cardiogenetics

Assessment of disease-associated missense variants in *RYR2* on transcript splicing

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Supplementary Table 1. Predicted splicing effects of *RYR2* missense variants.

c.DNA change	Protein change	Effect on splicing	Number of tools in agreement
c.37T>C	F13L	No	
c.38T>G	F13C	No	
c.85C>G	H29D	No	
c.184C>T	L62F	No	
c.217C>G	L73V	Introduce 5' Splice Site	1
c.230C>T	A77V	Introduce 5' Splice Site	2
c.241A>C	M81L	No	
c.344A>G	Y115C	No	
c.365G>A	R122H	No	1
c.490C>T	P164S	Deletion 5' Splice Site	1
c.494C>A	A165D	Deletion 5' Splice Site	1
c.497C>G	S166C	Introduce 5' Splice Site	4
c.506G>A	R169Q	Deletion 5' Splice Site	1
c.506G>T	R169L	Introduce 3' Splice Site	1
c.527G>A	R176Q	Deletion 5' Splice Site	4
c.533G>C	G178A	Deletion 5' Splice Site	1
c.556G>A	V186M	No	
c.567A>T	E189D	No	
c.649A>G	I217V	Introduce 5' Splice Site	1
c.688G>T	G230C	Deletion 5' Splice Site	1
c.719A>G	H240R	No	
c.725A>T	D242V	Introduce 5' Splice Site	1
c.727G>A	E243K	Introduce 5' Splice Site	1
c.985T>C	F329L	No	
c.994C>T	R332W	No	
c.1069G>A	G357S	Introduce 3' Splice Site	2
c.1144G>A	V382M	Deletion 5' Splice Site	2
c.1198G>C	D400H	No	
c.1202A>G	D401G	Introduce 5' Splice Site	1
c.1217C>T	S406L	No	
c.1220G>T	R407I	No	
c.1221A>T	R407S	No	
c.1237T>A	S413T	No	
c.1240C>T	R414C	No	
c.1241G>T	R414L	No	
c.1244C>G	T415R	No	
c.1244C>T	T415I	No	
c.1255A>T	I419F	Deletion 5' Splice Site	1
c.1259G>A	R420Q	Introduce 3' Splice Site	1
c.1258C>T	R420W	No	
c.1298T>C	L433P	No	
c.1318G>A	A440T	Deletion 3' Splice Site	1
c.1396C>G	P466A	No	
c.1454G>A	R485Q	Introduce 3' Splice Site	1
c.1458A>C	Q486H	No	
c.1519G>A	V507I	No	
c.1604A>G	E535G	Deletion 3' Splice Site	1
c.1640A>G	N547S	No	
c.1646C>T	A549V	No	
c.1663C>G	L555V	No	
c.1847C>T	S616L	No	
c.1871C>T	A624V	No	
c.1903A>C	N635H	No	

c.1918A>G	R640G	No	
c.1939C>T	R647C	No	
c.2216G>A	R739H	No	
c.2267G>A	S756N	Deletion 3' Splice Site	2
c.2306G>T	R769L	No	
c.2320C>A	P774T	No	
c.2389G>A	G797R	Deletion 3' Splice Site	4
c.2423A>G	H808R	No	
c.2701G>A	G901S	Introduce 3' Splice Site	1
c.2786G>A	R929H	Deletion 5' Splice Site	1
c.2828T>C	L943S	No	
c.3038G>A	R1013Q	Deletion 3' Splice Site	1
c.3070G>A	V1024I	Deletion 5' Splice Site	1
c.3152G>C	R1051P	No	
c.3230T>C	V1077A	Deletion 5' Splice Site	2
c.3265C>T	R1089C	Deletion 5' Splice Site	1
c.3271G>A	E1091L	Deletion 5' Splice Site	1
c.3320C>T	T1107M	Deletion 3' Splice Site	1
c.3380A>G	E1127G	Introduce 3' Splice Site	1
c.3407C>T	A1136V	No	
c.3667A>G	T1223A	No	
c.3766C>A	P1256T	No	
c.3803T>C	I1268T	No	
c.3827C>T	T1276I	No	
c.4040T>G	M1347R	Deletion 3' Splice Site	1
c.4196C>A	T1399L	No	
c.4465T>C	C1489R	No	
c.4552C>T	L1518F	No	
c.4652A>G	N1551S	Introduce 3' Splice Site	1
c.4692G>A	M1564I	No	
c.4693C>G	P1565A	No	
c.4742A>C	Q1581P	No	
c.4747C>T	P1583S	No	
c.4991T>A	V1664K	Deletion 5' Splice Site	1
c.5056C>T	L1686F	No	
c.5080A>C	M1694L	No	
c.5170G>A	E1724K	Introduce 5' Splice Site	3
c.5278C>T	R1760W	No	
c.5374A>T	I1792L	No	
c.5420G>A	R1807Q	Introduce 3' Splice Site	3
c.5428G>C	V1810L	Deletion 3' Splice Site	2
c.5509G>A	E1837K	No	
c.5614G>A	D1872N	No	
c.5654G>A	G1885E	Introduce 3' Splice Site	1
c.5656G>A	G1886S	Deletion 5' Splice Site	1
c.5762G>A	R1921Q	Introduce 3' Splice Site	1
c.6134A>G	E2045G	No	
c.6224T>C	I2075T	No	
c.6232C>T	P2078S	No	
c.6272A>G	Q2091R	Introduce 3' Splice Site	4
c.6337G>A	V2113M	Deletion 5' Splice Site	1
c.6380G>T	R2127L	No	
c.6412G>A	E2138K	Introduce 3' Splice Site	1
c.6445A>G	I2149V	Introduce 5' Splice Site	1
c.6457A>G	K2153E	No	
c.6504C>G	H2168Q	Introduce 3' Splice Site	2

