

Supplemental Table: Conservation across species of the novel *RYR2* variants. In Red mutations, in blue polymorphisms

	E243K	F329L	R332W
Homo sapiens	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Canis familiaris	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Equus caballus	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Gallus gallus	LLHGHMDECLTVPSG	ADIKSTAF ^F CFRSSKE	KSTAF ^F CF ^R SSKEKLD
Macaca mulatta	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Monodelphis domestica	LLHGHMDECLTVPSG	ADVKSTAF ^F SFRSSKE	KSTAF ^F S ^R SSKEKLD
Mus musculus	LLHGHMDECLTVPSG	ADVKSTAF ^F AFRSSKE	KSTAF ^F A ^F RSSKEKLD
Ornithorhynchus anatinu	LLHGHMDECLTVPSG	ADVKSTAF ^F CFRSSKE	KSTAF ^F CF ^R SSKEKLD
Otolemur garnettii	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Pan troglodytes	LLHGHMDECLTVPSG	ADVKSTAF ^F TFRSSKE	KSTAFTF ^R SSKEKLD
Rattus norvegicus	LLHGHMDECLTVPSG	ADVKSTAF ^F AFRSSKE	KSTAF ^F A ^F RSSKEKLD
Sorex araneus	LLHGHMDECLTVPSG	ADVKSTAF ^F AFRSSKE	KSTAF ^F A ^F RSSKEKLD
	G357S	V377M	T415R
Homo sapiens	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Canis familiaris	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Equus caballus	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Gallus gallus	GTPEIKY ^G D ^S I ^C F ^I Q	LWLSYQ ^S A ^D A ^K S ^V R ^M	SQHEESR ^T ARVIRST
Macaca mulatta	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Monodelphis domestica	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Mus musculus	GTSEIKY ^G D ^S I ^C Y ^I Q	LWLTYQ ^A V ^D V ^K S ^A R ^M	SQHEESR ^T ARVIRST
Ornithorhynchus anatinu	GTSEIKY ^G D ^S V ^C F ^I Q	LWLTYQ ^S A ^D A ^K S ^V R ^M	SQHEESR ^T ARVIRST
Otolemur garnettii	GTSEIKY ^G D ^S V ^C F ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	NK--ESR ^T GRVIRSN
Pan troglodytes	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST
Rattus norvegicus	GTSEIKY ^G D ^S I ^C Y ^I Q	LWLTYQ ^A V ^D V ^K S ^A R ^M	SQHEESR ^T ARVIRST
Sorex araneus	GTSEIKY ^G D ^S V ^C Y ^I Q	LWLTYQ ^S V ^D V ^K S ^V R ^M	SQHEESR ^T ARVIRST

	R420Q	V507I	A549V
Homo sapiens	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Canis familiaris	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Equus caballus	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Gallus gallus	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Macaca mulatta	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Monodelphis domestica	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Mus musculus	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Ornithorhynchus anatinu	SRTARVIRSTAFLEFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Otolemur garnettii	SRTGRVIRSNVFLFN	XXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXX
Pan troglodytes	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Rattus norvegicus	SRTARVIRSTVFLFN	ECIDRLH V YSSAAHF A	RGNRKNCAQFSGLD
Sorex araneus	SRTARVIRSTVFLFN	XXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXX

	R739H	R1013Q	T1107M
Homo sapiens	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E TVTAGDMR
Canis familiaris	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E TVTAGDMR
Equus caballus	LWSGCIAR T VSSPNQ	VWARDRV R QGWTYGI	RWYF E F E TVTAGDMR
Gallus gallus	LWSGCVAR T VNSPNQ	VWARDRI R QGWTYGI	KWYF E F E AVTAGDMR
Macaca mulatta	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E TVTAGDMR
Monodelphis domestica	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E AVTAGDMR
Mus musculus	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E AVTAGDMR
Ornithorhynchus anatinu	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E AVTAGDMR
Otolemur garnettii	LWSGCIAR T VSSPNQ	V-SRDR I QGWTYGI	XXXXXXXXXXXXXXXXXX
Pan troglodytes	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E TVTAGDMR
Rattus norvegicus	LWSGCIAR T VSSPNQ	VWARDRI R QGWTYGI	RWYF E F E AVTAGDMR
Sorex araneus	LWSXXXXXXXXXXQ	VWARDRI R QGWTYGI	RWYF E F E AVTAGDMR

	A1136V	E1837K	E2045G
Homo sapiens	GSDERAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVESDS
Canis familiaris	GSDEHAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPIESDS
Equus caballus	GSDECAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVESDS
Gallus gallus	GSDEEAF V FDGFKAQ	IMGIFHN G DLKHILQ	YLKKKQA E KPVDDDA
Macaca mulatta	GSDERAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVESDS
Monodelphis domestica	GSDEQAF A FDGFKAQ	IMGIFNN E DLKHILQ	YLKKKQT E KPIENDS
Mus musculus	GSDDRAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVASDS
Ornithorhynchus anatinu	GSDEHAF A FDGFKAQ	IMGVFHD G DLKHVLR	YLKKKQA Q RPVDGYS
Otolemur garnettii	XXXXXXXXXXXXXXXXXAQ	IMGVFHN E DLKHILQ	YLKKKQA E KPIESDL
Pan troglodytes	GSDERAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVESDS
Rattus norvegicus	GSDERAF A FDGFKAQ	IMGIFHN E DLKHILQ	YLKKKQA E KPVASDS
Sorex araneus	GSDDRAF A FDGFKAQ	IMGVFHN E DLKHILQ	XXXXXXXXXXXXXXXXXXX

