed as mean ± SD. The chi-square test, Student t test, or 1-way analysis of variance was performed when appropriate to test for statistical differences. All p values < 0.05 were considered statistically significant. Event rate curves were plotted according to the Kaplan-Meier method, and were analyzed with the log-rank test. Univariate and multivariate Cox regression were performed to assess whether 7 indexes can be significant and independent predictors of subsequent cardiac events. We used the forward step-wise approach with p to enter a value of 0.05 for multivariate analysis. Augmentation of STsegment elevation at early recovery, family history of SCD or BrS, spontaneous coved-type ST-segment elevation, presence of SCN5A mutation, late potential, VF inducibility during EPS, and previous episodes of VF were included as indexes.

Results

There were no significant differences between 93 BrS patients and 102 control subjects with respect to age at

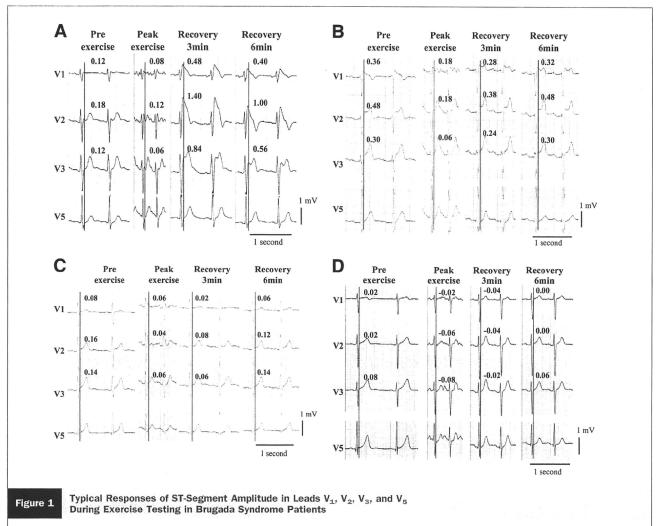
Table 1 Initial Characteristics of Patients and Control Subjects

	Brugada Patients (n = 93)	Control Subjects (n = 102)	p Value
Age at exercise testing, yrs	46 ± 14	46 ± 17	NS
Sex, male	91 (98%)	97 (95%)	NS
Electrocardiographic characteristics, ms			
RR	952 ± 151	903 ± 140	0.020
PR	178 ± 30	165 ± 24	0.001
QRS duration	98 ± 16	98 ± 20	NS
QTc	416 ± 44	406 ± 30	NS

Values are mean \pm SD or n (%). QTc = corrected QT interval.

exercise testing, sex, QRS duration (lead V_5), and QTc interval (lead V_2), as summarized in Table 1. The RR interval and PR interval (lead II) were significantly longer in BrS patients than in control subjects.

Response of ST-segment elevation during treadmill exercise testing. Among 93 BrS patients, significant augmentation of ST-segment elevation mostly associated with coved pattern at early recovery phase was observed in 34 BrS patients (37% [group 1]), but not in the remaining 59 BrS patients (63% [group 2]). Conversely, ST-segment augmentation was never observed in any of the 102 control subjects (34 of 93 [37%] vs. 0 of 102 [0%], p < 0.0001). Typical responses of ST-segment amplitudes of 3 groups are shown in Figure 1. Composite data of serial changes of STsegment amplitude in V₁ and V₂ leads during exercise testing are illustrated in Figure 2A. The serial changes of ST-segment amplitude in V₃ lead showed the same trend (not shown). In group 1, ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery (Figs. 1A and 2A). In contrast, ST-segment amplitude of group 2 patients and control subjects decreased at peak exercise, and gradually returned to the baseline amplitude rather than showing augmentation (Figs. 1B to 1D and 2A). Significant differences were identified between group 1 and group 2 patients in the ST-segment amplitude in leads V₁ and V₂ from peak exercise to 6 min of recovery, whereas no major differences were observed between group 2 patients and control subjects (Fig. 2A). Composite data of serial changes of peak J-point amplitude, ST40, and ST80 amplitudes are presented in Figure 2B. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude in Figure 2A. Significant differences were identified between group 1 and group 2 patients in the peak J-point and ST40 amplitudes from peak exercise to 6 min of recovery. The ST80 amplitude showed significant differences between group 1 and group 2 patients at 2, 3, and 4 min of recovery. At peak exercise, the peak J-point amplitude increased in 34 (37%) of 93 Brugada patients and in 26 (26%) of 102 control subjects, although the ST-segment



(A) In the group 1 Brugada patient showing saddle-back type ST-segment (lead V_2) at baseline, ST-segment amplitude slightly decreased at peak exercise, but reascended at early recovery (3 min), resulting in typical coved-type ST-segment elevation. (B, C) In the group 2 Brugada patient and (D) in the control subject, ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline at recovery. It is noteworthy that the peak J-point amplitude in lead V_2 was augmented despite not showing ST-segment augmentation in A and C. The ST-segment amplitudes are shown as numeric values expressed in millivolts (mV). The **red vertical line** indicates the line from the end point of the QRS interval at electrocardiography lead V_5 .

amplitude and ST40 amplitude decreased in most patients of both groups.

