SUPPLEMENTAL MATERIAL

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For more information on the Gene Curation Expert Panels, see the ClinGen pages for Catecholaminergic Polymorphic Ventricular Tachycardia: https://clinicalgenome.org/affiliation/40074 and Short QT Syndrome: https://clinicalgenome.org/affiliation/40075/.

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Supplemental Methods

Selection of genes for curation

Selection of genes for evaluation by the Gene Curation Expert Panel (GCEP) was performed by a PubMed search. For catecholaminergic polymorphic ventricular tachycardia (CPVT), this included all publications with the term (“gene” OR “genetic”) AND (“CPVT” OR “catecholaminergic polymorphic ventricular tachycardia”) in all fields. For short QT syndrome (SQTS), this included all publications with the term “short QT syndrome” or “SQTS” in all fields or “short QT” in the title/abstract: "short qt syndrome"[Supplementary Concept] OR "short qt syndrome"[All Fields] OR "short qt syndrome"[All Fields] OR "short qt"[Title/Abstract]. Publications were triaged to identify genes reported to be involved in causality of CPVT or SQTS.

The composition of CPVT/SQTS panels used in clinical and commercial genetic testing were also assessed using the National Centre for Biotechnology Information’s (NCBI) Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) (accessed in December 2020). Panels including conditions other than CPVT/SQTS (i.e. broad arrhythmia or cardiac panels) and those limited to single genes were excluded.

Gene curation framework

Three teams of biocurators (comprising three members per team) curated each gene, as previously described for the BrS and LQTS curation panels. Each team worked blinded to the other curation teams in applying the ClinGen Gene Curation Framework, utilising version 7 of the standard operating procedure. Each curation team reviewed, assessed and scored the same manuscripts identified during the literature search described above. Curation team members were required to review the standard operating procedure and received training in the application of the analytic process. This framework provides a systematic, evidence-based approach for assessing reported gene-disease associations. The semi-quantitative scoring system categorises each gene-disease relationship into a clinical validity classification level based on the sum of its accompanying evidence - Definitive (12–18 points and replicated over time in the literature), Strong (12–18 points), Moderate (7–11 points), and Limited (1–6 points). Genetic and experimental evidence were evaluated separately, allowing for a maximum of 12 and 6 points respectively for each gene. Gene-disease associations were evaluated for specific modes of inheritance (autosomal dominant or autosomal recessive), with one gene (CASQ2 in CPVT) assessed separately for both modes.

Genetic evidence was primarily based on case-level data for CPVT or SQTS probands with variants that were rare enough in the population to be potentially causative (depending on the mode of inheritance). Rare missense variants required additional evidence such as functional assay validation or proven de novo inheritance to be scored. Additional genetic evidence was derived from the demonstration of segregation of variants with disease in family pedigrees and the enrichment of rare variants in case-control cohort studies - the scores applied for these classes of evidence were weighted according to the design and quality of the study. Information on the phenotype of reported individuals was critical in the evaluation of genetic evidence, with scores downgraded where insufficient evidence was provided for a definitive CPVT or SQTS diagnosis, or where atypical features suggestive of an alternative phenotype were observed. For example, the observation of ventricular arrhythmias at rest (instead of or in addition to with exercise testing), ECG features like prolonged QTc or QUC, or structural heart abnormalities were deemed to indicate a non-CPVT diagnosis. Experimental evidence scores were based on the interpretation and phenotypic relevance of in vitro assays assessing
functional alterations of the disease-implicated gene variants, and model organism or rescue studies, as proposed by MacArthur et al.

A gene curation expert panel, consisting of 9 additional individuals with collectively dozens of years of experience in clinical care or research in the field of inherited arrhythmias and clinical genetics, was tasked with reviewing the three independent classifications, performing a synthesised evaluation and assigning a final classification on a gene-by-gene basis. For each gene, the scores and classifications of the curation groups and the underlying published evidence were presented and discussed at monthly Zoom meetings in order to reach a final consensus classification. The panel had the option of modifying the findings of the curation teams (upgrade, no change, downgrade) based on the available evidence, including deciding whether genes with Strong evidence should be classified as Definitive (i.e. the association has been replicated over time) and whether Limited evidence genes should be downgraded to Disputed (the absence of any substantial evidence to support causality with an unambiguous CPVT/SQTS phenotype). For any classifications where unanimity was not reached during discussion, panel members subsequently voted for their preferred classification (≥7/9 votes in agreement was deemed as a consensus finding, otherwise no consensus was reached).

Population rare variant frequencies

Because CACNA1C, CACNB2 and CACNA2D1 were included in the majority of genetic testing laboratories’ panels but were classified as Disputed for SQTS by the Expert Panel, we aimed to assess the expected number of missense variants identified in these genes in the general population. To that end, the cumulative allele frequency of rare missense variants (minor allele frequency<0.001) was calculated based on the total allele frequency in gnomAD (accessed in December 2020). After subtracting the frequency of the second allele in homozygous cases, the result was multiplied by 2 to in order reach the carrier rate in the population.
Supplemental References

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### Supplemental Table 1

| Diagnostic Laboratory                              | GTR ID               | Country | No. of genes | Genes on CPVT panel                                                                 |
|---------------------------------------------------|----------------------|---------|--------------|-------------------------------------------------------------------------------------|
| Cincinnati Children’s Hospital Medical Center      | GTR000530644.2       | USA     | 11           | RYR2, CASQ2, TRDN, TECRL, CALM1, CALM2, CALM3, ANK2, KCNJ2, SCN5A, KCNQ1             |
| Health in Code                                    | GTR000530672.1       | Spain   | 9            | RYR2, CASQ2, TRDN, CALM1, CALM2, CALM3, ANK2, KCNJ2, SCN5A                         |
| Connective Tissue Gene Tests                      | GTR000592144.1       | USA     | 9            | RYR2, CASQ2, TRDN, TECRL, CALM1, CALM2, CALM3, ANK2, KCNJ2                         |
| Blueprint Genetics                                | GTR000552718.3       | Finland | 9            | RYR2, CASQ2, TRDN, TECRL, CALM1, CALM2, CALM3, ANK2, KCNJ2                         |
| Fulgent Genetics                                  | GTR000515861.5       | USA     | 9            | RYR2, CASQ2, TRDN, CALM1, CALM2, CALM3, ANK2, KCNJ2, KCNJ2, KCNQ1                  |
| Prevention Genetics                               | GTR000507622.20      | USA     | 8            | RYR2, CASQ2, TRDN, CALM1, ANK2, KCNJ2, SCN5A, KCNQ1                                |
| Phosphorus Diagnostics LLC                        | GTR000558052.2       | USA     | 8            | RYR2, CASQ2, TRDN, CALM1, CALM2, CALM3, ANK2, KCNJ2                                |
| Invitae                                           | GTR000551806.3       | USA     | 8            | RYR2, CASQ2, TRDN, CALM1, CALM2, CALM3, ANK2, KCNJ2                                |
| Knight Diagnostic Laboratories                    | GTR000552153.1       | USA     | 6            | RYR2, CASQ2, TRDN, CALM1, ANK2, KCNJ2                                              |
| DDC Clinic Molecular Diagnostics Laboratory       | GTR000523353.10      | USA     | 6            | RYR2, CASQ2, TRDN, CALM1, CALM3, KCNJ2                                             |
| Amby Genetics                                     | GTR000560522.7       | USA     | 4            | RYR2, CASQ2, TRDN, CALM1                                                            |
| LifeLabs Genetics                                 | GTR000573949.1       | Canada  | 3            | RYR2, CASQ2, KCNJ2                                                                |

Details of CPVT-specific clinical genetic testing panels listed in the NCBI Genetic Testing Registry ([https://www.ncbi.nlm.nih.gov/gtr/](https://www.ncbi.nlm.nih.gov/gtr/)) (accessed in December 2020).
Gene curation summaries

Detail curation summaries and classification matrices for each gene are shown below. Please note that classifications may change over time as curations are updated to account for new evidence. The most up-to-date information can be found by searching for the genes on http://clinicalgenome.org.

CPVT

**RYR2 - autosomal dominant CPVT - DEFINITIVE**

RYR2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). RYR2 was the first gene to be associated with CPVT in 2001. It is the predominant gene associated with the condition, with approximately half of all CPVT probands carrying a pathogenic RYR2 variant. Most disease-causing variants in RYR2 are missense variants which tend to cluster in several pathogenic hotspots. Human genetic evidence supporting this gene-disease relationship includes case-level data, segregation data, and case-control data. A significant excess of rare (MAF<0.0001) RYR2 variants was observed in CPVT cohorts compared to ExAC population controls (Kapplinger et al, 2018, PMID:29453246), with rare variant yields higher in definitive CPVT cases (59%) than possible CPVT cases (31%) and all CPVT genetic testing referrals (18%). There is a plethora of case-level data to support the association of RYR2 with CPVT, including numerous examples of de novo inheritance (Priori et al, 2001, PMID:11208676; Priori et al, 2002, PMID:12093772). Segregation of RYR2 variants with disease in family pedigrees has also been noted, in particular a 1404 member extended pedigree from Gran Canaria island in Spain, covering 10 generations with 178 carriers of the RYR2:p.Gly357Ser variant (Wangüemert et al, 2015, PMID:25814417). In addition, this gene-disease assertion is supported by experimental evidence, including functional alteration, non-human model organism, and rescue in non-human model organism. Variants detected in patients have been introduced to non-patient cells in numerous studies (including HEK293, HL-1 cardiomyocytes and mouse ventricular cells) with clear effects on Ca\(^{2+}\) sensitivity and release (Wangüemert et al, 2015, PMID:25814417; George et al, 2003, PMID:12919952; Loaiza et al, 2013, PMID:23152493; Zhao et al, 2014, PMID:25775566). Knock-in mice have been generated for several RYR2 variants detected in CPVT patients which demonstrate arrhythmia phenotypes typical of CPVT (Cerrone et al, 2005, PMID:15890976; Kannankeril et al, 2006, PMID:16873551; Loaiza et al, 2013, PMID:23152493). Rescue of the CPVT phenotype in mouse models has also been noted, with correction of the p.Arg176Gln variant by AAV-CRISPR leading to a significant reduction in arrhythmias compared to uncorrected knock in mice (Pan et al, 2018, PMID:30355031). Additional evidence is available in the literature, but the maximum score for genetic evidence and experimental evidence has been reached. In summary, RYR2 variants are definitively associated with autosomal dominant CPVT. This has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time.

Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams' efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).
**CASQ2 - autosomal recessive CPVT - DEFINITIVE**

CASQ2 was evaluated for autosomal recessive catecholaminergic polymorphic ventricular tachycardia (CPVT). Biallelic loss-of-function variants in CASQ2 (homozygous and compound heterozygous) have been reported in numerous CPVT probands, including frameshift, nonsense and splice donor/acceptor variants, as well as other splice region variants with verified effects on splicing and missense variants with verified loss-of-function effects (Postma et al, 2002, PMID:12386154; di Barletta et al, 2006, PMID:16908766; Roux-Buisson et al, 2011, PMID:21618644). Additional genetic evidence comes from the segregation of the homozygous p.Asp307His variant with CPVT in a large family from Israel (LOD score = 8.2), which is highly likely to be the causative variant even though not every gene in the linked region was sequenced (Lahat et al, 2004, PMID:15176429). The association of CASQ2 with autosomal recessive CPVT is also supported by a plethora of experimental evidence, including functional alteration, non-human model organism, and rescue in non-human model organism. Most of this evidence has been generated from CASQ2 knockout mice and knock-in mice for variants detected in CPVT patients (di Barletta et al, 2006, PMID:16908766; Dirksen et al, 2007, PMID:17449018; Song et al, 2007, PMID:17607358; Rizzi et al, 2008, PMID:18583715). AAV-mediated injection of CASQ2 in knockout and p.Asp307His mice has been shown to at least partially rescue the CPVT phenotype (Kutzwald Josefson et al, 2017, PMID:28336343). Additional evidence is available in the literature, but the maximum score for genetic evidence and experimental evidence has been reached. In summary, CASQ2 variants are definitively associated with autosomal recessive CPVT. This has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**CASQ2 - autosomal dominant CPVT - MODERATE**

CASQ2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). Biallelic loss-of-function variants in CASQ2 are definitively associated with autosomal recessive CPVT but some reports have also associated monoallelic or heterozygous CASQ2 variants with this condition. The main evidence for autosomal dominant CASQ2 association comes from a multi-centre study describing CPVT patients with CASQ2 variants (Ng et al, 2020, PMID:32693635). This study includes 12 probands with heterozygous variants in CASQ2, as well as an assessment of heterozygous relatives of probands with homozygous/compound heterozygous CASQ2 variants (8/37 of these heterozygous relatives had a positive CPVT phenotype). While this study provides a substantive body of evidence to support autosomal dominant CASQ2 association with CPVT, the expert panel believed the findings should be cautiously interpreted and the default scoring for these variants was downgraded for a number of reasons. The multi-centre nature of the study precluded standardised phenotyping of the probands and relatives and therefore we could not assume that every phenotype-positive individual had a definitive diagnosis of CPVT. Additionally, several of the variants described have a gnomAD population minor allele frequency that is incompatible with being a penetrant autosomal dominant variant for a disease with the prevalence of CPVT (MAF>1x10⁻⁵). The CASQ2 variants described in a heterozygous state in this study include truncating variants (nonsense, frameshift, splice acceptor/donor), a splice region variant (c.738-3C>A) where the effect on splicing...
was not proven and missense variants (functional in vitro turbidity assays revealed that 6/7 missense variants exhibited filamentation defects but had dimerisation profiles similar to wildtype). In a separate study, the heterozygous p.Lys180Arg variant segregated with disease in a family (the published LOD score was 3.0 although there were only five meioses between genotype and phenotype positive individuals) (Gray et al, 2016, PMID:27157848). Additional functional evidence was observed in heterozygous null mice (catecholaminergic challenge and programmed stimulation induced significantly more ventricular ectopy in CASQ2+/- mice than in CASQ2+/+ mice) (Chopra et al, 2007, PMID:17656677). In summary, there is moderate evidence to support this gene-disease relationship. More evidence is needed to definitively establish the relationship of CASQ2 with autosomal dominant CPVT. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

### TRDN - autosomal recessive CPVT - DEFINITIVE

**TRDN** was evaluated for autosomal recessive catecholaminergic polymorphic ventricular tachycardia (CPVT). **TRDN** encodes Triadin, a protein important for calcium-release regulation from the sarcoplasmic reticulum. Biallelic loss of function variants in **TRDN** have been described in CPVT patients in a number of studies (Roux-Buisson et al, 2012, PMID:22422768; Rooryck et al, 2015, PMID:26200674; Walsh et al, 2016, PMID:26768964), including nonsense (p.Gln205Ter, p.Glu168Ter), frameshift (c.53_56del), intronic (c.22+29A>G, with effect on splicing functionally proven) and missense (p.Thr59Arg, the mutant protein was confirmed to be degraded in COS-7 cells and after transfection into knockout mice) variants. An additional report described a homozygous deletion of TRDN exon 2 in an infant who suffered cardiac arrest and subsequent arrhythmia episodes, but this case was scored with only one point due to uncertainty about the phenotype and the additional presence of a **Ryr2** variant of uncertain significance in this patient (O’Callaghan et al, 2018, PMID:30479949). Biallelic truncating variants in **TRDN** have also been reported in patients with Long QT syndrome, and the LQTS Gene Curation Expert Panel have previously classified **TRDN** as having strong evidence for association with LQTS, though with an atypical LQTS phenotype. The variable and atypical phenotypes associated with so-called “Triadin knockout syndrome” should therefore be taken into account when interpreting patients with **TRDN** biallelic loss of function variants. The association of **TRDN** with CPVT is also supported by substantial experimental evidence, including expression in heart tissue (Cacheux et al, 2019, PMID:31607542), protein interaction with **Ryr2** and **Casq2** (Guo et al, 1996, PMID:8550602) and relevant biochemical function in regulating the contractile properties of the heart (Kirchhefer et al, 2001, PMID:11069905). Additionally, knockout mice are directly relevant to the genotypes observed in CPVT patients with **TRDN** variants, with several studies demonstrating a relevant CPVT phenotype in knockout mice for non-human model organism (e.g. Cacheux et al, 2019, PMID:31607542; Chopra et al, 2009, PMID:19383796) and functional alteration in non-patient cells derived from these mouse knockouts (Chopra et al, 2009, PMID:19383796). Partial rescue of the CPVT phenotype has also been observed in knockout mice treated with AAV2/9 virus encoding rat **TRDN** isoform Trisk32 (Cacheux et al, 2019, PMID:31607542). In summary, **TRDN** variants are definitively associated with autosomal recessive CPVT. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s
analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**TECRL - autosomal recessive CPVT - DEFINITIVE**

*TECRL* was evaluated for autosomal recessive catecholaminergic polymorphic ventricular tachycardia (CPVT). Biallelic loss of function variants in *TECRL* were first reported in 2016 (Devalle et al, 2016, PMID:27861123), with a homozygous missense variant (p.Arg196Gln) detected in two unrelated patients of French Canadian origin and a homozygous splice donor variant (c.331+1G>A) detected in a large consanguineous Sudanese pedigree where 7/13 children (all homozygous) has exercise-induces arrhythmias or sudden cardiac death (LOD=4.36). Another report described compound heterozygous variants in a 13 year old child with CPVT (p.Arg196Gln and c.918+3T>G), although the effect of the splice region variant was not proven (Xie et al, 2019, PMID:30790670). A multi-centre review published in 2020 provided an update on these cases and described two additional CPVT cases (homozygous p.Tyr197Ter nonsense variant and homozygous exon 2 deletion) and a family with three children with sudden cardiac death, where one was homozygous for the c.331+1G>A splice donor variant (Webster et al, 2020, PMID:33367594). Finally, another study described 4 CPVT cases with *TECRL* variants detected by diagnostic sequencing, including homozygous missense (p.Pro290His) and nonsense variants (p.Gln139Ter), compound heterozygous variants (p.Ser309Ter/p.Val298Ala) and a large homozygous duplication that covered the *TECRL* gene (the effect of this variant on *TECRL* gene expression is unknown and the scoring was downgraded accordingly) (Mosku-Gregor et al, 2020, PMID:32173957). These cases presented with phenotypic features typical of CPVT, including exercise and emotion induced syncope and cardiac arrest and ventricular arrhythmias during exercise testing. A mild prolonged QT interval was observed in several cases, especially after stimulation by epinephrine or exercise, although overall the phenotypes are much more typical of CPVT than LQTS. The association of *TECRL* with CPVT is also supported by experimental evidence with clear functional effects observed in iPSC derived cardiomyocytes generated from a patient with the homozygous c.331+1G>A variant. In summary, *TECRL* variants are definitively associated with autosomal recessive CPVT. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**CALM1 - autosomal dominant CPVT – MODERATE**

