

Correlation of phenotype with genotype and protein structure in *RYR1*-related disorders

Supplementary Figures (1)

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Human	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Chimp	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Rat	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Mouse	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Opossum	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Frog	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Tetraodon	V	I									R	I	R	A	I	L	R	S	L	V	P
Fugu	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Stickleback	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Medaka	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P
Zebrafish	L	I	Q	A	G	K	G	E	A	L	R	I	R	A	I	L	R	S	L	V	P

p.Arg2452Trp



Human	G	S	H	L	R	W	G	Q	P	L	R	V	R	H	V	T	T	G	Q	Y	L
Chimp	G	S	H	L	R	W	G	Q	P	L	R	V	R	H	V	T	T	G	R	Y	L
Rat	G	S	H	L	R	W	G	Q	P	L	R	I	R	H	V	T	T	G	R	Y	L
Mouse	G	S	H	L	R	W	G	Q	P	L	R	I	R	H	V	T	T	G	R	Y	L
Opossum	G	S	H	L	R	W	G	Q	P	L	R	V	R	H	V	T	T	G	R	Y	L
Frog	G	S	H	M	K	W	G	Q	S	F	R	V	R	H	V	T	T	G	R	Y	L
Tetraodon	G	S	H	I	K	W	G	Q	S	F	R	I	R	H	I	T	T	G	R	Y	L
Fugu	G	S	H	M	K	W	G	Q	S	F	R	I	R	H	I	T	T	G	R	Y	L
Stickleback	G	G	H	I	K	W	G	Q	S	F	R	I	R	H	I	T	T	G	R	Y	L
Medaka	L	L	Y	A	R	V	G	W	P	S	R	L	K	H	W	Y	L	L	I	Y	K
Zebrafish	G	S	H	M	K	W	G	Q	S	F	R	V	R	H	I	T	T	G	R	Y	L

p.Arg280*



Human	I	L	G	L	P	N	S	V	E	E	M	C	P	D	I	P	V	L	E	R	L
Chimp	I	L	G	L	P	N	S	V	E	E	M	C	P	D	I	P	V	L	E	R	L
Rat	I	L	G	L	P	N	S	V	E	E	M	C	P	D	I	P	V	L	E	R	L
Mouse	I	L	G	L	P	N	S	V	E	E	M	C	P	D	I	P	V	L	E	R	L
Opossum	I	L	G	L	P	S	S	V	E	E	M	C	P	D	I	P	D	L	K	Q	L
Frog	I	L	G	L	P	N	S	V	E	E	M	C	P	D	I	P	D	L	E	T	L
Tetraodon	I	L	G	L	P	N	E	V	Q	E	L	C	P	D	I	P	E	L	D	V	L
Fugu	I	L	G	L	P	S	Q	V	E	E	L	C	P	D	I	P	E	L	E	V	L
Stickleback	I	L	G	L	P	N	E	V	Q	E	L	C	P	D	I	P	E	L	D	A	L
Medaka	I	L	G	I	P	N	Q	V	E	E	L	C	P	D	I	P	E	L	E	V	L
Zebrafish	I	L	G	L	P	N	Q	V	Q	E	L	C	L	D	I	P	E	L	D	V	L

p.Met3239Lys



Human	I	R	F	P	K	M	V	T	S	C	C	R	F	L	C	Y	F	C	R	I	S
Chimp	I	R	F	P	K	M	V	T	S	C	C	R	F	L	C	Y	F	C	R	I	S
Rat	I	R	F	P	K	M	V	T	S	C	C	R	F	L	C	Y	F	C	R	I	S
Mouse	I	R	F	P	K	M	V	T	S	C	C	R	F	L	C	Y	F	C	R	I	S
Opossum	I	R	F	P	K	M	V	T	S	C	C	R	F	L	C	Y	F	C	R	I	S
Frog	I	R	F	P	K	M	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S
Tetraodon	I	R	F	P	R	V	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S
Fugu	I	R	F	P	Q	M	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S
Stickleback	I	R	F	P	R	V	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S
Medaka	I	R	F	P	Q	M	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S
Zebrafish	I	R	F	P	R	M	V	T	N	C	C	R	F	L	C	Y	F	C	R	I	S

p.Cys2233Arg

Human	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Chimp	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Rat	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Mouse	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Opossum	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Frog	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	A	M	F
Tetraodon	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Fugu	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Stickleback	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F
Medaka	C	C	R	F	L	C	Y	F	C	R	I	S	R	R	N	Q	R	A	M	F
Zebrafish	C	C	R	F	L	C	Y	F	C	R	I	S	R	Q	N	Q	R	S	M	F

p.Arg2241*

Human	T	L	L	Y	G	H	A	I	L	L	R	H	A	H	S	R	M
Chimp	T	L	L	Y	G	H	A	I	L	L	R	H	A	H	S	R	M
Rat	T	L	L	Y	G	H	A	I	L	L	R	H	A	H	S	R	M
Mouse	T	L	L	Y	G	H	A	I	L	L	R	H	A	H	S	R	M
Opossum	T	L	L	Y	G	H	A	I	L	L	R	H	A	H	S	R	M
Frog	T	L	L	Y	G	H	A	I	L	L	R	H	C	H	S	D	M
Tetraodon	T	L	L	Y	G	H	A	I	L	L	R	H	I	H	S	S	M
Fugu	T	L	L	Y	G	H	A	I	L	L	R	H	N	H	S	G	M
Stickleback	T	L	L	Y	G	H	A	I	L	L	K	H	T	H	S	S	M
Medaka	T	L	L	Y	G	H	A	I	L	L	R	H	H	S	G	M	M
Zebrafish	T	L	L	Y	G	H	A	I	L	L	R	H	T	H	S	G	M

