Supplemental material

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Blueprint (Finland)
CeGat (Germany)
Cen4Gen (Canada)
CentoGene (Germany)
CGC Genetics (Portugal)
Children's Minnesota (US)
Cincinnati Children's (US)
CTGT (US)
DDC Clinic (US)
EGL (US)
Fulgent (US)
GeneDx (US)
GeneTaq (Spain)
GPS WUSTL (US)
Greenwood (US)
Health[in]Code (Spain)
Invitae (US)
LabGenetics (Spain)
LabPlus (New Zealand)
Mayo Clinic (US)
MNG Laboratories (US)
Montreal Heart Institute (Canada)
OHSU Knight (US)
Phosphorus (US)
PreventionGenetics (US)
Reference Laboratory (Spain)
Royal Brompton (UK)
Sistemas (Spain)
Sonic (Australia)
Transgenomic (US)
VSGS (Australia)

Supplemental Table. Genetic variants in KCNE1 and KCNE2 previously reported in aLQTS cases

AA change	cDNA change	MAF (all)*	MAF† (highest)	References
KCNE1				
Asp76Asn	226G>A	0.00007	0.0001 (Eu)	[1]
Asp85Asn	253G>A	0.009	0.025 (AJ)	[1-5]
KCNE2				
Thr8Ala	22A>G	0.004	0.006 (Eu)	[2,6-8]
Gln9Glu	25C>G	0.0015	0.016 (Af)	[6]
Leu11fsTer46	Unavailable	0	0	[8]
Ile57Thr	170T>C	0.001	0.002 (Latino)	[6-8]
Met54Thr	161T>C	0.0002	0.005 (AJ)	[7]
Ala116Val	347C>T	0.00002	0.00004 (Af)	[7]
Met121Lys	362T>A	0.000008	0.00002 (Eu)	[8]

* Minor allele frequency in gnomAD

† Highest minor allele frequency in any of the sub-populations available on gnomAD: Af- African; AJ- Ashkenazi Jewish; Eu- European (non-Finnish)

aLQTS- acquired long QT syndrome; MAF- minor allele frequency

Table references

1. Weeke P, Mosley JD, Hanna D, et al. Exome sequencing implicates an increased burden of rare potassium channel variants in the risk of drug-induced long QT interval syndrome. J Am Coll Cardiol 2014;63:1430-1437.
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3. Lane CM, Giudicessi JR, Ye D, et al. Long QT syndrome type 5-Lite: Defining the clinical phenotype associated with the potentially proarrhythmic p.Asp85Asn-KCNE1 common genetic variant. Heart Rhythm 2018;15:1223-1230.

4. Kaab S, Crawford DC, Sinner MF, et al. A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. Circ Cardiovasc Genet 2012;5:91-99.
5. Nishio Y, Makiyama T, Itoh H, et al. D85N, a KCNE1 polymorphism, is a disease-causing gene variant in long QT syndrome. J Am Coll Cardiol 2009;54:812-819.
6. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175-187.
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8. Roberts JD, Krahn AD, Ackerman MJ, et al. Loss-of-Function KCNE2 Variants: True Monogenic Culprits of Long-QT Syndrome or Proarrhythmic Variants Requiring Secondary Provocation? Circ Arrhythm Electrophysiol 2017;10: e005282.

Gene classification matrices

AKAP9

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	1	1.25	1.5	18093912; 28003625; 26132555; 29350269; 26189708
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
		Segregation		Candidate gene sequencing	0	0	0	
				Exome/genome or all genes sequenced in linkage region				
	Case-Control				0	0	0	
	Genetic Evidence Total				**1**	**1.25**	**1.5**	
Experimental Evidence	Functional			Biochemical functions	1	2	0.5	25037568; 11799244
				Protein interactions				18093912; 22778270; 11799244
				Expression				
	Functional Alteration			Patient cells	0.5	0.5	0	
				Non-patient cells				18093912
	Models			Non-human model organism	0	0	0	
				Cell-culture model				
	Rescue			Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
	Experimental Evidence Total				**1.5**	**2.5**	**0.5**	
Total Points					**2.5**	**3.75**	**2**	
Summary Classification					**Disputed**			