*CALM1* was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). The *CALM1* gene is located on chromosome 14 and encodes for calmodulin 1, a 149 amino acid protein that is identical in sequence to two other calmodulin genes (*CALM2* on chromosome 2 and *CALM3* on chromosome 19). All three CALM genes have been classified as Definitive for Long QT syndrome by the LQTS Gene Curation Expert Panel, noting that these genes tend to be associated with atypical features of LQTS (presentation in infancy or early childhood and with heart block and severe QT prolongation). The CALM genes have also been associated with CPVT phenotypes although less evidence has thus far been published for CPVT compared to LQTS. Evidence
for the association of CALM genes to CPVT comes from the International Calmodulin Registry study (Crotti et al, 2019, PMID:31170290) and other genetic and experimental studies. Genetic evidence for CALM1 comes from a study that described familial CPVT cases. The p.Asn54Ile variant segregated with disease in a large family pedigree (Nyegaard et al, 2012, PMID:23040497), with a second family with this variant described in the Registry (Crotti et al, 2019, PMID:31170290). The p.Asn98Ser variant occurred de novo in a proband with CPVT (Nyegaard et al, 2012, PMID:23040497) - the same p.Asn98Ser variant was detected de novo in CALM2 in a CPVT patient (Jiménez-Jáimez et al, 2016, PMID:27100291). These variants have also been studied experimentally and shown to cause CPVT-like phenotypes in zebrafish (Søndergaard et al, 2015, PMID:25557436) and mouse models (Tsai et al, 2020, PMID:32929985) and in non-patient cellular assays (Hwang et al, 2014, PMID:24563457; Søndergaard et al, 2015, PMID:26309258). A family with the CALM1 p.Ile53Val variant has also been investigated in Toronto (as yet unpublished and therefore not scored during this curation). The affected father and two children carried the variant - all had structurally normal hearts and PVCs during exercise and the children suffered cardiac arrests at the ages of 12 while swimming and 18 while dancing (no other relevant variants were found in a broad 147 gene panel). Based on this genetic and experimental evidence, CALM1 scored with moderate evidence of association with CPVT. However, the expert panel unanimously agreed that, despite this classification and the modest amount of published evidence linking CALM1 variants with a CPVT phenotype, all three CALM genes have unequivocal evidence for causation of isolated CPVT, in addition to LQTS and hybrid phenotypes. The three CALM genes encode for identical proteins which are all expressed in heart tissue, and multiple identical variants in two or more of the CALM genes have been shown to cause the same phenotypes, e.g. the de novo variant p.Asp130Gly has been shown in all 3 CALM genes to provoke LQTS in children, which demonstrates the functional similarity of these genes/proteins. Collectively, the three CALM genes would have strong/definitive evidence for association with CPVT. CALM1 has previously been classified as a definitive gene for atypical LQTS, unambiguously demonstrating the pathogenicity of this gene for inherited arrhythmia syndromes. Finally, as described above, multiple patients with CALM1 variants have been shown to present with a classical CPVT phenotype. Therefore this gene should be included in CPVT genetic testing panels. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP's analysis according to evidence teams' efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**CALM2 - autosomal dominant CPVT – MODERATE**

CALM2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). The CALM1 gene is located on chromosome 2 and encodes for calmodulin 2, a 149 amino acid protein that is identical in sequence to two other calmodulin genes (CALM1 on chromosome 14 and CALM3 on chromosome 19). All three CALM genes have been classified as Definitive for Long QT syndrome by the LQTS Gene Curation Expert Panel, noting that these genes tend to be associated with atypical features of LQTS (presentation in infancy or early childhood and with heart block and severe QT prolongation). The CALM genes have also been associated with CPVT phenotypes although less evidence has thus far been published for CPVT compared to LQTS. Evidence for the association of CALM genes to CPVT comes from the International Calmodulin Registry study (Crotti et al, 2019, PMID:31170290) and other genetic and experimental studies. Genetic evidence for the association of CALM2 with CPVT comes from two apparently de novo cases with the p.Glu46Lys
variant in the Registry (Crotti et al, 2019, PMID:31170290). Another de novo case was described with the p.Asn98Ser variant (Jiménez-Jáimez et al, 2016, PMID:27100291) - the same p.Asn98Ser variant was detected de novo in CALM1 in a CPVT patient (Nygård et al, 2012, PMID:23040497). A de novo case with the p.Asp132Glu variant was detected in a patient with mixed features of CPVT and LQTS and was therefore scored less than the default (Makita et al, 2014, PMID:24917665) - the same p.Asp132Glu variant was also detected de novo in CALM3 in a CPVT patient (Crotti et al, 2019, PMID:31170290). As the p.Asn98Ser variant was also observed in CALM1 in a CPVT case, the experimental evidence demonstrating a CPVT phenotype for this variant from zebrafish models (Søndergaard et al, 2015, PMID:25557436) and non-patient cellular assays (Søndergaard et al, 2015, PMID:26309258) is also relevant for supporting the association of CALM2 with CPVT. Based on this genetic and experimental evidence, CALM2 scored with moderate evidence of association with CPVT. However, the expert panel unanimously agreed that, the despite this classification and the modest amount of published evidence linking CALM2 variants with a CPVT phenotype, all three CALM genes have unequivocal evidence for causation of isolated CPVT, in addition to LQTS and hybrid phenotypes. The three CALM genes encode for identical proteins which are all expressed in heart tissue, and multiple identical variants in two or more of the CALM genes have been shown to cause the same phenotypes, e.g. the de novo variant p.Asp130Gly has been shown in all 3 CALM genes to provoke LQTS in children, which demonstrates the functional similarity of these genes/proteins. Collectively, the three CALM genes would have strong/definitive evidence for association with CPVT. CALM2 has previously been classified as a definitive gene for atypical LQTS, unambiguously demonstrating the pathogenicity of this gene for inherited arrhythmia syndromes. Finally, as described above, multiple patients with CALM2 variants have been shown to present with a classical CPVT phenotype. Therefore this gene should be included in CPVT genetic testing panels. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP's analysis according to evidence teams' efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**CALM3 - autosomal dominant CPVT - LIMITED upgraded to MODERATE**

CALM3 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). The CALM3 gene is located on chromosome 19 and encodes for calmodulin 3, a 149 amino acid protein that is identical in sequence to two other calmodulin genes (CALM1 on chromosome 14 and CALM2 on chromosome 2). All three CALM genes have been classified as Definitive for Long QT syndrome by the LQTS Gene Curation Expert Panel, noting that these genes tend to be associated with atypical features of LQTS (presentation in infancy or early childhood and with heart block and severe QT prolongation). The CALM genes have also been associated with CPVT phenotypes although less evidence has thus far been published for CPVT compared to LQTS. Evidence for the association of CALM genes to CPVT comes from the International Calmodulin Registry study (Crotti et al, 2019, PMID:31170290) and other genetic and experimental studies. Genetic evidence for the association of CALM3 with CPVT comes from an apparently de novo case in the Registry with the p.Asp132Glu variant - the same variant in the CALM2 gene was also detected de novo in a patient with mixed features of CPVT and LQTS (Crotti et al, 2019, PMID:31170290). The p.Ala103Val variant was detected in a CPVT patient with its pathogenicity supported by functional evidence (Gomez-Hurtado et al, 2016, PMID:27516456). Based on this genetic and experimental evidence, CALM3 scored with limited evidence of association with CPVT but was upgraded to a Moderate classification by the expert
panel. However, the expert panel unanimously agreed that, despite this classification and the modest amount of published evidence linking CALM3 variants with a CPVT phenotype, all three CALM genes have unequivocal evidence for causation of isolated CPVT, in addition to LQTS and hybrid phenotypes. The three CALM genes encode for identical proteins which are all expressed in heart tissue, and multiple identical variants in two or more of the CALM genes have been shown to cause the same phenotypes, e.g. the de novo variant p.Asp130Gly has been shown in all 3 CALM genes to provoke LQTS in children, which demonstrates the functional similarity of these genes/proteins. Collectively, the three CALM genes would have strong/definitive evidence for association with CPVT. CALM3 has previously been classified as a definitive gene for atypical LQTS, unambiguously demonstrating the pathogenicity of this gene for inherited arrhythmia syndromes. Finally, as described above, multiple patients with CALM3 variants have been shown to present with a classical CPVT phenotype. Therefore this gene should be included in CPVT genetic testing panels. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

ANK2 - autosomal dominant CPVT – LIMITED downgraded to DISPUTED

ANK2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). ANK2, which encodes the ankyrin B protein, has been implicated in a number of arrhythmia phenotypes but has been classified as Disputed for both Brugada syndrome and Long QT syndrome by the respective Gene Curation Expert Panels. Variants in ANK2 have been detected in 3 patients/families with CPVT-like symptoms (Mohler et al, 2004, PMID:15178757; Mohler et al, 2007, PMID:17242276). However the population frequencies of these variants are too high to be an autosomal dominant cause of CPVT – p.Leu1622Ile (gnomAD max MAF = 0.034), p.Arg1788Trp (gnomAD max MAF = 0.002) and p.Val1516Asp (gnomAD max MAF = 0.004). AnkB heterozygous null mice have been shown to display exercise and epinephrine-induced polymorphic ventricular arrhythmias before death (Mohler et al, 2003, PMID:12571597). While this phenotype can be rescued with transfection of wild type ankyrin-B, mutant ankyrin-B with the human arrhythmia-associated variants described above (and variants associated with other arrhythmias) were unable to rescue this phenotype (Mohler et al, 2004, PMID:15178757; Mohler et al, 2007, PMID:17242276). Nevertheless, despite this experimental evidence, there is no convincing human genetic evidence to associate ANK2 as an autosomal dominant cause of CPVT and therefore this gene has been classified as Disputed. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