p.Arg109Trp

Human	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Chimp	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Rat	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Mouse	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Opossum	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Frog	G	E	G	W	G	A	N	G	V	G	D	D	L	Y	S	F	G	F	D	G	L
Tetraodon	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Fugu	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	S	F	D	G	L
Stickleback	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Medaka	G	E	G	W	G	G	N	G	V	G	D	D	L	Y	S	Y	G	F	D	G	L
Zebrafish	G	E	G	W	G	G	N	G	V	G	D	D	L	H	S	Y	G	F	D	G	L

p.Asp708Asn

Human	G	M	L	S	M	V	L	N	C	I	D	R	L	N
Chimp	G	M	L	S	M	V	L	N	C	I	D	R	L	N
Rat	G	M	L	S	L	V	L	N	C	I	D	R	L	N
Mouse	G	M	L	S	L	V	L	N	C	I	D	R	L	N
Opossum	G	M	L	T	L	V	L	N	C	I	D	R	L	N
Frog	G	I	I	S	L	V	L	D	C	V	D	R	L	N
Tetraodon	G	M	I	S	L	V	L	D	C	V	D	R	L	N
Fugu	G	M	I	T	I	V	L	E	C	I	D	R	L	N
Stickleback	G	M	I	T	H	V	L	D	C	V	D	R	L	N
Medaka	G	M	I	T	I	V	L	E	C	I	D	R	L	N
Zebrafish	G	M	I	T	L	V	L	D	C	V	D	R	L	N

p.Met485Val

Human	M	S	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	Q
Chimp	M	S	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	Q
Rat	M	S	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	Q
Mouse	M	S	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	Q
Opossum	M	S	L	L	E	S	L	C	Q	I	R	S	L	L	I	V	Q	M	G	P	Q
Frog	M	N	L	L	E	S	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E
Tetraodon	M	D	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E
Fugu	M	D	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E
Stickleback	M	D	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E
Medaka	M	D	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E
Zebrafish	M	E	L	L	E	C	L	G	Q	I	R	S	L	L	I	V	Q	M	G	P	E

p.Arg2163His



Human	A	S	L	I	R	G	N	R	R	S	N	C	A	L	F	S
Chimp	A	S	L	I	R	G	N	R	R	S	N	C	A	L	F	S
Rat	A	S	L	I	R	G	N	R	R	T	N	C	A	L	F	S
Mouse	A	S	L	I	R	G	N	R	R	T	N	C	A	L	F	S
Opossum	A	S	L	I	R	G	N	R	R	T	N	C	A	L	F	S
Frog	A	A	L	I	R	G	N	R	R	S	N	C	A	L	F	S
Tetraodon	A	S	L	I	R	G	N	R	R	A	N	C	A	L	F	C
Fugu	A	S	L	I	R	G	N	R	R	S	N	C	A	L	F	C
Stickleback	A	S	L	I	R	G	N	R	R	A	N	C	A	L	F	C
Medaka	A	S	L	I	R	G	N	R	R	S	N	C	A	L	F	C
Zebrafish	A	S	L	I	R	G	N	R	R	A	N	C	A	L	F	C

p.Arg530His



Human	S	N	R	D	S	L	C	Q	A	V	R	T	L	L	G	Y	G	Y	N	I
Chimp	S	N	R	D	S	L	C	Q	A	V	R	T	L	L	G	Y	G	Y	N	I
Rat	S	N	R	D	S	L	C	Q	A	V	R	T	L	L	G	Y	G	Y	N	I
Mouse	S	N	R	D	S	L	C	Q	A	V	R	T	L	L	G	Y	G	Y	N	I
Opossum	S	C	P	P	C	P	S	P	I	F	L	N	S	A	S	F	H	L	T	C
Frog	T	N	R	D	S	L	C	E	A	V	R	T	L	I	G	Y	G	Y	N	I
Tetraodon	T	N	R	D	T	V	C	S	A	V	R	T	L	I	G	Y	G	Y	N	I
Fugu	T	N	R	D	S	V	N	N	A	V	R	T	L	I	G	Y	G	Y	N	I
Stickleback	T	N	R	D	T	V	F	A	A	V	R	T	L	I	G	Y	G	Y	N	I
Medaka	T	N	R	D	S	V	N	N	A	V	R	T	L	I	G	Y	G	Y	N	I
Zebrafish	T	N	R	D	T	V	C	A	A	V	R	T	L	I	G	Y	G	Y	N	I

p.Arg1043Cys



Human	C	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Chimp	C	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Rat	C	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Mouse	C	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Opossum	G	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Frog	V	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Tetraodon	C	G	G	E	K	Y	L	D	F	L	R	F	A	V	F	V	N	G
Fugu	C	G	G	E	R	Y	L	D	F	L	R	F	A	V	F	V	N	G
Stickleback	C	G	G	E	K	Y	L	D	F	L	R	F	A	V	F	V	N	G
Medaka	C	G	G	E	K	Y	L	D	F	L	R	F	A	V	F	V	N	G
Zebrafish	V	G	G	E	K	Y	L	D	F	L	R	F	A	V	F	V	N	G