	Y2156C	H2168Q	E2183V
Homo sapiens	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Canis familiaris	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Equus caballus	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Gallus gallus	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Macaca mulatta	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Monodelphis domestica	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Mus musculus	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Ornithorhynchus anatinu	LPYAEH S TQRPMLR	LMRALGM H ETVMEVM	VNVLGGG E MKEITFP
Otolemur garnettii	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKXXXXX
Pan troglodytes	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Rattus norvegicus	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP
Sorex araneus	IMNNKVF Y QHNPMLR	LMRALGM H ETVMEVM	VNVLGGG E SKEITFP

	D2216V	E2296Q	R2420W
Homo sapiens	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Canis familiaris	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Equus caballus	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Gallus gallus	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Macaca mulatta	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Monodelphis domestica	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Mus musculus	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Ornithorhynchus anatinu	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Otolemur garnettii	XXXXXXXXXXXXXXXXXX	GWNPVEG E RYLDFLR	XGEATRI R SILRSLI
Pan troglodytes	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Rattus norvegicus	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI
Sorex araneus	QNQKAMF D HLSYLLE	GWNPVEG E RYLDFLR	KGEAIRI R SILRSLI

	M3972I	D3973H	L3974Q
Homo sapiens	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Canis familiaris	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Equus caballus	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Gallus gallus	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Macaca mulatta	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Monodelphis domestica	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Mus musculus	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Ornithorhynchus anatinu	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Otolemur garnettii	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Pan troglodytes	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Rattus norvegicus	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM
Sorex araneus	IELLKEL M DLQKDMV	ELLKEL M DLQKDMV	LLKEL M DLQKDMVM

	K3997E	S4124G	Y4149S
Homo sapiens	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Canis familiaris	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Equus caballus	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Gallus gallus	VVNGTIG K QMVDMLV	TFLELSE S VLNYFQP	AKRIERV Y FEISESS
Macaca mulatta	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Monodelphis domestica	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Mus musculus	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Ornithorhynchus anatinu	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Otolemur garnettii	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Pan troglodytes	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Rattus norvegicus	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS
Sorex araneus	VVNGTIG K QMVDMLV	TFLELAE S VLNYFQP	AKRIERV Y FEISESS

	R4157Q	Q4159P	N4178S
Homo sapiens	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Canis familiaris	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Equus caballus	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Gallus gallus	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Macaca mulatta	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Monodelphis domestica	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Mus musculus	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Ornithorhynchus anatinu	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Otolemur garnettii	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Pan troglodytes	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Rattus norvegicus	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK
Sorex araneus	FEISESS R TQWEKPQ	ISESSRT Q WEKPQVK	QFIFD V NEGGEKEK

	E4187Q	G4315E	K4650E
Homo sapiens	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Canis familiaris	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Equus caballus	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Gallus gallus	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Macaca mulatta	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Monodelphis domestica	GGEKEKM E LFVNFCE	IMCSLLL G GSLVEGA	NYWDFV K RKVMDKY
Mus musculus	GGEKEKM E LFVNFCE	IVSSLLL G GSLVEGA	NYWDFV K RKVMDKY
Ornithorhynchus anatinu	GGEKEKM E LFVSFCE	XXXSWLS E KCLGHGA	NYWDFV K RKVMDKY
Otolemur garnettii	GGEKEKM E LFVNFCE	IVCSLLL G ASLVEGA	NYWDFV K RKVMDKY
Pan troglodytes	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY
Rattus norvegicus	GGEKEKM E LFVNFCE	IVSSLLL G GSLVEGA	NYWDFV K RKVMDKY
Sorex araneus	GGEKEKM E LFVNFCE	IICSLLL G GSLVEGA	NYWDFV K RKVMDKY

	N4736Del	R4790Q	K4805R
Homo sapiens	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC
Canis familiaris	SILGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC
Equus caballus	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC
Gallus gallus	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGD M PDM K CDDMLTC
Macaca mulatta	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGD M PDM K CDDMLTC
Monodelphis domestica	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGD M PDM K CDDMLTC
Mus musculus	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGD M PDM K CDDMLTC
Ornithorhynchus anatinu	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGD M PDM K CDDMLTC
Otolemur garnettii	SVLGHY N NFFFAAH	XXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXX
Pan troglodytes	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC
Rattus norvegicus	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC
Sorex araneus	SVLGHY N NFFFAAH	VVAFNFF R KFYNKSE	DGDT P DM K CDDMLTC

R4822H

Homo sapiens	FHMYVGV R AGGGIGD
Canis familiaris	FHMYVGV R AGGGIGD
Equus caballus	FHMYVGV R AGGGIGD
Gallus gallus	FHMYVGV R AGGGIGD
Macaca mulatta	FHMYVGV R AGGGIGD
Monodelphis domestica	FHMYVGV R AGGGIGD
Mus musculus	FHMYVGV R AGGGIGD
Ornithorhynchus anatinu	FHMYVGV R AGGGIGD
Otolemur garnettii	FHMYVGV R AGGGIGD
Pan troglodytes	FHMYVGV R AGGGIGD
Rattus norvegicus	FHMYVGV R AGGGIGD
Sorex araneus	FHMYVGV R AGGGIGD