KCNJ2 - autosomal dominant CPVT - LIMITED downgraded to DISPUTED

KCNJ2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). Variants in KCNJ2 are associated with Andersen-Tawil syndrome (ATS), a condition associated with dysmorphic features, periodic paralysis and prominent U waves on ECG. It has been classified as
a definitive gene for ATS by the LQTS Gene Curation Expert Panel. As the ECG abnormalities in patients with KCNJ2 variants can be interpreted as prolonged QT intervals, it was also curated for isolated LQTS and found to have limited evidence. KCNJ2 variants have also been implicated in CPVT (referred to as CPVT3 in early reports). However, as in the case with isolated LQTS, it is unclear if these reports actually represent atypical presentations of ATS without extra-cardiac features. A number of reports describe patients with KCNJ2 variants presenting with CPVT-like arrhythmogenic symptoms and without any extra-cardiac features (Tester et al, 2006, PMID:16818210; Kimura et al, 2012, PMID:22589293; Kalscheur et al, 2014, PMID:24561538), supported by functional studies demonstrating effects of the variants on IK1 current in cellular assays (Vega et al, 2009, PMID:19843922; Kimura et al, 2012, PMID:22589293; Kalscheur et al, 2014, PMID:24561538). As a consequence, KCNJ2 scored with limited evidence for involvement in CPVT based on these reports. However, none of these patients presented unequivocally with a classical CPVT phenotype and demonstrated features such as subtle ECG U wave abnormalities and bidirectional VT at rest which may be suggestive of atypical and cardiac-specific ATS rather than a true CPVT diagnosis. The expert panel therefore agreed to classify KCNJ2 as Disputed for CPVT. As patients with pathogenic KCNJ2 variants may present with a phenotype that can resemble typical features of CPVT, it may be beneficial to include this gene in extended arrhythmia genetic testing panels for patients with a CPVT-like phenotype if no causative variants are found when sequencing validated CPVT genes. However, any detected variants should be interpreted in the context of the known genotype-phenotype relationships for KCNJ2, in particular by investigating for subtle phenotypic features associated with ATS. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP’s analysis according to evidence teams’ efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

PKP2 - autosomal dominant CPVT - LIMITED downgraded to DISPUTED

PKP2 was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). Variants in PKP2 (in particular truncating loss of function variants) are associated with arrhythmogenic cardiomyopathy (ACM/ARVC) and it has been classified as a Definitive gene by the ARVC Gene Curation Expert Panel. The evidence for a role of PKP2 variants in CPVT comes from a single study in which PKP2 was sequenced in a cohort of 18 patients that had been diagnosed with CPVT and were negative for variants in established CPVT genes (in addition to 19 sudden cardiac death cases with structurally normal hearts) (Tester et al, 2019, PMID:30678776). Although truncating variants in PKP2 were detected in 6 cases, the expert panel (and indeed the authors of the paper) believed that these patients were likely to have concealed ARVC and had been diagnosed with CPVT due to exercise-associated arrhythmias prior to structural heart changes. Indeed one of these cases was subsequently diagnosed with ARVC and right ventricular structural changes were subsequently observed in two others. A cardiomyocyte-specific PKP2 mouse knockout model displayed similar phenotypes, with isoproterenol triggered polymorphic ventricular arrhythmias mimicking CPVT observed prior to structural changes (Cerrone et al, 2017, PMID:28740174). In conclusion, we believe that PKP2 variants are not associated with CPVT and therefore the expert panel decided to classify PKP2 as disputed for CPVT. However, as a CPVT-like phenotype can be observed in ARVC patients with truncating PKP2 variants (during the concealed cardiomyopathy phase of the disease), it may be beneficial to include this gene in extended arrhythmia genetic testing panels for patients with a CPVT-like phenotype if no causative variants are found when sequencing validated CPVT genes. If truncating
variants in PKP2 are detected in such cases, it would suggest a diagnosis of ARVC. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP's analysis according to evidence teams' efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).

**SCN5A - autosomal dominant CPVT - LIMITED downgraded to DISPUTED**

SCN5A was evaluated for autosomal dominant catecholaminergic polymorphic ventricular tachycardia (CPVT). Variants in SCN5A, encoding the Nav1.5 sodium channel, are associated with a number of arrhythmia phenotypes including Brugada syndrome (loss of function variants) and Long QT syndrome (gain of function variants) for both of which SCN5A has previously been classified as a Definitive gene. The evidence for a role of SCN5A variants in CPVT comes from a single study in a large Finnish pedigree where the p.Ile141Val was found to segregate with a phenotype of exercise-induced polymorphic ventricular arrhythmias (LOD score = 3.56) with the effect of the variant confirmed by functional studies in HEK293 cells (Swan et al, 2014, PMID:25210054). Based on this study, SCN5A scored with limited evidence for association with CPVT. However, the clinical presentations in this family are atypical of a classical CPVT phenotype. While affected individuals presented with premature ventricular complexes and non-sustained polymorphic ventricular tachycardia after exercise in a similar manner to other CPVT patients (but also abundantly at rest in some), some also displayed atrial flutter and ectopic atrial rhythm that are not typical of CPVT. The expert panel therefore agreed to classify SCN5A as Disputed for CPVT. As patients with pathogenic SCN5A variants may present with a phenotype that can resemble some typical features of CPVT, it may be beneficial to include this gene in extended arrhythmia genetic testing panels for patients with a CPVT-like phenotype if no causative variants are found when sequencing validated CPVT genes. Any variants detected should be interpreted with caution however and in the context of the phenotypes of the patient being tested and those associated with SCN5A, in particular the phenotypes described by Swan et al. Note: All CPVT genes were curated by 3 separate blinded teams. The evidence and scores reached by these 3 teams was reviewed by the CPVT Gene Curation Expert Panel (GCEP). The classification and summary presented here is the conclusion of this GCEP's analysis according to evidence teams' efforts. This classification was approved by the ClinGen Catecholaminergic Polymorphic Ventricular Tachycardia Gene Curation Expert Panel on 20th January, 2021 (SOP Version 7).
SQTS

**CACNA1C**

*CACNA1C* encodes for the alpha-1c subunit of the voltage-dependent L-type calcium channel which is important for the development of the action potential in human cardiomyocytes. Genetic variants in this gene have been identified in 5 probands with suggested SQTS phenotype. Three of these probands, however, had Brugada syndrome with a relatively short QT interval (PMIDs 17224476, 20817017) and one had hypertrophic cardiomyopathy without a convincing SQTS phenotype (PMID 28427417). Accordingly, the Expert Panel decided these patients did not have an isolated SQTS phenotype and the genetic evidence derived from these cases should not be scored toward relationship of *CACNA1C* with SQTS. The final proband was identified as having a de novo variant (PMID 24291113), however, the gnomAD MAF was regarded as too high for a rare condition such as SQTS and there was no other evidence supporting this variant’s impact. Therefore, the Expert Panel classified the relationship of *CACNA1C* with SQTS as ‘Disputed’.

**CACNA2D1**

*CACNA2D1* encodes the alpha-2/delta-1 subunit of the calcium voltage-gated channel. A genetic variant in this gene was identified using a candidate-gene approach in a single case with cardiac arrest and a short QT interval (PMID 21383000). Other family members carrying this variant did not have a SQTS phenotype. Furthermore, this variant is now known to be present in >1% of Ashkenazi Jewish alleles, ruling it out as a monogenic cause of SQTS. In the absence of other genetic data, *CACNA2D1* was classified as ‘Disputed’.

**CACNB2**

*CACNB2* encodes a beta subunit of the calcium voltage-gated channel. The relationship of this gene with SQTS is based on a single report which used a candidate-gene approach in patients with Brugada syndrome and a short QT interval (PMID 17224476). Because the proband identified as carrying the rare genetic variant (ClinVar Variation ID# 9547) had a positive ajmaline test, his phenotype was regarded by the Expert Panel to be concordant with Brugada syndrome and not SQTS. Therefore, the Expert Panel classified the relationship of this gene with SQTS as ‘Disputed’.

**KCNH2**

*KCNH2* encodes the alpha subunit of the rapidly activating delayed rectifier cardiac potassium channel (Ikr). Brugada et al. (PMID 14676148) were the first to identify 2 rare *KCNH2* missense variants leading to the same amino-acid change (p.Asn588Lys, ClinVar Variation ID# 14436 & 14437) in 2 small families with Short QT Syndrome (SQTS) using a candidate-gene approach. This genetic evidence was subsequently supported by multiple other publications identifying rare missense *KCNH2* variants in SQTS patients. Experimental evidence derived from non-patient cells, human-induced pluripotent stem cell-derived cells and a rabbit animal model (PMID 30496390) all support this gene’s relationship with SQTS. These experimental studies demonstrate that genetic variants identified in SQTS patients lead to potassium current perturbations concordant with SQTS phenotype and shortening of the QT
interval. It is noteworthy that of the 18 probands with SQTS in whom KCNH2 variants were identified, 13 had one of 2 variants; 7 with p.Thr618Ile variant (ClinVar Variation ID# 67297) and 6 with p.Asn588Lys.

**KCNJ2**

*KCNJ2* encodes the alpha subunit of Ik1, the inward rectifier cardiac potassium channel. Variants in *KCNJ2* have been identified in 6 patients from 5 families with unique variants, including at least 2 probands with a de-novo variant. Experimental evidence demonstrated these variants lead to gain-of-function of the late repolarizing, KCNJ2-encoded Ik1 current in the heart, and abbreviation of the action potential duration (PMID 15761194). These data were considered sufficient for classifying the gene-disease relationship of *KCNJ2* as ‘Moderate’ but, in the absence of segregation or case-control data, the genetic evidence was not abundant enough for a stronger classification.

**KCNQ1**

*KCNQ1* encodes the alpha subunit of the slowly activating delayed rectifier cardiac potassium channel (Iks). Bellocq et al. were the first to identify a rare KCNQ1 missense variant (p.Val180Leu ClinVar Variation ID#3148) in a patient with SQTS (PMID 15159330). Subsequently, 8 other probands with SQTS were found to carry another variant (p.Val141Met, ClinVar Variation ID#67072). Interestingly, all of these 8 cases presented with severe bradycardia in-utero or at birth and in 6 atrial fibrillation was also documented (PMIDs 24818999, 26279191, 16109388, 24380499, 25974115, 28491547). Importantly, in none of the p.Val141Met cases was cardiac arrest or SCD described. In fact, cardiac arrest was described only in the first case described by Bellocq et al. In 3 cases the p.Val141Met variant was demonstrated to be de-novo although paternity was not proven in all. In another 4 cases no other family members were diagnosed and in one family the father of the proband was identified with the p.Val141Met variant and demonstrated a mild phenotype. The fact that almost all genetic evidence was derived from a single variant led the Expert Panel to limit the classification of *KCNQ1* as a SQTS-causing gene to “Strong”, despite evidence being reproducible over time.