p.Arg2336His



Human	K	P	A	P	L	D	L	S	H	V	R	L	T	P	A	Q	T	T	L	V	D
Chimp	K	P	A	P	L	D	L	S	H	V	R	L	T	P	A	Q	T	T	L	V	D
Rat	K	P	A	P	L	D	L	S	H	V	R	L	T	P	A	Q	T	T	L	V	D
Mouse	K	P	A	P	L	D	L	S	H	V	K	L	T	P	A	Q	T	T	L	V	D
Opossum	K	P	A	P	L	D	L	S	H	V	K	L	T	P	A	Q	N	T	L	V	D
Frog	K	P	A	P	L	D	L	S	H	V	K	L	T	P	A	Q	N	T	L	V	D
Tetraodon	K	P	A	P	L	D	L	N	H	V	K	L	T	P	N	Q	N	T	L	V	E
Fugu	K	P	A	P	L	D	L	S	H	V	K	L	T	P	N	Q	N	T	L	V	E
Stickleback	K	P	A	P	L	D	L	N	H	V	K	L	T	P	N	Q	N	T	L	V	E
Medaka	K	P	A	P	L	D	L	N	H	V	K	L	T	P	N	Q	N	T	L	V	E
Zebrafish	K	P	A	P	L	D	L	N	H	V	K	L	T	P	N	Q	N	T	L	V	E

p.Arg975Trp



Human	A	I	E	E	A	I	R	I	S	E	D	P	A	R	D	G	P	G	I	R	R
Chimp	A	I	E	E	A	I	R	I	S	E	D	P	A	R	D	G	P	G	I	R	R
Rat	A	I	E	E	A	I	R	I	S	E	D	P	A	R	D	G	P	G	I	R	R
Mouse	A	I	E	E	A	I	R	I	S	E	D	P	A	R	D	G	P	G	V	R	R
Opossum	A	M	E	E	A	I	R	I	S	E	D	P	A	R	D	G	P	G	V	R	R
Frog	A	I	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	T	V	K	K
Tetraodon	A	I	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	S	T	K	K
Fugu	A	M	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	T	V	K	K
Stickleback	A	I	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	S	V	K	K
Medaka	A	M	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	T	V	K	K
Zebrafish	A	I	E	E	A	I	K	I	S	E	D	P	A	R	D	G	P	T	V	K	K

p.Asp2389Glyfs*16

Human	S	L	K	C	S	N	C	Y	M	V	W	G	G	D	F	V	S	P	G	Q	Q
Chimp	S	L	K	C	S	N	C	Y	M	V	W	G	G	D	F	V	S	P	G	Q	Q
Rat	S	L	K	C	S	N	C	Y	M	V	W	G	G	D	F	V	S	P	G	Q	Q
Mouse	S	L	K	C	S	N	C	Y	M	V	W	G	G	D	F	V	S	P	G	Q	Q
Opossum	S	L	K	R	S	N	C	Y	M	V	W	G	G	D	F	V	S	P	G	Q	Q
Frog	S	I	K	R	S	N	C	Y	M	V	W	G	G	E	F	G	N	N	T	Q	Q
Tetraodon	S	I	K	R	S	N	C	Y	M	V	W	G	G	E	F	S	N	S		Q	Q
Fugu	S	M	K	H	S	N	C	Y	M	V	W	G	D	D	L	V	S	N		H	Q
Stickleback	S	I	K	R	S	N	C	Y	M	V	S	G	G	E	F	G	S	S		Q	Q
Medaka	S	M	K	H	S	N	C	Y	M	V	W	G	G	D	L	V	S	N		Q	Q
Zebrafish	S	V	K	R	S	N	C	Y	M	V	W	G	G	E	F	S	S	S		Q	Q

p.Trp1495*

Human	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	K	P	E	C	F
Chimp	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	K	P	E	C	F
Rat	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	K	P	E	C	F
Mouse	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	K	P	E	C	F
Opossum	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Frog	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Tetraodon	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Fugu	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Stickleback	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Medaka	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F
Zebrafish	E	S	V	E	E	N	A	N	V	V	V	R	L	L	I	R	R	P	E	C	F

p.Val2354del

Human	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Chimp	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Rat	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Mouse	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Opossum	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Frog	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Tetraodon	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Fugu	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Stickleback	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Medaka	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G
Zebrafish	N	L	M	R	A	L	G	M	H	E	T	V	M	E	V	M	V	N	V	L	G

p.Thr2206Met

Human	L	D	F	L	R	F	A	V	F	V	N	G
Chimp	L	D	F	L	R	F	A	V	F	V	N	G
Rat	L	D	F	L	R	F	A	V	F	V	N	G
Mouse	L	D	F	L	R	F	A	V	F	V	N	G
Opossum	L	D	F	L	R	F	A	V	F	V	N	G
Frog	L	D	F	L	R	F	A	V	F	V	N	G
Tetraodon	L	D	F	L	R	F	A	V	F	V	N	G
Fugu	L	D	F	L	R	F	A	V	F	V	N	G
Stickleback	L	D	F	L	R	F	A	V	F	V	N	G
Medaka	L	D	F	L	R	F	A	V	F	V	N	G
Zebrafish	L	D	F	L	R	F	A	V	F	V	N	G

p.Asn2342Ser

Human	N	I	M	P	L	S	A	A	M	F	Q	S
Chimp	N	I	M	P	L	S	A	A	M	F	Q	S
Rat	N	I	M	P	L	S	A	A	M	F	L	S
Mouse	N	I	M	P	L	S	A	A	M	F	L	S
Opossum	N	I	M	P	L	S	A	A	M	F	L	S
Frog	N	I	M	P	I	S	A	A	M	F	R	S
Tetraodon	N	I	M	P	I	S	A	A	M	F	R	S
Fugu	N	I	M	P	I	S	A	A	M	F	R	S
Stickleback	N	I	M	P	I	S	A	A	M	F	R	S
Medaka	N	I	M	P	I	S	A	A	M	F	R	S
Zebrafish	N	I	M	P	I	S	A	A	M	F	R	S