Comparison of HRR is shown in Figure 3. The HRR of group 1 patients was significantly larger than that of group 2 patients (32 \pm 15 vs. 23 \pm 10, p = 0.0007) and control subjects (32 \pm 15 vs. 26 \pm 10, p = 0.021). The differences of HRR between group 2 patients and control subjects were also statistically significant (23 \pm 10 vs. 26 \pm 10, p = 0.026)

Although there were no sustained or nonsustained ventricular arrhythmias throughout exercise testing, single premature ventricular complexes were observed during exercise in 8 of the group 1 patients and in 11 of the group 2 patients, and at recovery in 10 of the group 1 patients and in 9 of the group 2 patients. There were no significant differences between groups 1 and 2 in incidences of premature ventricular complexes.

Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics. Comparison of the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics between groups 1 and 2 patients are shown in Table 2. There were no significant differences in these characteristics between groups 1 and 2 except for the presence of SCN5A mutation and late potential (SCN5A mutation, 17% vs. 5%, p = 0.048; late potential, 82% vs. 53%, p = 0.004).

Follow-up. The mean follow-up period for the 93 BrS patients was 75.7 ± 38.4 months. During follow-up, 25 of all 93 BrS patients (27%) had cardiac events, and the incidence of cardiac events was significantly higher in group 1 than in group 2 patients (44% vs. 17%, p = 0.004). The period from exercise testing to cardiac events ranged from 1 to 78 months (median 12 months). One patient in group 2, who refused implantation of ICD and was taking disopyr-

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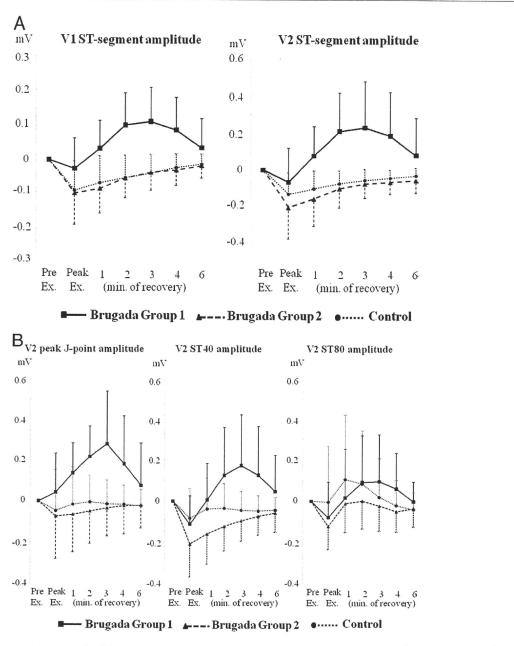


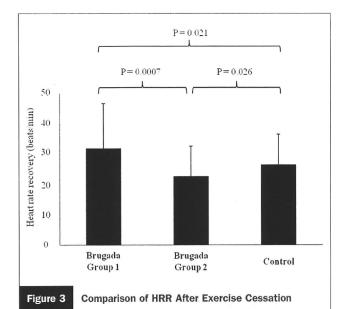
Figure 2 Composite Data of Serial Changes of ST-Segment Amplitude

(A) Composite data of serial changes of ST-segment amplitude in lead V_1 (left) and lead V_2 (right) during exercise (Ex.) testing in group 1 Brugada syndrome patients (squares) and group 2 Brugada syndrome patients (triangles), and in control subjects (circles). (B) Peak J-point amplitude (left), ST40 amplitude (middle), and ST80 amplitude (right) in lead V_2 . The ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery in group 1 Brugada patients. In the group 2 Brugada patients and control subjects, the ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline level during recovery. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude. Since ST80 amplitude was influenced by T wave, especially at rapid heart rate, the trends of the 3 groups were somewhat different from ST-segment amplitude or ST40 amplitude. The ST-segment amplitudes are shown as values compared to pre-exercise ST-segment amplitudes. p < 0.05.

amide 300 mg daily, died of VF. Three of 7 patients with medication had cardiac events, including 1 death.