**SCN5A**

*SCN5A* encodes the alpha subunit of the cardiac voltage-gated sodium channel. Genetic evidence supporting its relationship with SQTS is derived from a single case in which a rare SCN5A variant was discovered (PMID 22490985). The patient, however, had a type 1 Brugada pattern with a relatively short QT interval and the Expert Panel regarded this phenotype as being concordant with Brugada syndrome and not SQTS. In the absence of additional genetic evidence this gene was classified as ‘Disputed’.

**SLC4A3**

*SLC4A3* encodes a plasma membrane anion exchange protein. Genetic evidence supporting SLC4A3 as a SQTS-causing gene is derived from a single publication in which exome sequencing was performed in 2 families, including one large pedigree (PMID 29167417). The same rare genetic variant (p.Arg370His, c.1109G>A) was identified in both families, suggesting they are possibly distantly
related. Experimental evidence from in vitro and zebrafish models suggests reduced membrane localization of the mutated protein leads to intracellular alkalinization and shortening of the cardiomyocyte action potential duration. The genetic evidence, including the unbiased gene discovery approach of whole exome sequencing and segregation of the identified genetic variant with a large number of affected individuals within the presented pedigree, was considered strong. However, lack of other publications supporting this gene-disease relationship led to a score in the moderate range using the gene curation template. The Expert Panel discussed upgrading the final classification but was divided on this issue with 4 panellists voting for ‘strong’ and 5 for ‘moderate’.

**SLC22A5**

*SLC22A5* encodes a sodium ion-dependent, high affinity carnitine transporter protein. Genetic variants in this gene cause primary systemic carnitine deficiency, an autosomal recessive disorder. Homozygote or compound heterozygote variants in *SLC22A5* have been identified in unexplained SCD or resuscitated cardiac arrest cases with abbreviation of the QT interval and without overt extra-cardiac manifestations (PMIDs 26190315, 31472821). Because the QT interval abbreviation was reversible by oral carnitine supplementation, the Expert Panel viewed this gene as a SQTS-mimic but as a cause of true SQTS classified it as ‘Disputed’.
### Gene Classification Matrices - CPVT

**RYR2**

#### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case range | G1 | G2 | G3 | Max Score |
|---------------|------------------|-----------------------------|----|----|----|-----------|
| Variant Evidence | Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo | 2 | 0-3 | 12 | 14 | 12 | 12 | Priore et al 2001 (PMID:11209678); Priori et al 2002 (PMID:12093772) |
|                | Proband with predicted or proven null variant | 1.5 | 0-2 | 0 | 0 | 2 | 10 | |
|                | Proband with other variant type with some evidence of gene impact | 0.5 | 0-1.5 | 0 | 0.5 | 6.5 | 7 | |
|                | Autosomal recessive disease, OR X linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 | |
|                | Two non-LOF variants in trans | 1 | 0-1.5 | 0 | 0 | 0 | |

| Case-Level Data | Evidence of Segregation in one or more families | 
|-----------------|-----------------------------------------------|
| Segregation Evidence | Candidate Gene Sequencing | 
| Total LOD Score | 0-3 | 3 | 1.5 | 1.5 | 3 | |
| Sequencing Method | Wangensteen et al 2015 (PMID:25814417) | 

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | G2 | G3 | G1 | Max Score |
|-------------------------|-------------------------------|------------------------|----|----|----|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-6 | 0 | 0 | 0 | 12 | Kaplinger et al 2018 (PMID:29453266) |
|                        | Power                         |                        |    |    |    |          |
| Aggregate Variant Analysis | Bias and Confounding Factors |                       |    |    |    |          |
|                        | Statistical Significance      |                        |    |    |    |          |

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item range | G1 | G2 | G3 | Max Score |
|-------------------|---------------|-----------------------------|----|----|----|-----------|
| Function          | Biochemical Function | 0.5 | 0-2 | 0.5 | 0 | 0 | 2 | Otsu et al 1990 (PMID:2380170) |
|                   | Protein Interaction | 0.5 | 0-2 | 0 | 0 | 0 | 2 | |
|                   | Expression      | 0.5 | 0-2 | 0 | 0 | 0 | 2 | |
| Functional Alteration | Patient Cells | 1 | 0-2 | 0 | 0 | 1 | 2 | Wangensteen et al 2015 (PMID:25814417); George et al 2003 (PMID:12913992); Loiaza et al 2013 (PMID:23852693); Zhao et al 2014 (PMID:15756666) |
|                   | Non-Patient Cells | 0.5 | 0-1 | 1.5 | 2 | 2 | 2 | |
| Models            | Non-human model organism | 2 | 0-4 | 3 | 6 | 4 | 4 | Cerrone et al 2005 (PMID:15890078); Kannankeril et al 2006 (PMID:16875551); Loiaza et al 2013 (PMID:23852493) |
|                   | Cell culture model | 1 | 0-2 | 0 | 0 | 0 | |
| Rescue            | Rescue in human | 2 | 0-4 | 0 | 0 | 0 | 4 | Pan et al 2018 (PMID:30850031) |
|                   | Rescue in non-human model organism | 2 | 0-4 | 0 | 0 | 0 | |
|                   | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | |
|                   | Rescue in Patient Cells | 1 | 0-2 | 0 | 0 | 0 | |

### Total Experimental Evidence Points (Maximum 6)

| | Total: | 18 | 18 | 18 |
# CASQ2 (autosomal recessive)

## Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case | References |
|---------------|------------------|-----------------------|------------|
| Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo Proband with predicted or proven null variant | 3 | 0 0 0 12 | Postma et al 2002 (PMID:12388514); Raffaele di Barletta et al 2006 (PMID:16508766); Roux-Buisson et al 2011 (PMID:21618644) |
| Autosomal recessive disease, OR X linked disease, affected females | Two variants in trans, at least one is LOF or de novo Two non-LOF variants in trans | 1 | 0 1 1 3 | Lahat et al 2004 (PMID:15176439) |

### Segregation Evidence

| Sequencing Method | Candidate Gene Sequencing | Total LOD Score | References |
|-------------------|----------------------------|-----------------|------------|
| Exon trapping or all genes sequenced in lineage region | 0-3 | 2.75 0 1.5 3 | Lahat et al 2004 (PMID:15176439) |

## Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item | References |
|-------------------|---------------|-----------------------|------------|
| Function | Biochemical Function | 0.5 | 0-2 | Yano et al 1994 (PMID:7816057) |
| | Protein interaction | 0.5 | 0-2 | Zhang et al 1997 (PMID:9287354) |
| | Expression | 0.5 | 0-2 | Fagerberg et al 2014 (PMID:24508696) |
| Functional Alteration | Patient Cells | 1 | 0-2 | di Barletta et al 2006 (PMID:16508766); Dirksen et al 2007 (PMID:17449618); Rizzi et al 2008 (PMID:18538715) |
| | Non-Patient Cells | 0.5 | 0-1 | Dirksen et al 2007 (PMID:17449618); Song et al 2007 (PMID:17607538); Rizzi et al 2008 (PMID:18538715) |
| Models | Non-human model organism | 2 | 0-4 | Kutzwald Joesfson et al 2017 (PMID:28336343) |
| | Cell culture model | 1 | 0-2 |  |
| Rescue | Rescue in Human | 2 | 0-4 |  |
| | Rescue in non-human model organism | 2 | 0-4 |  |
| | Rescue in cell culture model | 1 | 0-2 |  |
| | Rescue in Patient Cells | 1 | 0-2 |  |

## Total

- **Genetic Evidence Points (Maximum 12):** 12 12 12 12
- **Experimental Evidence Points (Maximum 6):** 6 6 6 6
- **Total:** 18 18 18
### CASQ2 (autosomal dominant)

#### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case Default Range | G1 | G2 | G3 | Max Score | References |
|---------------|------------------|------------------------------------|----|----|----|-----------|------------|
| Variant Evidence | Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo | 2 0-3 | 0 | 0 | 0 | 12 | Ng et al 2020 (PMID:32693635) |
| | | Proband with predicted or proven null variant | 1.5 0-2 | 3 | 0 | 0 | 10 |  |
| | | Proband with other variant type with some evidence of gene impact | 0.5 0-1.5 | 2.25 | 2 | 1 | 7 |  |
| | Autosomal recessive disease, OR X linked disease, affected females | Two variants in trans, at least one in LOF or de novo | 2 0-3 | 0 | 0 | 0 | 12 |  |
| | | Two non-LOF variants in trans | 1 0-1.5 | 0 | 0 | 0 | 12 |  |

**Segregation Evidence**

Evidence of Segregation in one or more families

| Total LOF Score | Candidate Gene Sequencing Method | Score |
|-----------------|--------------------------------|-------|
| 0-3             | Exon/Exon boundaries (gene or protein region) | 2 |
| 2-2.99          | 0.5                             | 1 |
| 3-4.99          | 1.0                             | 2 |
| ≥5              | 1.5                             | 3 |

**Case-Control Study Type**

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | G2 | G3 | G1 | Max Score |
|-------------------------|-------------------------------|------------------------|----|----|----|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-8                    | 0  | 0  | 0  | 12        |
|                         | Power                         |                        |    |    |    | 12        |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-8                    | 0  | 0  | 0  | 12        |
|                         | Statistical Significance      |                        |    |    |    | 12        |