p.Ile1571Val

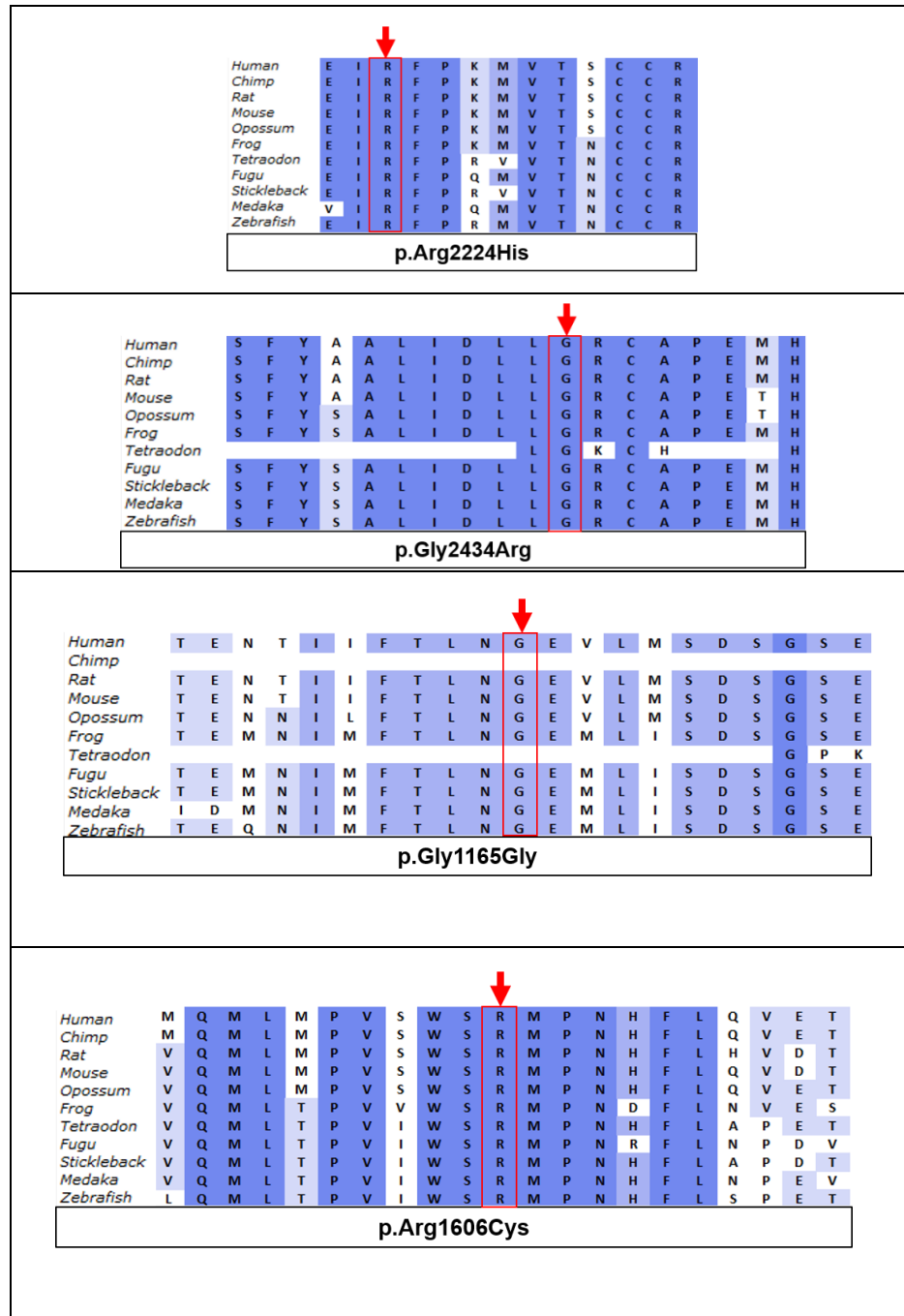


Figure S1. Orthologue alignments for each *RYR1* variant affecting the RyR1 cytosolic shell domain. With the exception of p.Met485Val and p.Arg1043Cys, all affected amino acid residues are highly conserved evolutionarily.



Human	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Chimp	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Rat	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Mouse	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Opossum	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Frog	F	L	A	L	F	L	A	F	A	I	N	F	I	L	L	F	Y	K
Tetraodon	F	L	A	L	F	L	A	F	A	L	N	F	I	L	L	F	Y	R
Fugu	Y	L	A	L	F	I	A	F	A	L	N	F	I	L	L	F	Y	K
Stickleback	F	L	A	L	F	L	A	F	A	L	N	F	I	L	L	F	Y	K
Medaka	F	L	A	L	F	I	A	F	A	L	N	F	I	L	L	F	Y	K
Zebrafish	F	L	A	L	F	L	A	F	A	L	N	F	I	L	L	F	Y	K

p.Asn4575Thr



Human	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Chimp	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Rat	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Mouse	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Opossum	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Frog	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Tetraodon	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Fugu	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Stickleback	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Medaka	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A
Zebrafish	E	L	Y	R	V	V	F	D	I	T	F	F	F	V	I	V	I	L	L	A

p.Phe4921Leu



Human	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Chimp	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Rat	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Mouse	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Opossum	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Frog	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Tetraodon	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Fugu	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Stickleback	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D
Medaka	L	L	E	I	I	Y	K	S	G	G	I	G	D	E	I	E	D	P	A	G	D
Zebrafish	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D	P	A	G	D

p.Ile4898Thr



Human	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Chimp	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Rat	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Mouse	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Opossum	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Frog	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Tetraodon	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Fugu	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Stickleback	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Medaka	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E
Zebrafish	G	L	I	I	D	A	F	G	E	L	R	D	Q	Q	E