Predictors of outcome. Kaplan-Meier analysis demonstrated significant differences in the time to the first cardiac event depending on the presence of ST-segment augmentation during recovery from exercise (Fig. 4A). Group 1 patients had

a significantly higher cardiac event rate than group 2 patients (log-rank, p=0.0029). Previous history of VF (Fig. 4B) and positive *SCN5A* mutation (Fig. 4C) also had significant values for occurrence of subsequent cardiac events (p=0.0013 and p=0.028, respectively); however, spontaneous coved-type ST-segment elevation did not predict cardiac events (p=0.028).



Comparison of heart rate recovery (HRR) 1 min after exercise cessation among Brugada syndrome patients of groups 1 and 2 and control subjects. The HRR in group 1 patients was significantly larger than that in group 2 (32 \pm 15 beats/min vs. 23 \pm 10 beats/min, p = 0.007) and in control subjects (32 \pm 15 beats/min vs. 26 \pm 10 beats/min, p = 0.021). The differences of HRR between group 2 patients and control subjects were also significant (23 \pm 10 beats/min vs. 26 \pm 10 beats/min, p = 0.026).

0.068) (Fig. 4D). The results of Cox regression analysis are shown in Table 3. In univariate analysis, indexes predictive of cardiac events were previous episodes of VF (p = 0.003), ST-segment augmentation at early recovery (group 1; p = 0.005), and presence of *SCN5A* mutation (p = 0.037). In multivariate Cox regression analysis, previous episodes of VF and ST-segment augmentation at early recovery were significant and independent predictors of subsequent cardiac events (p = 0.005 and p = 0.007, respectively).

The incidence of cardiac events during follow-up in the subgroups according to symptoms before exercise testing is shown in Table 4. In the subgroup of 35 BrS patients with syncope alone, group 1 had a significantly higher cardiac event rate than group 2 (log-rank, 6 of 12 [50%] vs. 3 of 23 [13%], p = 0.016). Of note, among 36 asymptomatic patients, only 3 patients (9%) in group 1 experienced cardiac events. The log-rank test also demonstrated higher cardiac event risk in group 1 compared with group 2 (3 of 15 [20%] vs. 0 of 21 [0%], p = 0.039).

Discussion

The major findings of the present study were the following: 1) 37% of BrS patients showed ST-segment augmentation at early recovery during exercise testing; 2) ST-segment augmentation at early recovery was specific in BrS patients, and was significantly associated with a higher cardiac event rate, notably for patients with previous episode of syncope or for asymptomatic patients; and 3) BrS patients with ST-segment augmentation at early recovery showed signifi-

cantly larger HRR. This is the first systematic report on the relationship between ST-segment augmentation during recovery from exercise and prognosis for BrS patients.

Augmentation of ST-segment elevation and possible mechanism. It is well known that autonomic function influences an extent of ST-segment elevation in BrS (8). The ST-segment elevation is mitigated by administration of β -adrenergic agonists and is enhanced by parasympathetic agonists such as acetylcholine in experimental and clinical investigations (5,14-16). Parasympathetic reactivation is thought to occur at early recovery after treadmill exercise testing, especially in the first minute after cessation of exercise (10,17). In the present study, we measured the ST-segment amplitude as a repolarization parameter rather than a depolarization parameter, and evaluated HRR to investigate the correlation between ST-segment augmentation and parasympathetic activity (9,18). The BrS patients who had ST-segment augmentation had significantly larger HRR compared with patients who did not, suggesting that the ST-segment augmentation was closely related to higher parasympathetic activity. However, it is still unclear whether ST-segment augmentation observed in the 34 BrS patients was simply due to more increased parasympathetic activity or to more increased susceptibility (hypersensitivity) to the parasympathetic reactivation.

Conversely, the SCN5A mutation was more frequently identified in group 1. Scornik et al. (19) reported that SCN5A mutation can accentuate parasympathetic activity toward the heart directly. It was also reported that specific mutations in the SCN5A gene may lead to augmentation of J-point amplitude or ST-segment amplitude during beta-adrenergic stimulation (20,21). Veldkamp et al. (20) demonstrated that a specific SCN5A mutation, 1795insD, augments slow inactivation, and delays recovery of sodium channel availability, thus reducing the sodium current and resulting in augmented peak J-point amplitude at rapid heart rate. Increased body temperature induced by exercise can be a risk of life-threatening arrhythmias in patients with BrS (22). A specific SCN5A missense mutation, T1620M, was reported to cause a faster decay of the sodium channel but slower recovery from inactivation, resulting in increased ST-segment elevation in precordial leads at higher temperatures during exercise. Although Amin et al. (13) reported that exercise induced augmentation of peak J-point amplitude, a depolarization parameter or at least combined parameter of both depolarization and repolarization, in all subjects tested, the incidence of increase in the peak J-point amplitude at peak exercise was lower (37%) in our Brugada patients. This is probably in part because only 9 (10%) of our 93 BrS patients had the SCN5A mutation. We could not identify significant differences in HRR, QRS duration, peak J-point amplitude (lead V₂), and ST-segment amplitude (leads V_1 , V_2 , V_3) at peak exercise between patients with and without SCN5A mutation (not shown), and that may be also due to the small number of BrS patients with SCN5A mutation.