**Total Genetic Evidence Points (Maximum 12):** 7.25 7.2 10.5 12

#### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item Default Range | G1 | G2 | G3 | Max Score | References |
|-------------------|---------------|------------------------------------|----|----|----|-----------|------------|
| Function          | Biochemical Function | 0.5 0-2 | 0.5 | 0 | 0.5 | 2 | Zhang et al 1997 (PMID:9287354) |
| | Protein Interaction | 0.5 0-2 | 0.5 | 0 | 0.5 | 2 |  |
| | Expression        | 0.5 0-2 | 0.5 | 0.5 | 0.5 | 2 | Fagerberg et al 2014 (PMID:24305908) |
| Functional Alteration | Patient Cells | 1 0-2 | 0 | 0 | 0 | 2 | di Barletta et al 2006 (PMID:16907646) |
| | Non-Patient Cells | 0.5 0-1 | 0.25 | 0 | 0.5 | 2 |  |
| Models            | Non-human model organism | 2 0-4 | 0 | 0 | 0 | 2 | Chopra et al 2007 (PMID:17006677) |
| | Cell culture model | 1 0-2 | 0 | 0 | 0 | 1 |  |
| Rescue            | Rescue in Human | 2 0-4 | 0 | 0 | 0 | 4 |  |
| | Rescue in non-human model organism | 2 0-4 | 0 | 0 | 0 | 2 |  |
| | Rescue in cell culture model | 1 0-2 | 0 | 0 | 0 | 1 |  |
| | Rescue in Patient Cells | 1 0-2 | 0 | 0 | 0 | 1 |  |

**Total Experimental Evidence Points (Maximum 6):** 1.75 1.5 4 6

| Total: | 9 8.7 14.5 |
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case | Default | G1 | G2 | G3 | Max Score |
|---------------|------------------|-----------------------|---------|----|----|----|-----------|
| Autosomal dominant disease, ORX-linked disease, affected males | Variant is de novo | 2 | 0-3 | 0 | 0 | 0 | 12 |
| | Proband with predicted or proven null variant | 1.5 | 0-2 | 0 | 0 | 0 | 10 |
| | Proband with other variant type with some evidence of gene impact | 0.5 | 0-1.5 | 0 | 0 | 0 | 7 |
| Autosomal recessive disease, ORX-linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 |
| | Two non-LOF variants in trans | 1 | 0-1.5 | 0 | 0 | 0 | 7 |

### Segregation Evidence

- Evidence of Segregation in one or more families

| Evidence Type | Suggested points/case | Default | G1 | G2 | G3 | Max Score |
|---------------|-----------------------|---------|----|----|----|-----------|
| Total VAF score | 0-3 | 0 | 0 | 0 | 3 |
| 2.2-99 | 0.5 | 1 |
| 3.4-99 | 1 | 2 |
| 15 | 1.5 | 3 |

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item | Default | G1 | G2 | G3 | Max Score |
|-------------------|---------------|-----------------------|---------|----|----|----|-----------|
| Function | Biochemical Function | 0.5 | 0-2 | 0 | 0.5 | 0 | 2 |
| | Protein Interaction | 0.5 | 0-2 | 0 | 1 | 0.5 | 2 |
| | Expression | 0.5 | 0-2 | 0.5 | 0.5 | 0.5 | 2 |
| Functional Alteration | Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 2 |
| | Non-Patient Cells | 0.5 | 0-1.5 | 0 | 0 | 0 | 2 |
| Models | Non-human model organism | 2 | 0-4 | 2 | 3 | 3 | 4 |
| | Cell culture model | 1 | 0-2 | 0 | 0 | 1 | 2 |
| Rescue | Rescue in human | 2 | 0-4 | 0 | 0 | 0 | 2 |
| | Rescue in non-human model organism | 2 | 0-4 | 0 | 1.5 | 2 | 4 |
| | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 2 |
| | Rescue in Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 2 |

| Total Experimental Evidence Points (Maximum 6): | 4 | 6 | 5 | 6 |

**Total:** 12 16 17
## Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case | G1 | G2 | G3 | Max Score |
|---------------|------------------|-----------------------|----|----|----|-----------|
| Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo | 2 | 0 | 0 | 0 | 0 | 12 |
| | Proband with predicted or proven null variant | 1.5 | 0 | 0 | 0 | 0 | 10 |
| | Proband with other variant type with some evidence of gene impact | 0.5 | 0.1-5 | 1.5 | 0 | 0 | 7 |
| Autosomal recessive disease, OR X linked disease, affected males | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 11 | 10 | 2 | 19 |
| | Two non-LOF variants in trans | 1 | 0-1.5 | 2.5 | 7 | 2 | 12 |

**References**
- Devalla et al 2016 (PMID:27861123);
- Webster et al 2020 (PMID:33367594);
- Mosuku-Gregor et al 2020 (PMID:32173957);
- Xie et al 2019 (PMID:10790670)

### Segregation Evidence
- Evidence of Segregation in one or more families
- **Total LOD Score**: 0.3
  - Candidate Gene Sequencing: 2.5
  - Total LOD Score: 2

**References**
- Devalla et al 2016 (PMID:27861123);
- Webster et al 2020 (PMID:33367594)

### Case-Control Data

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | G2 | G3 | G1 | Max Score |
|-------------------------|-------------------------------|-----------------------|----|----|----|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-6                   | 0  | 0  | 0  | 12 |
| | Power                        |                        |                      |    |    |    |          |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-6                  | 0  | 0  | 0  | 12 |
| | Statistical Significance    |                        |                      |    |    |    |          |

**Total Genetic Evidence Points (Maximum 12):** 12 12 12 12 12

## Experimental Evidence Summary

| Evidence Category | Suggested points/item | G1 | G2 | G3 | Max Score |
|-------------------|-----------------------|----|----|----|-----------|
| Function          | 0.5 0-2               | 0  | 0  | 0  | 1          |
| Protein interaction | 0.5 0-2             | 0  | 0  | 0  | 1          |
| Expression        | 0.5 0-2               | 0  | 0  | 0  | 1          |
| Functional Alteration | 1 0-2                | 1  | 1  | 2  | 2          |
| Cell culture model | 1 0-2                | 0  | 0  | 0  | 1          |
| Non-human model organism | 2 0-4             | 0  | 0  | 0  | 1          |
| Patient Cells     | 1 0-2                | 0  | 0  | 0  | 1          |
| Non-Patient Cells | 0.5 0-1              | 0  | 0  | 0  | 1          |
| Models             |                       |    |    |    |            |
| Rescue             | 2 0-4                | 0  | 0  | 0  | 1          |
| Rescue in Patient Cells | 1 0-2            | 0  | 0  | 0  | 1          |
| Rescue in cell culture model | 2 0-4        | 0  | 0  | 0  | 1          |
| Rescue in non-human model organism | 1 0-2 | 0  | 0  | 0  | 1          |

**Total Experimental Evidence Points (Maximum 6):** 2.5 1.5 4 6

**Total:** 14.5 13.5 16
### Genetic Evidence Summary

| Evidence Type                                      | Suggested points/case | G3 | G2 | G1 | Max Score |
|---------------------------------------------------|-----------------------|----|----|----|-----------|
| **Variant Evidence**                              |                       |    |    |    |           |
| Autosomal dominant disease, OR X linked disease, affected males | 2                     | 2  | 3  | 2  | 12        |
| Proband with predicted or proven null variant     | 1.5                   | 1.5 | 1.5 | 1.5 | 7        |
| Autosomal recessive disease, OR X linked disease, affected females | 2                     | 0  | 0  | 0  | 10        |
| Two variants in trans, at least one is LOF or de novo | 2                     | 0  | 1  | 0  | 7        |
| Two-n-LOF variants in trans                       | 1                     | 0  | 0  | 0  | 7        |
| **Segregation Evidence**                          |                       |    |    |    |           |
| Evidence of Segregation in one or more families   |                       |    |    |    |           |
| **Case-Control Data**                             |                       |    |    |    |           |
| Single Variant Analysis                           |                       |    |    |    |           |
| Variant Detection Methodology                     | 2                     | 0  | 0  | 0  | 12        |
| Power                                             | 0                     | 0  | 0  | 0  | 12        |
| Aggregate Variant Analysis                        |                       |    |    |    |           |
| Bias and Confounding Factors                      | 2                     | 0  | 0  | 0  | 12        |
| Statistical Significance                          | 0                     | 0  | 0  | 0  | 12        |
| **Total Genetic Evidence Points (Maximum 12)**    |                       |    |    |    |       |
|                                                     | 2                     | 0  | 0  | 0  | 12        |

### Experimental Evidence Summary

| Evidence Category | Evidence Type                                      | Suggested points/item | G3 | G2 | G1 | Max Score |
|-------------------|---------------------------------------------------|-----------------------|----|----|----|-----------|
| Function          | Biochemical Function                              | 0.5                   | 0  | 0  | 0  | 0.5       |
|                   | Protein interaction                               | 0.5                   | 0  | 0  | 0  | 0.5       |
|                   | Expression                                        | 0.5                   | 0  | 0  | 0  | 0.5       |
|                   | Patient cells                                     | 1                     | 0  | 0  | 0  | 1         |
|                   | Non-Patient Cells                                  | 0.5                   | 0  | 0  | 0  | 0.5       |
|                   | Models                                             |                       |    |    |    |           |
|                   | Non-human model organism                          | 2                     | 0.25 | 1  | 1  | 2         |
|                   | Cell culture model                                 | 1                     | 0  | 0  | 0  | 1         |
|                   | Rescue                                             |                       |    |    |    |           |
|                   | Rescue in human                                    | 2                     | 0  | 0  | 0  | 2         |
|                   | Rescue in non-human model organism                 | 2                     | 0  | 0  | 0  | 2         |
|                   | Rescue in cell culture model                       | 1                     | 0  | 0  | 0  | 1         |
|                   | Rescue in Patient Cells                            | 1                     | 0  | 0  | 0  | 1         |
| **Total Experimental Evidence Points (Maximum 6)** |                       | 3.25                  | 2.5 | 4.5 | 5 |           |