p.Ala4940Thr



Human	F	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Chimp	F	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Rat	F	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Mouse	F	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Opossum	F	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Frog	Y	A	A	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Tetraodon	F	A	C	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Fugu	F	A	C	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Stickleback	F	A	C	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S
Medaka	F	S							A	F	D	P	H	S	C	S	K	L	T	F	D
Zebrafish	F	A	C	H	L	L	D	I	A	M	G	V	K	T	L	R	T	I	L	S	S

p.Gly4820Arg

Human	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Chimp	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Rat	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Mouse	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Opossum	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Frog	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Tetraodon	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Fugu	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D
Stickleback	L	Y	T	V	V	A	F	I	F	F	R	K	F	Y	N	K	G	E	E	E	D
Medaka	F	S	F	K	K	N	R	L	W	L	H	F	Y	N	K	K	V	I	N	A	
Zebrafish	L	Y	T	V	V	A	F	N	F	F	R	K	F	Y	N	K	S	E	D	E	D

p.Arg4861His

Human	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Chimp	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Rat	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Mouse	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Opossum	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Frog	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Tetraodon	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Fugu	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Stickleback	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E
Medaka	C	F	F	L	Y	L	L	E	I	I	Y	K	S	G	G	I	G	D	E	I	E
Zebrafish	C	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E

p.Arg4893Gln

Human	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Chimp	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Rat	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Mouse	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Opossum	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Frog	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Tetraodon	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Fugu	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Stickleback	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D
Medaka	F	F	L	Y	L	L	E	I	I	Y	K	S	G	G	I	G	D	E	I	E	D
Zebrafish	Y	L	F	H	M	Y	V	G	V	R	A	G	G	G	I	G	D	E	I	E	D

p.Arg4894Asp

Human	A	D	G	A	V	A	V	T	D	G	G	P	F	R	P	E	G	A	G	G	L
Chimp	A	D	G	A	V	A	V	T	D	G	G	P	F	R	P	E	G	A	G	G	L
Rat	A	D	R	T	V	A	V	A	D	G	S	P	F	R	P	E	G	A	G	G	L
Mouse	A	D	G	A	V	A	V	A	D	G	S	P	F	R	P	E	G	A	G	G	L
Opossum	W	E	R	I	L									R	E	T	G	L	D	R	E
Frog	H	Y	R	A	S									A	P	D	A	P	G	G	L
Tetraodon			R	I	P									G	I	D	A	P	G	G	L
Fugu			R	L	P									G	F	N	T	P	G	G	L
Stickleback			R	V	A									G	V	D	A	P	G	G	L
Medaka			R	L	P									G	F	N	T	P	G	G	L
Zebrafish			K	I	P									G	I	D	T	P	G	G	L

p.Gly4444-Gly4450dup

Human	G	L	I	I	D	A	F	G	E	L	R	D
Chimp	G	L	I	I	D	A	F	G	E	L	R	D
Rat	G	L	I	I	D	A	F	G	E	L	R	D
Mouse	G	L	I	I	D	A	F	G	E	L	R	D
Opossum	G	L	I	I	D	A	F	G	E	L	R	D
Frog	G	L	I	I	D	A	F	G	E	L	R	D
Tetraodon	G	L	I	I	D	A	F	G	E	L	R	D
Fugu	G	L	I	I	D	A	F	G	E	L	R	D
Stickleback	G	L	I	I	D	A	F	G	E	L	R	D
Medaka	G	L	I	I	D	A	F	G	E	L	R	D
Zebrafish	G	L	I	I	D	A	F	G	E	L	R	D

p.Leu4936Arg

Human	D	K	H	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Chimp	D	K	H	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Rat	D	K	H	G	D	I	F	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Mouse	D	K	H	G	D	I	F	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Opossum	E	K	H	G	D	I	F	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Frog	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Tetraodon	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	V	D	L	A
Fugu	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Stickleback	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	V	D	L	A
Medaka	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A
Zebrafish	D	K	Y	G	D	I	Y	G	R	E	R	I	A	E	L	L	G	M	D	L	A

p.Arg4737Gln

Human	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Chimp	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Rat	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Mouse	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Opossum	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Frog	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Tetraodon	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Fugu	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Stickleback	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Medaka	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Zebrafish	L	K	E	L	L	D	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G

p.Met4022Thrfs*4

Human	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Chimp	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Rat	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Mouse	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Opossum	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Frog	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Tetraodon	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Fugu	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Stickleback	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Medaka	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G
Zebrafish	L	Q	K	D	M	V	V	M	L	L	S	L	L	E	G

p.Ser4028Leu

Human	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Chimp	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Rat	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Mouse	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Opossum	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Frog	V	M	S	L	L	G	H	Y	N	N	F	F	Y	A	A	H	L	L	D	I	A
Tetraodon	I	M	S	L	L	G	H	Y	N	N	F	F	F	A	C	H	L	L	D	I	A
Fugu	L	M	S	L	L	G	H	Y	N	N	F	F	F	A	A	H	L	L	D	I	A
Stickleback	I	M	S	L	L	G	H	Y	N	N	F	F	F	A	C	H	L	L	D	I	A
Medaka	I	L	S	T	L	S	R	Q	N	G	F	G	F	S							A
Zebrafish	V	M	S	L	L	G	H	Y	N	N	F	F	F	A	C	H	L	L	D	I	A

p.Phe4808Asn

Human	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Chimp	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Rat	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Mouse	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Opossum	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Frog	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Tetraodon	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Fugu	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F
Stickleback	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	I	F	F	R	K	F
Medaka	E	R	F	C							F	S	F	K	K	N	R	L	W	L	H
Zebrafish	G	L	L	A	V	V	V	Y	L	Y	T	V	V	A	F	N	F	F	R	K	F