Risk stratification in BrS. Implantation of an ICD is a first line of therapy for secondary prevention in patients with BrS who exhibited previous history of VF. The American College

Table 2

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Clinical, Laboratory, Electrocardiographic, and Electrophysiologic Characteristics and Long-Term Follow-Up of Groups 1 and 2 Brugada Syndrome Patients

Characteristic	Group 1 (n = 34)	Group 2 (n = 59)	p Value
Clinical characteristics			8
Age at exercise testing, yrs	42 ± 11	48 ± 15	NS
Men	34 (100%)	57 (97%)	NS
Family history of SCD at age $<$ 45 yrs or Brugada syndrome	7 (21%)	16 (27%)	NS
Documented AF	7 (21%)	12 (20%)	NS
Documented VF before exercise testing	7 (21%)	15 (25%)	NS
Syncope alone before exercise testing	12 (35%)	23 (39%)	NS
Asymptomatic before exercise testing	15 (44%)	21 (36%)	NS
Age at first cardiac event, yrs	42 ± 13	45 ± 15	NS
ICD implantation	25 (74%)	38 (64%)	NS
Laboratory characteristics			
SCN5A mutation	6 (17%)	3 (5%)	0.048
Electrocardiographic characteristics		, ,	
RR, ms	951 170	953 ± 140	NS
PR, ms	184 ± 28	175 ± 31	NS
QRS, ms	98 ± 14	98 ± 17	NS
QTc, ms	418 ± 46	415 ± 43	NS
ST-segment amplitude (mV) at baseline			
V ₁	0.14 ± 0.09	0.16 ± 0.12	NS
V_2	0.41 ± 0.22	0.38 ± 0.26	NS
V_3	0.22 ± 0.13	0.19 ± 0.14	NS
Spontaneous coved-type ST-segment elevation in right precordial leads	30 (88%)	43 (73%)	NS
Signal-averaged electrocardiogram			
TfQRS, ms	$\textbf{122} \pm \textbf{15}$	118 ± 17	NS
Late potential	28/34 (82%)	30/57 (53%)	0.004
Premature ventricular complexes during exercise	8 (24%)	11 (19%)	NS
Premature ventricular complexes at recovery	10 (29%)	9 (15%)	NS
Electrophysiologic characteristics			
AH interval, ms	107 ± 24	98 ± 27	NS
HV interval, ms	45 ± 8	44 ± 11	NS
Induction of VF	26/31 (84%)	33/47 (70%)	NS
Follow-up			
Cardiac events	15 (44%)	10 (17%)	0.004
Follow-up period, months	74.1 ± 42.2	76.5 ± 36.4	NS

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; TfQRS = total filtered QRS duration; VF = ventricular fibrillation; other abbreviations as in Table 1.

of Cardiology/American Heart Association/Heart Rhythm Society guidelines refer to BrS patients who have had syncope as having Class IIa indication for ICD therapy (23). However, there is still much room for argument with respect to treatments for patients who have had only syncope, and for asymptomatic patients (24–28). Although inducibility of VF during EPS (25,26), family history of SCD (24), spontaneous type 1 ECG (25,27), and late potential (28) have been proposed as predictors of cardiac events, the availability of these indexes remains controversial (7,29).