c.6503A>G	H2168R	No	
c.6532G>A	V2178I	No	
c.6574A>T	M2192L	Introduce 5' Splice Site	2
c.6636A>C	K2212N	Introduce 5' Splice Site	1
c.6637G>T	A2213S	No	
c.6647A>T	D2216V	No	
c.6649C>T	H2217Y	No	
6680 G>T	G2227V	No	
c.6683G>T	G2228V	Deletion 5' Splice Site	1
c.6737C>T	S2246L	No	
c.6800G>A	R2267H	Deletion 5' Splice Site	1
c.6886G>C	E2296Q	Deletion 3' Splice Site	1
c.6916G>A	V2306I	No	
c.6919T>C	F2307L	No	
c.6933G>T	E2311D	Deletion 3' Splice Site	1
c.6950C>A	A2317E	Deletion 5' Splice Site	1
c.6961G>A	V2321M	Deletion 5' Splice Site	4
c.6982C>T	P2328S	Introduce 5' Splice Site	3
c.6992T>C	F2331S	No	
c.7024G>A	G2342R	Deletion 3' Splice Site	2
c.7076G>A	R2359Q	No	
c.7099G>A	G2367R	Introduce 3' Splice Site	2
c.7157A>T	N2386I	No	
c.7159G>A	A2387T	Deletion 3' Splice Site	1
c.7159G>C	A2387P	Deletion 3' Splice Site	1
c.7160C>T	A2387V	Introduce 5' Splice Site	1
c.7169C>T	T2390I	Introduce 5' Splice Site	5
c.7175A>G	Y2392C	No	
c.7181C>G	A2394G	Introduce 5' Splice Site	4
c.7199G>T	G2400V	No	
c.7202G>T	R2401L	No	1
c.7202G>A	R2401H	No	
c.7205G>A	C2402Y	No	
c.7207G>A	A2403T	No	
c.7210C>A	P2404T	No	
c.7258A>T	R2420W	Deletion 3' Splice Site	1
c.7259G>C	R2420T	Deletion 3' Splice Site	1
c.7260G>T	R2420S	Deletion 5' Splice Site	1
c.7400C>T	A2467V	No	
c.7422G>C	R2474S	Deletion 5' Splice Site	1
c.7420A>G	R2474G	Deletion 3' Splice Site	5
c.7423G>T	V2475F	No	
c.7447T>A	F2483I	No	
c.7469T>C	V2490A	Deletion 5' Splice Site	3
c.7493C>T	A2498V	Introduce 5' Splice Site	1
c.7511C>T	T2504M	No	
c.7528A>G	T2510A	No	
c.7598C>T	P2533L	No	
c.7600C>G	L2534V	No	
c.7813A>G	M2605V	Introduce 5' Splice Site	4
c.7820T>C	L2607P	No	
c.7883G>A	G2628E	No	
c.7925G>A	R2642K	No	
c.8018C>T	A2673V	Introduce 5' Splice Site	1
c.8145G>T	E2715D	Deletion 3' Splice Site	1
c.8147A>T	K2716I	No	