**Total:** 6.75
## Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case Range | G1 | G2 | G3 | Max Score |
|---------------|------------------|----------------------------|----|----|----|-----------|
| Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo | 2 | 0-3 | 4.5 | 7 | 4.5 | 12 |
| Autosomal recessive disease, OR X linked disease, affected males | Proband with predicted or proven null variant | 1.5 | 0-2 | 0 | 0 | 0 | 10 |
| Autosomal recessive disease, OR X linked disease, affected males | Proband with other variant type with some evidence of gene impact | 0.5 | 0-1.5 | 0 | 0 | 0.3 | 7 |
| Autosomal recessive disease, OR X linked disease, affected males | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 |
| Autosomal recessive disease, OR X linked disease, affected males | Two non-LOF variants in trans | 1 | 0-1.5 | 0 | 0 | 0 | 12 |

### Segregation Evidence

| Candidate Gene Sequencing | Evidence of Segregation in one or more families | Total LOD Score | G1 | G2 | G3 | Max Score |
|---------------------------|-----------------------------------------------|----------------|----|----|----|-----------|
| Examining all gene sequenced in linkage region | 0-3 | 0 | 0 | 0 | 3 |
| 2-2.99 | 0.5 | 1 |
| 3-4.99 | 1 | 2 |
| >5 | 1.5 | 3 |

### Case-Control Study Type

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | G1 | G2 | G3 | Max Score |
|-------------------------|-------------------------------|------------------------|----|----|----|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-6 | 0 | 0 | 0 | 12 |
| Aggregate Variant Analysis | Power | 0-6 | 0 | 0 | 0 | 12 |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-6 | 0 | 0 | 0 | 12 |
| Aggregate Variant Analysis | Statistical Significance | 0-6 | 0 | 0 | 0 | 12 |

### Total Genetic Evidence Points (Maximum 12):

| | G1 | G2 | G3 | Max Score |
|--------------------------|----|----|----|-----------|
| | 4.5 | 7.3 | 4.5 | 12 |

## Experimental Evidence Summary

| evidence Category | evidence type | Suggested points/item Range | G1 | G2 | G3 | Max Score |
|-------------------|---------------|-----------------------------|----|----|----|-----------|
| Function          | Biochemical Function | 0.5 | 0-2 | 1 | 0.5 | 2 | Paterson et al 1999 (PMID:10197534) |
|                   | Protein interaction | 0.5 | 0-2 | 0.5 | 0.5 | 0 | Yamaguchi et al 2003 (PMID:13767280) |
|                   | Expression      | 0.5 | 0-2 | 0.5 | 0.5 | 0 | Crotti et al 2013 (PMID:23313621) |
| Functional Alteration | Patient Cells | 1 | 0-1 | 0 | 0 | 0 | Sendtner et al 2015 (PMID:26305256) |
|                   | Non-Patient Cells | 0.5 | 0-1 | 0.5 | 0.5 | 0.5 | Sendtner et al 2015 (PMID:26305256) |
| Models             | Non-human model organism | 0 | 0 | 0 | 0 | 0 | |
|                   | Cell culture model | 0 | 0 | 0 | 0 | 0 | |
| Training           | Rescue in human | 0 | 0 | 0 | 0 | 0 | |
|                   | Rescue in non-human model organism | 0 | 0 | 0 | 0 | 0 | |
|                   | Rescue in cell culture model | 0 | 0 | 0 | 0 | 0 | |
|                   | Rescue in patient cells | 0 | 0 | 0 | 0 | 0 | |

### Total Experimental Evidence Points (Maximum 6):

| | G1 | G2 | G3 | Max Score |
|--------------------------|----|----|----|-----------|
| | 2 | 2.5 | 3.5 | 6 |

Total: 6.5 9.8 8
| Genetic Evidence Summary | References |
|--------------------------|------------|
| **Variant Evidence**     |            |
| **Autosomal dominant disease, OR X-linked disease, affected males** |            |
| Proband with predicted or proven null variant | 2 | 0-3 | 0 | 0 | 3 | 12 | Crotti et al 2019 (PMID:21170220); Gomez-Hurtado et al 2016 (PMID:27516656) |
| Proband with other variant type with some evidence of gene impact | 0.5 | 0-1.5 | 1.5 | 1 | 0 | 7 |  |
| **Autosomal recessive disease, OR X-linked disease, affected females** |            |
| Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 6 | 12 |  |
| Two non-LOF variants in trans | 1 | 0-1.5 | 0 | 0 | 0 |  |
| **Segregation Evidence** |            |
| Evidence of Segregation in one or more families | | | | | | 3 | |
| **Case-Control Study Type** |            |
| **Case-Control Quality Criteria** |            |
| **Suggested points/study** | G2 | G3 | G1 | Max score |
| **Single Variant Analysis** | Variant Detection Methodology | | | | | 12 | |
| **Power** | | | | | |  |
| **Aggregate Variant Analysis** | Bias and Confounding Factors | | | | |  |
| **Statistical Significance** | | | | | |  |
| **Total Genetic Evidence Points (Maximum 12):** | 1.5 | 1 | 3 | 12 |  |

| Experimental Evidence Summary | References |
|-------------------------------|------------|
| **Evidence Category** |            |
| **Evidence type** | Suggested points/item Default | S1 | S2 | S3 | Max score |
| **Function** | | | | | | | |
| Biochemical Function | 0.5 | 0-2 | 1 | 0.5 | 0.5 | 2 | Paterson et al 1999 (PMID:10197534) |
| Protein Interaction | 0.5 | 0-2 | 0.5 | 0.5 | 0 |  | Yamaguchi et al 2003 (PMID:12767260) |
| **Functional Alteration** | | | | | | | |
| Patient Cells | | | | | | | |
| Non-Patient Cells | | | | | | | |
| **Models** | | | | | | | |
| Non-human model organism | | | | | | | |
| Cell culture model | | | | | | | |
| **Rescue** | | | | | | | |
| Rescue in human | | | | | | | |
| Rescue in non-human model organism | | | | | | | |
| Rescue in cell culture model | | | | | | | |
| Rescue in Patient Cells | | | | | | | |
| **Total Experimental Evidence Points (Maximum 6):** | 2.5 | 2 | 1 | 6 |  |

**Total:** 4 2 4
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case | G1 | G2 | G3 | Max score |
|---------------|------------------|-----------------------|----|----|----|-----------|
| Autosomal dominant disease, OR X-linked disease, affected males | Variant is de novo, Proband with predicted or proven null variant | 2 | 0-3 | 0 | 0 | 0 | 12 |
| | Proband with other variant type with some evidence of gene impact | 1.5 | 0-2 | 0 | 0 | 0 | 10 |
| Autosomal recessive disease, OR X-linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 0.5 | 0-1.5 | 0 | 0.25 | 0 | 7 |
| | Two non-LOF variants in trans | 2 | 0-2 | 0 | 0 | 0 | 12 |

### References

- Enrichment of one or all genes sequenced in linkage region.
- Total LOD Score: 0.3
- Evidence of Segregation in one or more families
- Total LOD Score (Maximum 12): 0.25
- Single Variant Analysis
- Aggregate Variant Analysis
- Total Genetic Evidence Points (Maximum 12): 0.25

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item | G1 | G2 | G3 | Max score |
|-------------------|---------------|-----------------------|----|----|----|-----------|
| Function          | Biochemical Function | 0.5 | 0-2 | 0 | 0 | 0 | 2 |
| | Protein Interaction | 0.5 | 0-2 | 0 | 0 | 0 | 2 |
| | Expression | 0.5 | 0-2 | 0 | 0 | 0 | 2 |
| Functional Alteration | Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 2 |
| | Non-Patient Cells | 0.5 | 0-1 | 0 | 0.5 | 0.5 | 2 |
| Models | Non-human model organism | 2 | 0-4 | 0 | 0 | 1 | 3 |
| | Cell culture model | 1 | 0-2 | 0 | 0 | 0 | 2 |
| Rescue | Rescue in human | 2 | 0-4 | 0 | 0 | 0 | 2 |
| | Rescue in non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 2 |
| | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 1 |
| | Rescue in Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 1 |

- Total Experimental Evidence Points (Maximum 6): 0.25
- Total: 0.25
### KCNJ2

#### Genetic Evidence Summary

| Evidence Type                                      | Case Information                                             | Suggested points/case | G1 | G2 | G3 | Max Score |
|----------------------------------------------------|--------------------------------------------------------------|-----------------------|----|----|----|----------|
| Variant Evidence                                   |                                                              |                       |    |    |    |          |
| Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo                                          | 2                     | 0-3| 0  | 0  | 0        |
| Regional disease, affected males                   | Proband with predicted or proven null variant                | 1.5                   | 0-2| 0  | 0  | 0        |
| Autosomal recessive disease, OR X linked disease, affected females | Two variants in trans, at least one is LOF or de novo       | 2                     | 0-3| 0  | 0  | 0        |
|                                                   | Two non-LOF variants in trans                               | 1                     | 0-1.5| 0  | 0  | 0        |
| Segregation Evidence                               | Evidence of Segregation in one or more families              |                       |    |    |    | 3        |
| Sequencing Method                                  |                                                              |                       |    |    |    |          |
|                                                   |                                                              |                       |    |    |    |          |

**Total Genetic Evidence Points (Maximum 12):** 2, 0, 1, 12

#### Case-Control Data

| Case-Control Type                                | Case-Control Quality Criteria                               | Suggested points/study | G2 | G3 | G1 | Max Score |
|--------------------------------------------------|--------------------------------------------------------------|-----------------------|----|----|----|----------|
| Single Variant Analysis                           | Variant Detection Methodology, Power                         | 0-6                   | 0  | 0  | 0  | 12       |
| Aggregate Variant Analysis                        | Bias and Confounding Factors, Statistical Significance       | 0-6                   | 0  | 0  | 0  | 0        |