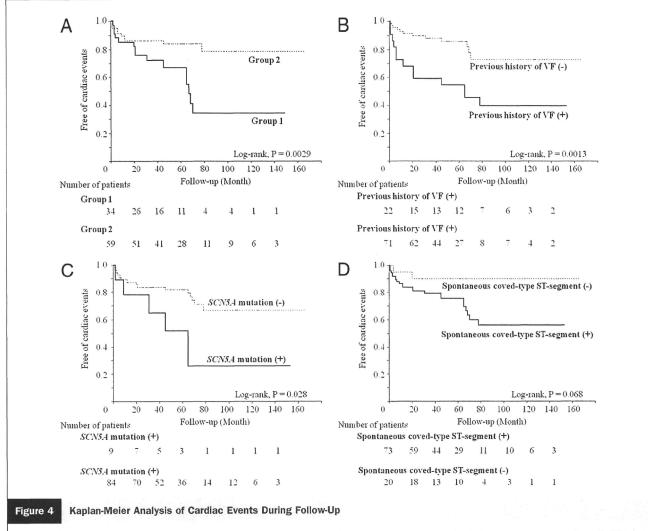
In the present study, a previous episode of VF (or aborted cardiac arrest) was the strongest predictor of subsequent cardiac events, as in previous studies (7,30,31). Moreover, ST-segment augmentation at early recovery during exercise testing was a significant and independent predictor of subsequent cardiac events in the present study. The results suggested that parasympathetic activity plays an important role in both ST-segment augmentation and subsequent cardiac events. As previously noted, it remains unclear that the cause of ST-segment augmentation in our 34

patients was a result of more increased parasympathetic activity or of more increased susceptibility of the patients to the increased parasympathetic reactivation.

Study limitations. First, BrS patients were confined to those who were hospitalized in our hospital for close investigation. That indicates these patients can be biased toward relatively high risk. Second, the present study is based on data from a small population of 93 patients; hence, it was not sufficient to evaluate the prognosis, and there also was a small number of events. Although we adopted a step-wise approach, the limited number of events can lessen the precision of the consequences for multivariate Cox regression analysis.

Conclusions

The presence of *SCN5A* mutation was a significant predictor of subsequent cardiac events by univariate Cox regression analysis. However, multivariate Cox regression analysis showed it was not a significant predictor of prognosis.



Kaplan-Meier analysis of **(A)** cardiac events during follow-up, depending on patterns in response to ST-segment elevation during exercise test (groups 1 and 2), **(B)** incidence of previous episode of ventricular fibrillation (VF), **(C)** SCN5A mutation, and **(D)** spontaneous coved-type ST-segment elevation. Group 1 Brugada patients had a significantly higher cardiac event rate than did group 2 Brugada patients (log-rank, p = 0.0029). Brugada patients with previous episodes of VF or with SCN5A mutation had significantly greater values for occurrence of subsequent cardiac events than did patients without VF episodes or SCN5A mutation (p = 0.0013, p = 0.028, respectively), whereas spontaneous coved-type ST-segment elevation in Brugada patients did not predict cardiac events compared with patients not having such ST-segment elevation (p = 0.0068).

Further study with a larger number of BrS patients will be required to evaluate the significance of the index as a predictor of subsequent cardiac events.

As for BrS patients with only syncope, subsequent cardiac events occurred in 50% (6 of 12) patients who exhibited ST-segment augmentation at early recovery. Asymptomatic

Table 3	Predictive	Capabilities	of	Cardiac	Events	
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		Univariate Ana	alysis	Multivariate Analysis		
	Positive, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value	
Previous episodes of VF	22 (24%)	3.40 (1.54-7.53)	0.003	3.25 (1.43-7.37)	0.005	
Augmentation of ST-segment elevation at early recovery phase	34 (37%)	3.17 (1.42-7.09)	0.005	3.17 (1.37-7.33)	0.007	
SCN5A mutation	9 (10%)	2.86 (1.07-7.66)	0.037			
Spontaneous coved-type ST-segment	72 (77%)	3.51 (0.83-14.9)	0.089			
Late potential	58/91 (64%)	2.25 (0.84-5.99)	0.11			
VF inducible in EPS	59/78 (76%)	0.73 (0.30-1.75)	0.48			
Family history of SCD or BrS	23 (25%)	1.19 (0.47-3.02)	0.72			

BrS = Brugada syndrome; CI = confidence interval; EPS = electrophysiologic study; HR = hazard ratio; other abbreviations as in Table 2.

Table 4

Incidence of Cardiac Events According to Symptoms Before Exercise Testing

Туре	n	Treadmill Exercise Test	n	VF Occurrence	p Value (vs. Group 1)
Documented VF	22	Group 1	7	6 (86%)	
		Group 2	15	7 (47%)	0.14
Syncope alone	35	Group 1	12	6 (50%)	
		Group 2	23	3 (13%)	0.016
Asymptomatic	36	Group 1	15	3 (20%)	
		Group 2	21	0 (0%)	0.039

The p value was calculated according to the log-rank test.

VF = ventricular fibrillation.

patients who had ST-segment augmentation at early recovery had a higher incidence of cardiac events than patients who did not. These data suggested the potential utility of exercise testing to predict cardiac events for patients with BrS who have had previous episodes of only syncope but not VF or who have had no symptoms.

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Key Words: Brugada syndrome ■ exercise testing ■ ST-segment elevation.