c.8162T>C	I2721T	No	
c.8470C>T	R2824W	No	
c.8794T>C	Y2932H	No	
c.8873A>G	Q2958R	No	
c.9352G>A	G3118R	Deletion 3' Splice Site	1
c.9560A>G	K3187R	Introduce 5' Splice Site	2
c.9569G>A	R3190Q	No	
c.9655G>A	V3219M	No	
c.9688C>A	Q3230K	No	
c.9910C>G	Q3304E	No	
c.10708C>T	R3570W	No	
c.10742G>A	R3581K	No	
c.10844G>A	R3615Q	Introduce 5' Splice Site	1
c.10913A>C	D3638A	No	
c.11017C>T	R3673W	No	
c.11197G>A	D3733N	Introduce 5' Splice Site	1
c.11332C>T	L3778F	Deletion 5' Splice Site	1
c.11395T>C	S3799P	No	
c.11399G>T	C3800F	Deletion 5' Splice Site	5
c.11426A>G	E3809G	Deletion 3' Splice Site	1
c.11515C>T	L3839F	No	
c.11570A>G	Y3857C	No	
c.11583G>C	Q3861H	Deletion 3' Splice Site	1
c.11628C>G	D3876E	Introduce 5' Splice Site	1
c.11636T>C	L3879P	No	
c.11773C>G	Q3925E	No	
c.11814C>A	S3938R	No	
c.11827G>A	A3943T	No	
c.11836G>A	G3946S	Introduce 3' Splice Site	2
c.11837G>C	G3946A	No	
c.11837G>A	G3946D	No	
c.11876C>T	S3959L	No	
c.11916G>T	M3972I	No	
c.11917G>A	D3973N	Deletion 3' Splice Site	1
c.11917G>C	D3973H	No	
c.11921T>A	L3974Q	Deletion 3' Splice Site	2
c.11929G>T	D3977Y	Introduce 5' Splice Site	2
c.11934G>A	M3978I	Deletion 5' Splice Site	1
c.11969T>A	V3990D	No	
c.11989A>G	K3997E	No	
c.12006G>A	M4002I	No	
c.12013G>A	E4005K	Introduce 5' Splice Site	1
c.12058T>C	F4020L	No	
c.12121G>A	G4041R	Introduce 3' Splice Site	1
c.12226G>A	E4076K	No	
c.12272C>T	A4091V	Introduce 5' Splice Site	1
c.12271G>A	A4091T	No	
c.12290A>G	N4097S	Deletion 3' Splice Site	1
c.12312C>G	N4104K	Introduce 3' Splice Site	3
c.12311A>T	N4104I	No	
c.12313C>T	L4105F	No	
c.12643A>G	M4107V	No	
c.12322C>A	H4108N	No	
c.12324C>A	H4108Q	No	
c.12326T>G	M4109R	Introduce 3' Splice Site	2
c.12325A>G	M4109V	No	

c.12343C>T	L4115F	No	
c.12364A>C	S4122R	No	
c.12370A>G	S4124G	Deletion 3' Splice Site	1
c.12371G>C	S4124T	Deletion 3' Splice Site	1
c.12371G>A	S4124N	Deletion 5' & 3 Splice Site	5 & 3
c.12372C>A	S4124R	No	
c.12415A>G	M4139V	No	
c.12430C>T	R4144C	No	
c.12438G>C	E4146D	Deletion 3' Splice Site	1
c.12436G>A	E4146K	No	
c.12446A>G	Y4149C	No	
c.12457A>C	S4153R	Deletion 3' Splice Site	3
c.12458G>T	S4153I	No	
c.12464C>A	S4155Y	No	
c.12470G>A	R4157Q	No	
c.12472A>C	T4158P	No	
c.12476A>C	Q4159P	Deletion 3' Splice Site	1
c.12502T>A	S4168T	No	
c.12533A>G	N4178S	Introduce 3' Splice Site	3
c.12532A>T	N4178Y	No	
c.12545A>C	E4182A	Introduce 5' Splice Site	1
c.12544G>C	E4182Q	Introduce 3' Splice Site	1
c.12559G>C	E4187Q	Introduce 5' Splice Site	1
c.12563T>C	L4188P	No	
c.12579C>G	C4193W	No	
c.12586A>G	T4196A	No	
c.12602A>G	Q4201R	Deletion 3' Splice Site	3
c.12611C>T	A4204V	Introduce 5' Splice Site	1
c.12639G>C	E4213D	Deletion 3' Splice Site	1
c.12767T>C	M4256T	No	
c.12791T>C	L4264P	No	
c.12892G>A	V4299M	No	
c.12917T>C	F4306S	No	
c.12919C>T	R4307C	No	
c.12944G>A	G4315E	No	
c.13081G>C	E4361Q	No	
c.13175A>G	K4392R	Introduce 3' Splice Site	1
c.13249G>C	E4417Q	No	
c.13291G>A	E4431K	No	
c.13411G>A	G4471R	No	
c.13463A>C	Q4488P	No	
c.13489C>T	R4497C	No	
c.13496T>G	F4499C	No	
c.13512G>A	M4504I	Deletion 5' Splice Site	2
c.13528G>A	A4510T	No	
c.13655A>G	H4552R	Deletion 3' Splice Site	1
c.13666G>A	A4556T	No	
c.13672C>T	H4558Y	No	
c.13695C>A	S4565R	Introduce 5' Splice Site	1
c.13735C>T	H4579Y	Introduce 3' Splice Site	1
c.13737C>A	H4579Q	Introduce 3' Splice Site	1
c.13759A>G	I4587V	No	
c.13759A>C	I4587L	No	
c.13781A>G	K4594R	Introduce 3' Splice Site	2
c.13781A>G	L4594R	No	
c.13798T>C	F4600L	No	