ANK2

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	2	2.3	2.1	26132555;28196901;16253912;15178757;16864073;17242276;27784853;28003625
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	12571597
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	1.5	0	16253912;17242276;16864073
			Genetic Evidence Total		2	3.8	2.1	
Experimental Evidence			Functional	Biochemical functions	0	0	0	
				Protein interactions				
				Expression				
			Functional Alteration	Patient cells	0.5	2	2	
				Non-patient cells				28196901;15178757;17242276;10579720;28196901
			Models	Non-human model organism	1	0	0	12571597
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		1.5	2	2	
Total Points					3.5	5.8	4.1	
Summary Classification					Disputed			

CACNA1C

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	5	7	6	25633834;23677916;24728418;27390944
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	15863612
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	1	24728418
				Exome/genome or all genes sequenced in linkage region				23677916
			Case-Control		0	0	0	
			Genetic Evidence Total		5	7	7	
Experimental Evidence			Functional	Biochemical functions	0	0	0	
				Protein interactions				
				Expression				
			Functional Alteration	Patient cells	1.5	2	1.5	
				Non-patient cells				25633834;23677916;24728418;27390944
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		1.5	2	1.5	
Total Points					6.5	9	8.5	
Summary Classification					Moderate			

CALM1

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	1	1	0	23388215;24076290;26969752
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	12	12	12	23388215;27374306;26969752
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0.5	
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		2	2	6	26969752;24076290
			Genetic Evidence Total		**12**	**12**	**12**	
Experimental Evidence			Functional	Biochemical functions	1	0.5	0.5	
				Protein interactions				16556865
				Expression				23388215
			Functional Alteration	Patient cells	2	2	2	28158429
				Non-patient cells				23388215;26969752;27374306;24958779;24816216;26309258
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		**3**	**2.5**	**2.5**	
Total Points					**15**	**14.5**	**14.5**	
Summary Classification					**Defintive**			

CALM2

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	0	0	26969752
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	12	12	12	24917665;23388215;27374306
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		2	2	8	26969752
			Genetic Evidence Total		**12**	**12**	**12**	
Experimental Evidence			Functional	Biochemical functions	1	0.5	1	
				Protein interactions				16556865;28575668
				Expression				23388215;
			Functional Alteration	Patient cells	1	2	2	28335032;27765793
				Non-patient cells				23388215;27374306;24917665;24958779;24816216;26309258
			Models	Non-human model organism	2	1	2	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				28335032;27765793
			Experimental Evidence Total		**4**	**3.5**	**5**	
Total Points					**16**	**15.5**	**17**	
Summary Classification					**Definitive**			

CALM3

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	1.5	0.5	0.5	28491681
				Proband with predicted or proven null variant	0	0	0	
				Variant is de *novo*	10.5	10.5	12	25460178;28491681
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	26969752
			Genetic Evidence Total		12	11	12	
Experimental Evidence			Functional	Biochemical functions	1	1	0.5	
				Protein interactions				16556865
				Expression				23388215
			Functional Alteration	Patient cells	0	0	0.5	
				Non-patient cells				
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		1	1	1	
Total Points					13	12	13	
Summary Classification					Definitive			

CAV3

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	0	1	17060380;26132555;24917393;24021552
				Proband with predicted or proven null variant	0	0	0	
				Variant is de *novo*	3.5	2	3	17060380
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	
			Genetic Evidence Total		3.5	2	4	
Experimental Evidence			Functional	Biochemical functions	1	1.5	0	
				Protein interactions				17060380;24021552;23640888
				Expression				14663034
			Functional Alteration	Patient cells	0.5	1.5	0.5	
				Non-patient cells				17060380;17275750;23640888;23541953
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		1.5	3	0.5	
Total Points					5	5	4.5	
Summary Classification					Limited			