p.Thr4853Ile



Human	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Chimp	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Rat	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Mouse	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Opossum	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Frog	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Tetraodon	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Fugu	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Stickleback	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Medaka	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F
Zebrafish	E	I	E	D	P	A	G	D	E	Y	E	L	Y	R	V	V	F	D	I	T	F

p.Glu4911Lys



Human	P	E	P	E	P	E	L	E	P	E	K	A	D
Chimp	P	E	P	E	P	E	L	E	P	E	K	A	D
Rat	P	E	P	E	P	E	L	E	P	E	K	A	D
Mouse	P	E	P	E	P	E	L	E	P	E	K	A	D
Opossum	P	E	P	E	P	E	L	E	P	E	K	A	D
Frog	E	E	P	A	P	E	P	E	P	E	K	A	D
Tetraodon	S	L	E	E	K	L	E	K	P	K	K	S	A
Fugu	A								A	R	E	L	D
Stickleback	P	V	E	E	P	P	P	K	P	E	K	A	D
Medaka	P	G	E	E	V	P	Q	E	T	E	K	A	D
Zebrafish	A	I	E	E	P	P	P	E	P	E	K	A	D

p.Asp4505His



Human	L	V	M	T	V	G	L	L	A	V	V	V	Y
Chimp	L	V	M	T	V	G	L	L	A	V	V	V	Y
Rat	L	V	M	T	V	G	L	L	A	V	V	V	Y
Mouse	L	V	M	T	V	G	L	L	A	V	V	V	Y
Opossum	L	V	M	T	V	G	L	L	A	V	V	V	Y
Frog	L	M	M	T	V	G	L	L	A	V	V	V	Y
Tetraodon	L	M	M	T	V	G	L	L	A	V	V	V	Y
Fugu	L	M	M	T	V	G	L	L	A	V	V	V	Y
Stickleback	L	M	M	T	L	G	L	L	A	V	V	V	Y
Medaka	L	T	M	S	L	E	R	F	C				
Zebrafish	L	M	M	T	V	G	L	L	A	V	V	V	Y

p.Met4840Arg



Human	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	V	I	E
Chimp	E	S	I	R	D	F	Y	W	Y	Y	S	G	K	D	V	I	E
Rat	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	V	I	E
Mouse	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	V	I	E
Opossum	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	V	I	D
Frog	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D
Tetraodon	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D
Fugu	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D
Stickleback	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D
Medaka	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D
Zebrafish	E	S	I	S	D	F	Y	W	Y	Y	S	G	K	D	I	I	D

p.Tyr3933Cys



Human	K	G	Q	W	D	R	L	V	L	N	T	P
Chimp	K	G	Q	W	D	R	L	V	L	N	T	P
Rat	K	G	Q	W	D	R	L	V	L	N	T	P
Mouse	K	G	Q	W	D	R	L	V	L	N	T	P
Opossum	K	G	Q	W	D	R	L	V	L	N	T	P
Frog	K	G	Q	W	D	R	L	V	L	N	T	P
Tetraodon	K	G	Q	W	D	R	L	V	L	N	T	P
Fugu	K	G	Q	W	D	R	L	V	L	N	T	P
Stickleback	K	G	Q	W	D	R	L	V	L	N	T	P
Medaka	K	G	Q	W	D	R	L	V	L	N	T	P
Zebrafish	K	G	Q	W	D	R	L	V	L	N	T	P

p.Thr4709Met

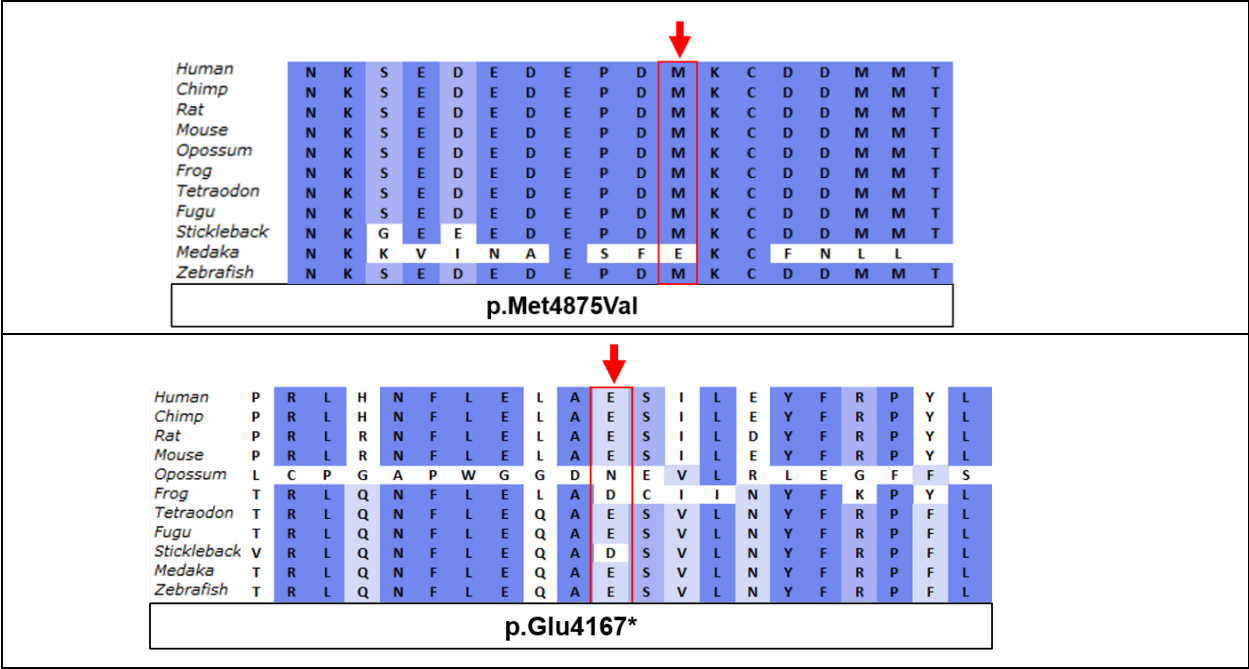


Figure S2. Orthologue alignments for each *RYR1* variant affecting the channel and activation core. All affected amino acid residues are highly conserved evolutionarily except p.Gly4444-Gly4450dup.