c.13819G>C	A4607P	No	
c.13823G>A	R4608Q	Introduce 3' Splice Site	1
c.13822C>T	R4608W	No	
c.13831G>A	E4611K	No	
c.13892A>T	D4631V	Introduce 5' Splice Site	2
c.13933T>A	W4645R	Introduce 3' Splice Site	3
c.13948A>G	K4650E	No	
c.13957G>T	V4653F	Deletion 5' Splice Site	3
c.13984G>A	G4662S	Introduce 3' Splice Site	1
c.14009T>A	L4670H	Introduce 5' Splice Site	1
c.14011G>C	G4671R	No	
c.14148C>A	D4716E	No	
c.14174A>G	Y4725C	Introduce 5' Splice Site	1
c.14222C>T	A4741V	No	
c.14224C>T	H4742Y	No	
c.14251A>C	K4750Q	No	
c.14285A>C	H4762P	No	
c.14301C>G	L4767L	Introduce 5' Splice Site	2
c.14311G>A	V4771I	Deletion 5' Splice Site	1
c.14314G>A	G4772S	Introduce 3' Splice Site	2
c.14369G>A	R4790Q	No	
c.14414A>G	K4805R	Introduce 3' Splice Site	1
c.14461G>A	V4821I	Deletion 5' Splice Site	1
c.14465G>A	R4822H	Deletion 5' Splice Site	1
c.14542A>G	I4848V	Introduce 5' Splice Site	1
c.14552T>G	F4851C	No	
c.14553C>A	F4851L	No	
c.14579C>G	A4860G	No	
c.14593C>G	L4865V	Introduce 5' Splice Site	1
c.14601T>G	I4867M	Deletion 3' Splice Site	1
c.14599A>G	I4867V	No	
c.14635C>A	Q4879K	No	
c.14639T>C	V4880A	Deletion 5' Splice Site	1
c.14683A>G	N4895D	Deletion 5' Splice Site	1
c.14704C>T	P4902S	Deletion 3' Splice Site	1
c.14705C>T	P4902L	Deletion 3' Splice Site	1
c.14711G>A	G4904D	Introduce 3' Splice Site	1
c.14713T>C	F4905L	No	
c.14726C>T	T4909I	Deletion 3' Splice Site	1
c.14756T>C	L4919S	No	
c.14803 G>A	G4936R	No	
c.14806C>A	Q4936K	No	
c.14813C>T	S4938F	No	
c.15162T>C	W4949R	No	
c.14848G>A	E4950K	No	
c.14876G>A	R4959Q	Introduce 3' Splice Site	2
c.14885A>G	Y4962C	Introduce 5' Splice Site	1

Supplementary Table 2: Clinical information for individuals with predicted spliceogenic RYR2 variants.

cDNA change	Protein change	Variant hotspot region	Sex	Age (years)	Inheritance	Ethnicity	Trigger	Cardiac Phenotype	Reference
c.497C>G	p.(Ser166Cys)	I	Female	11	Unknown	Unknown	Exercise	Syncope	(Shigemizu et al., 2015)
c.527G>A	p.(Arg176Gln)	I	Male	12	Unknown	Unknown	Excitement	Syncope	(Tester et al., 2005b)
c.6272A>G	p.(Gln2091Arg)	Non-hotspot region	Male	29	Paternal	White British	Unknown	Sudden death	unpublished
c.6961G>A	p.(Val2321Met)	II	Female	23	Unknown	Japanese	Stress	Sudden death	(Nishio et al., 2008)
c.7169C>T	p.(Thr2390Ile)	II	Male	11	Paternal	Unknown	Exercise	Cardiac arrest. Sinus bradycardia. Exercise induced premature ventricular contractions	(Ohno et al., 2015)
c.7181C>G	p.(Arg2394Gly)	II	Female	15	Unknown	European	Exercise	Monomorphic premature ventricular beats	(Postma et al. 2005)
c.7420A>G	p.(Arg2474Gly)	II	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	(Kawamura et al., 2013)
c.7813A>G	p.(Met2605Val)	Non-hotspot region	Unknown	40	Paternal	Unknown	Unknown	Unknown	(van der Werf et al., 2012)
c.11399G>T	p.(Cys3800Phe)	III	Female	58	Unknown	Unknown	Startled	Aborted cardiac arrest	(Tester et al., 2005)
c.12371G>A	p.(Ser4124Asn)	III	Male	9	Maternal	Unknown	Unknown	Syncope	(Ohno et al., 2015)

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