KCNE1

Evidence Type					Points Counted G1	Points Counted G2	Points Counted G3	PMID
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	1.5	2.85	0.75	21712262;17341399;9445165;14499862;9354802;10400998;29672598;16155735
				Proband with predicted or proven null variant	0	0	0	
				Variant is de *novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	9354783;9445165;29625280;9354802
				Exome/genome or all genes sequenced in linkage region				
		Case-Control			0	0	0	
		Genetic Evidence Total			**1.5**	**2.85**	**0.75**	
Experimental Evidence	Functional			Biochemical functions	0.5	0	1	1939241
				Protein interactions				9201970;20196769
				Expression				
	Functional Alteration			Patient cells	1.5	2	2	
				Non-patient cells				9354802;10400998;29625280;16945797;14499862;17341399;19907016;27076034;14499862
	Models			Non-human model organism	2	1	2	27076034;11320260
				Cell-culture model				
	Rescue			Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
	Experimental Evidence Total				**4**	**3**	**5**	
Total Points					**5.5**	**5.85**	**5.75**	
Summary Classification					**Limited**			

KCNE2

Evidence Type					Points Counted G1	Points Counted G2	Points Counted G3	PMID
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	1.5	1.6	10219239;28794082;18006462;12185453;23631727
				Proband with predicted or proven null variant	0	0	0	
				Variant is de *novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	
				Exome/genome or all genes sequenced in linkage region				
		Case-Control			0	1	0	10219239;12185453;28794082;23714088
		Genetic Evidence Total			**0**	**2.5**	**1.6**	
Experimental Evidence	Functional			Biochemical functions	1.5	0.5	0	10219239;15292247;11927665
				Protein interactions				11101505;12185453
				Expression				
	Functional Alteration			Patient cells	0.5	2	0.5	
				Non-patient cells				10219239;18006462;12185453;12923204;
	Models			Non-human model organism	0	0	0	
				Cell-culture model				
	Rescue			Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
	Experimental Evidence Total				**2**	**2.5**	**0.5**	
Total Points					**2**	**5**	**2.1**	
Summary Classification					**Disputed**			

KCNH2

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	4.5	0	19668779;19187913;8635257;7889573;21240260;19070294;21109023
				Proband with predicted or proven null variant	9	1.5	9	15840476;10973849;7889573;18551196;
				Variant is *de novo*	0	0	2	7889573
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	1.5	3	3	7889573;19668779;19187913;8635257;
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		1	3	0	24606995;19841300
			Genetic Evidence Total		12	12	12	
Experimental Evidence			Functional	Biochemical functions	2	1.5	0.5	7736582;20850565
				Protein interactions				18551196
				Expression				7889573;9012748
			Functional Alteration	Patient cells	1.5	2	2	21240260;28433559;
				Non-patient cells				16432067;23997099;21536673;19187913;10753933
			Models	Non-human model organism	4	2.5	4	12612061
				Cell-culture model				15760896
			Rescue	Rescue in human				
				Rescue in non-human model organism				21458413;23303164
				Rescue in cell culture model				21536673
				Rescue in patient cells				24213244
			Experimental Evidence Total		6	6	6	
Total Points					18	18	18	
Summary Classification					Definitive			

KCNJ2

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	1.5	2.6	20111058;24395924;23644778;22589293;15276028;28003625
				Proband with predicted or proven null variant	0	0	0	21148745;
				Variant is *de novo*	0	0	0	11371347;
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	11371347;16571646;29017447;12148092;15276028
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	
			Genetic Evidence Total		0	1.5	2.6	
Experimental Evidence			Functional	Biochemical functions	0.5	0	0	11371347
				Protein interactions				
				Expression				
			Functional Alteration	Patient cells	1.5	0.5	1.5	
				Non-patient cells				15831539;16541386;17582433;23644778;22589293;15276028
			Models	Non-human model organism	1	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				21493816
				Rescue in patient cells				
			Experimental Evidence Total		3	0.5	1.5	
Total Points					3	2	4.1	
Summary Classification					Limited			

KCNJ5

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	0	0.5	20560207
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	23872692;25417227
				Exome/genome or all genes sequenced in linkage region				
		Case-Control			0	0	0	
		Genetic Evidence Total			**0**	**0**	**0**	
Experimental Evidence	Functional			Biochemical functions	0	1	1	24148898
				Protein interactions				
				Expression				24148898;20560207
	Functional Alteration			Patient cells	0	0.5	0.5	
				Non-patient cells				24574546;20560207
	Models			Non-human model organism	0	0	0	
				Cell-culture model				
	Rescue			Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
	Experimental Evidence Total				**0**	**1.5**	**1.5**	
Total Points					**0**	**1.5**	**2**	
Summary Classification					**Disputed**			