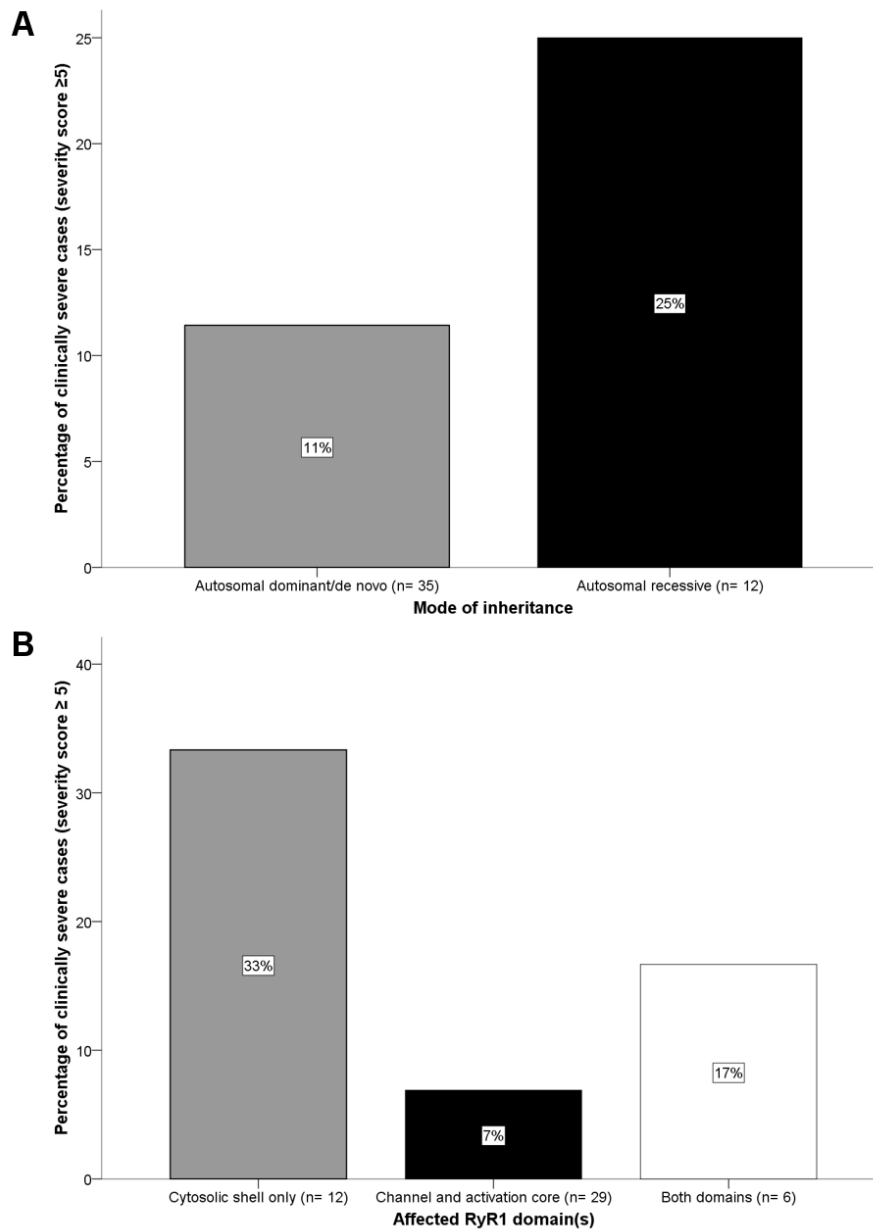


Figure S3. Percentage of cases deemed to be clinically severe by mode of inheritance (A) and affected RyR1 domain(s) (B). (A) Although a greater proportion of autosomal dominant/*de novo* cases were deemed clinically severe than recessive cases, this difference was not statistically significant (11% versus 25% respectively, $p = 0.35$). (B) The difference in the proportion of clinically severe cases between those with the RyR1 cytosolic shell affected, compared those with the RyR1 channel and activation core affected bordered statistical significance (33% versus 7% respectively, $p = 0.05$). There were no other statistically significant differences between groups.