KCNQ1

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	1	3.5	2.5	17655673;15950200;20660394;8528244;25889101;10220144;
				Proband with predicted or proven null variant	1.5	1.5	7.5	22739119;8528244
				Variant is *de novo*	3.5	2	0	8872472;10220144;25139741
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0		0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	1.5	2.5	3	8528244;10220144;15950200;25139741;20660394;25889101
				Exome/genome or all genes sequenced in linkage region				
		Case-Control			6	3	0	19841300;11216980
		Genetic Evidence Total			**12**	**12**	**12**	
Experimental Evidence	Functional			Biochemical functions	1	0.5	0	8900283;9108097
				Protein interactions				
				Expression				25889101
	Functional Alteration			Patient cells	1.5	2	2	20660394;22739119;25889101
				Non-patient cells				9323054;9312006;20421371;17655673;15950200;25139741;20660394;22739119;16246960;15358555;22095730
	Models			Non-human model organism	4	5	4	15498462;18464931;17360457
				Cell-culture model				
	Rescue			Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				25889101
	Experimental Evidence Total				**6**	**6**	**6**	
Total Points					**18**	**18**	**18**	
Summary Classification					**Definitive**			

SCN4B

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0.75	0.5	17592081;20226894;23861362;23631430
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	17592081
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	
			Genetic Evidence Total		0.5	0.75	0.5	
Experimental Evidence			Functional	Biochemical functions	1	0.5	0	15007009;17592081
				Protein interactions				12930796
				Expression				
			Functional Alteration	Patient cells	0.5	1.5	0.5	17592081;20226894
				Non-patient cells				
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		1.5	2	0.5	
Total Points					2	2.75	1	
Summary Classification					Disputed			

SCN5A

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	3.5	2	1	10377081;24871449;27566755;21076026;26467377;14654377;23963187;12673799;12650885
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	6	6	8	11535573;12123767;15485686;22721569;10200053;19808432;
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	1.5	1	3	7889574;28782696;10627139;10590249
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		1	3	1	19841300;10508990
			Genetic Evidence Total		12	12	12	
Experimental Evidence			Functional	Biochemical functions	1	0	0	1309946;
				Protein interactions				
				Expression				1309946;
			Functional Alteration	Patient cells	1.5	2	2	23998552;
				Non-patient cells				7651517;17698727;21799153;21076026;14654377;10807877;8917568;9495298;
			Models	Non-human model organism	4	4	4	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				11533705;14736542;17145985
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		6	6	6	
Total Points					18	18	18	
Summary Classification					Definitive			

SNTA1

Summary Classification					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0.5	0.75	19684871;18591664;27028743
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	1	19684871
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	0	0	0	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	19684871
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	
			Genetic Evidence Total		0.5	0.5	1.75	
Experimental Evidence			Functional	Biochemical functions	0.5	1.5	0.5	18591664
				Protein interactions				18591664;19684871
				Expression				
			Functional Alteration	Patient cells	2	2	1	
				Non-patient cells				19684871;18591664;27028743;23376825
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		2.5	3.5	1.5	
Total Points					3	4	3.25	
Summary Classification					Disputed			

TRDN

Evidence Type					Points Counted			PMID
					G1	G2	G3	
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact	0	0	0	25922419;26768964
				Proband with predicted or proven null variant	0	0	0	
				Variant is *de novo*	0	0	0	
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene impact in *trans*	11	11.5	3	
				Two variants in *trans* and at least one *de novo* or a predicted/proven null variant				
			Segregation	Candidate gene sequencing	0	0	0	26768964
				Exome/genome or all genes sequenced in linkage region				
			Case-Control		0	0	0	
			Genetic Evidence Total		11	11.5	3	
Experimental Evidence			Functional	Biochemical functions	0	0	0	
				Protein interactions				
				Expression				
			Functional Alteration	Patient cells	0	0	0	
				Non-patient cells				
			Models	Non-human model organism	0	0	0	
				Cell-culture model				
			Rescue	Rescue in human				
				Rescue in non-human model organism				
				Rescue in cell culture model				
				Rescue in patient cells				
			Experimental Evidence Total		0	0	0	
Total Points					11	11.5	3	
Summary Classification					Strong			

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