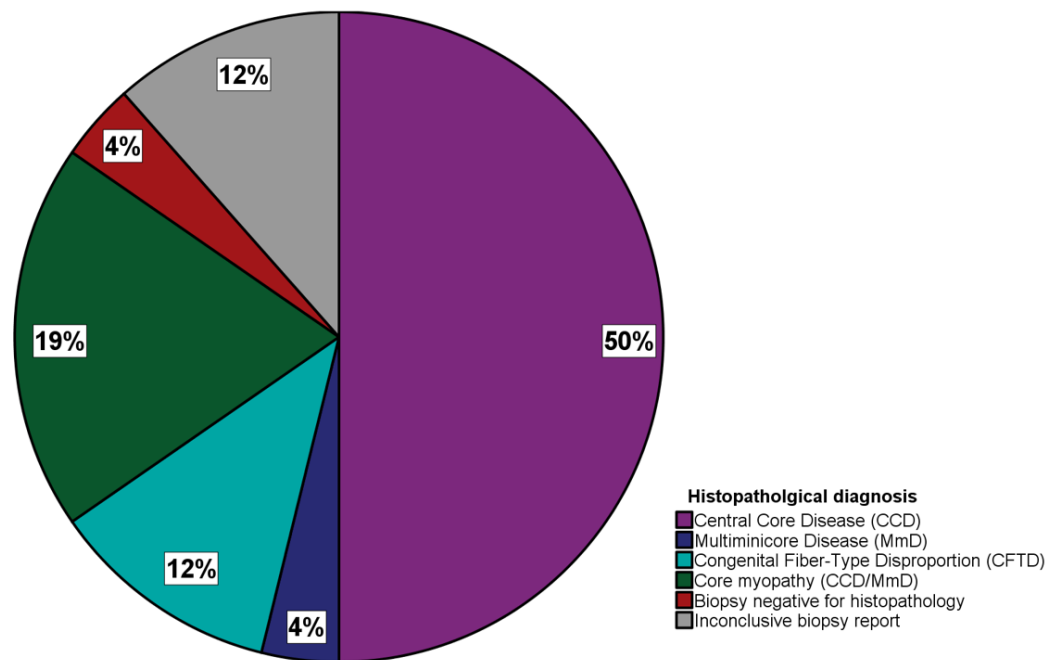


Figure S4. Overview of histopathologic diagnoses. Results are representative of participants with skeletal muscle biopsy reports ($n = 26$).

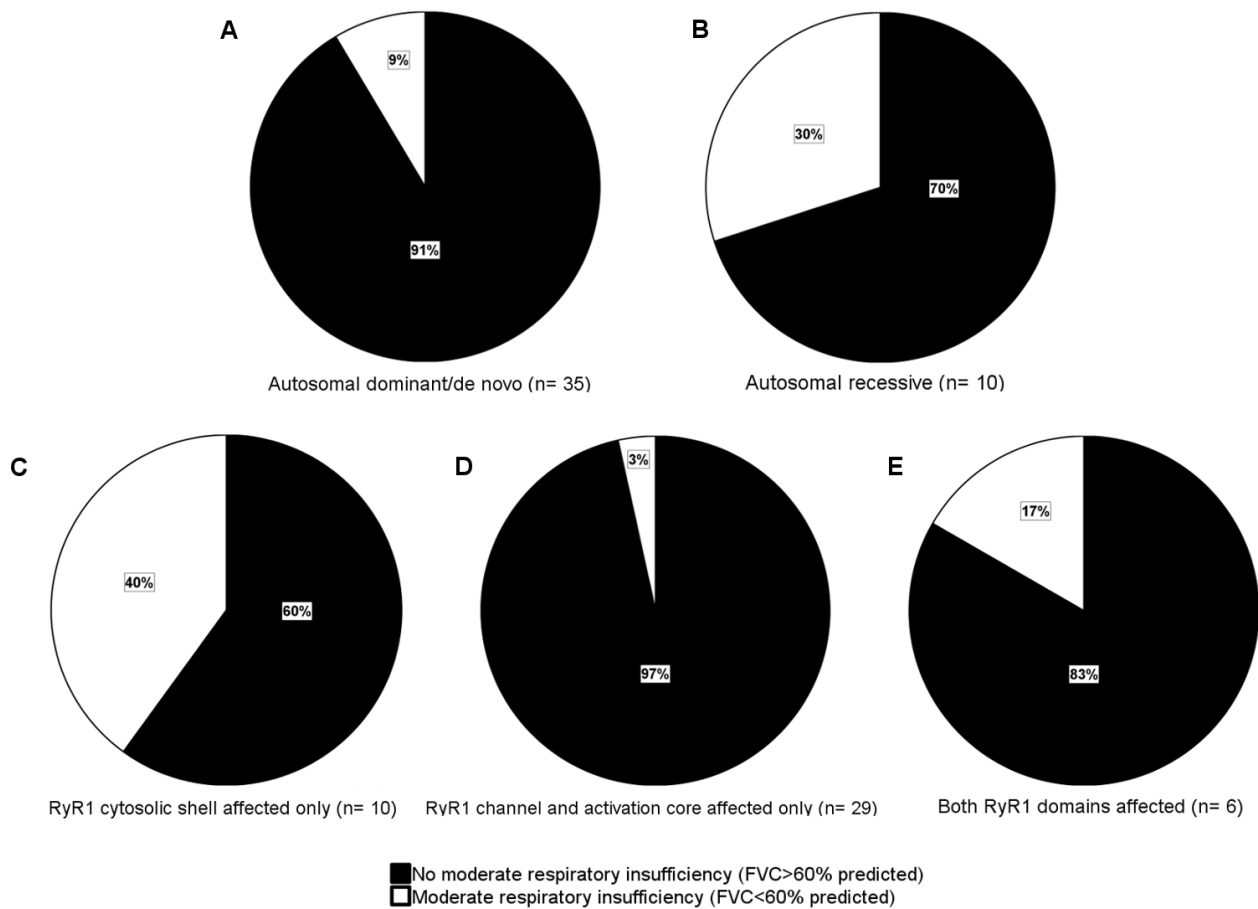


Figure S5. Pie charts detailing proportion of individuals with moderate respiratory insufficiency by mode of inheritance (A-B) and affected RyR1 structural domain(s) (C-E). Although a greater proportion of recessive cases exhibited moderate respiratory insufficiency, this difference fell short of statistical significance (30% versus 9% respectively, $p = 0.11$). A greater proportion of participants with the RyR1 cytosolic shell affected only exhibited moderate respiratory insufficiency compared to those with the RyR1 channel and activation core affected only (40% versus 3% respectively, $p = 0.01$). There were no other statistically significant differences between groups.