**Total Genetic Evidence Points (Maximum 12):** 2, 0, 1, 12

#### Experimental Evidence Summary

| Evidence Category       | Evidence Type                               | Suggested points/item | G1 | G2 | G3 | Max Score |
|-------------------------|--------------------------------------------|-----------------------|----|----|----|----------|
| Function                | Biochemical Function                        | 0.5                   | 0  | 0  | 0  | 0        |
|                         | Protein Interaction                         | 0.5                   | 0  | 0  | 0  | 0        |
|                         | Expression                                  | 0.5                   | 0  | 0  | 0  | 0        |
| Functional Alteration   | Patient Cells                               | 1                     | 0-2| 0  | 0  | 0        |
|                         | Non-Patient Cells                           | 0.5                   | 0-1| 0  | 0  | 0        |
| Models                  | Non-human model organism                    | 2                     | 0-4| 0  | 0  | 0        |
|                         | Cell culture model                          | 1                     | 0-2| 0  | 0  | 0        |
| Rescue                  | Rescue in human                             | 2                     | 0-4| 0  | 0  | 0        |
|                         | Rescue in non-human model organism          | 2                     | 0-4| 0  | 0  | 0        |
|                         | Rescue in cell culture model                | 2                     | 0-4| 0  | 0  | 0        |
|                         | Rescue in Patient Cells                     | 2                     | 0-2| 0  | 0  | 0        |

**Total Experimental Evidence Points (Maximum 6):** 0.5, 2, 3.5, 6

**Total:** 2.5, 2, 4.5
### Genetic Evidence Summary

| Variant Evidence | Evidence Type | Case Information | Suggested points/case Default | G1 | G2 | G3 | Max Score | References |
|------------------|---------------|------------------|-----------------------------|----|----|----|----------|------------|
| Autosomal dominant disease, OR X-linked disease, affected males | Variant is de novo | Proband with predicted or proven null variant | 2 | 0 | 0 | 0 | 7 | Tester et al, 2019 (PMID:30678776) |
| Autosomal recessive disease, OR X-linked disease, affected females | Two variants in trans, at least one is LOF or de novo | Proband with other variant type with some evidence of gene impact | 1.5 | 0 | 0 | 0 | 7 | |
| | Two non-LOF variants in trans | | 1 | 0.15 | 0 | 0 | 0 | |

#### Segregation Evidence

| Evidence Type | Case Information | Suggested points/case Default | G1 | G2 | G3 | Max Score |
|---------------|------------------|-------------------------------|----|----|----|---------|
| Evidence of Segregation in one or more families | | | 0 | 0 | 0 | 3 |

#### Case-Control Data

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | G2 | G3 | G1 | Max Score |
|-------------------------|-------------------------------|-------------------------|----|----|----|---------|
| Single Variant Analysis | Variant Detection Methodology | 0-6 | 0 | 0 | 0 | 12 |
| | Power | | | | | |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-6 | 0 | 0 | 0 | |
| | Statistical Significance | | | | | |

**Total Genetic Evidence Points (Maximum 12): 29.5**

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item Default | G1 | G2 | G3 | Max Score |
|-------------------|---------------|-------------------------------|----|----|----|---------|
| Function | Biochemical Function | 0.5 | 0 | 0 | 0 | 2 |
| | Protein interaction | 0.5 | 0 | 0 | 0 | |
| Functional Alteration | Patient cells | 1 | 0 | 0 | 0 | 2 |
| | Non-Patient cells | 0.5 | 0 | 0 | 0.5 | |
| Models | Non-human model organism | 2 | 0 | 0 | 0 | 4 |
| | Cell culture model | 1 | 0 | 0 | 0 | |
| Rescue | Rescue in human | 2 | 0 | 0 | 0 | |
| | Rescue in non-human model organism | 2 | 0 | 0 | 0 | |
| | Rescue in cell culture model | 1 | 0 | 0 | 0 | |
| | Rescue in patient cells | 1 | 0 | 0 | 0 | |

**Total Experimental Evidence Points (Maximum 6): 3.5**

**Total: 3.5**
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested points/case | G1 | G2 | G3 | Max Score |
|---------------|------------------|-----------------------|----|----|----|-----------|
| **Variant Evidence** | | | | | | |
| Autosomal dominant disease, OR X linked disease, affected males | Variant is de novo | 2 | 0-3 | 0 | 0 | 0 | 12 |
| | Probands with predicted or proven null variant | 1.5 | 0-2 | 0 | 0 | 0 | 10 |
| | Probands with other variant type with some evidence of gene impact | 0.5 | 0-1.5 | 0.25 | 0 | 0 | 7 |
| Autosomal recessive disease, OR X linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 |
| | Two non-LOF variants in trans | 1 | 0-1.5 | 0 | 0 | 0 | 12 |

**Segregation Evidence**

Evidence of Segregation in one or more families

**Sequencing Method**

| Total LOD score | Candidate Gene Sequencing | Excluding one or all genes sequenced in linkage region | 0-3 | 2 | 2 | 0 | 3 |
|-----------------|---------------------------|------------------------------------------------------|----|----|----|----|
| 2-2.99          | 0.5                       | 1                                                    |    |    |    |    |
| &ge; 3.99       | 1                         | 2                                                    |    |    |    |    |

Swan et al 2014 (PMID:25216054)

### Case-control Data

| Case-control Study Type | Case-control Quality Criteria | Suggested points/study | G2 | G3 | G1 | Max score |
|-------------------------|-------------------------------|------------------------|----|----|----|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-8                    |    |    |    | 12        |
| | Power                     | 0-8                    |    |    |    | 12        |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-8                    |    |    |    | 12        |
| | Statistical Significance  | 0-8                    |    |    |    | 12        |

**Total Genetic Evidence Points (Maximum 12):** 12

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested points/item | G1 | G2 | G3 | Max Score |
|-------------------|---------------|-----------------------|----|----|----|-----------|
| Function | Biochemical Function | 0.5 | 0-2 | 0 | 0 | 0 | 2 |
| | Protein Interaction | 0.5 | 0-2 | 0 | 0 | 0 | 2 |
| | Expression | 0.5 | 0-2 | 0.25 | 0 | 0 | 2 |
| Functional Alteration | Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 2 |
| | Non-Patient Cells | 0.5 | 0-1 | 0.25 | 0 | 0 | 2 |
| Models | Non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 4 |
| | Cell culture model | 1 | 0-2 | 0 | 0 | 0 | 4 |
| Rescue | Rescue in Human | 2 | 0-4 | 0 | 0 | 0 | 8 |
| | Rescue in non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 8 |
| | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 8 |
| | Rescue in Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 8 |

**Total Experimental Evidence Points (Maximum 8):** 8

Total: 3 2.5 0 8
### CACNA1C

| Evidence Type | Case Information | Suggested Default | Range | Points Given | Max Score | PMIDs |
|---------------|------------------|-------------------|-------|--------------|-----------|-------|
| Autosomal dominant disease, CFX-linked disease, affected males | Variant is absent | 2 | 0-3 | 0 | 0 | 0 | 12 | 2423115 |
| Autosomal recessive disease, CRX-linked disease, affected females | Proband with predicted or proven null variant | 15 | 0-2 | 0 | 0 | 0 | 10 | 17224470, 20427417, 2087017 |
| Autosomal recessive disease, CRX-linked disease, affected females | Proband with other variants, type with some evidence of gene impact | 0.5 | 0-15 | 0 | 0 | 0 | 7 | |
| Autosomal recessive disease, CRX-linked disease, affected females | Two variants in exons; at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 | |
| Autosomal recessive disease, CRX-linked disease, affected females | Two non-LOF variants in exons | 1 | 0-15 | 0 | 0 | 0 | |

#### Segregation Evidence

- Evidence of Segregation in one or more families
- Total LOD Score: 0-3
  - 2-2.99: 0.5 points
  - 3-4.99: 1 point
  - >5: 2 points
- Total LOD Score: 3

#### Case-Control Study Type

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | Points Given | Max Score |
|-------------------------|--------------------------------|------------------------|--------------|-----------|
| Single Variant Analysis | Variant Detection Methodology  | 0-6                    | 0 | 0 | 0 | 12 |
| Aggregate Variant Analysis | Power | 0-6 | 0 | 0 | 0 | |
| Aggregate Variant Analysis | Bias and Confounding Factors | 0-6 | 0 | 0 | 0 | |
| Aggregate Variant Analysis | Statistical Significance | 0-6 | 0 | 0 | 0 | |

Total Genetic Evidence Points (Maximum 12): 0 | 0 | 0 | 12

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested Default | Range | Points Given | Max Score | PMIDs |
|-------------------|---------------|-------------------|-------|--------------|-----------|-------|
| Function          | Biochemical Function | 0.5 | 0-2 | 0 | 0 | 0 | 2 | 17224470, 20427417, 2087017 |
| Function          | Protein Interaction | 0.5 | 0-2 | 0 | 0 | 0 | 2 | |
| Function          | Expression | 0.5 | 0-2 | 0 | 0 | 0 | 2 | |
| Functional Alteration | Pattern Cells | 1 | 0-2 | 0 | 0 | 0 | 2 | |
| Functional Alteration | Non-Patient Cells | 0.5 | 0-1 | 0 | 0 | 0 | 2 | |
| Models            | Non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 2 | |
| Models            | Cell culture model | 1 | 0-2 | 0 | 0 | 0 | 2 | |
| Rescue            | Rescue in human | 2 | 0-4 | 0 | 0 | 0 | 4 | |
| Rescue            | Rescue in human model organism | 2 | 0-4 | 0 | 0 | 0 | 4 | |
| Rescue            | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 2 | |
| Rescue            | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 2 | |

Total Experimental Evidence Points (Maximum 6): 1 | 0 | 2 | 6

Summary: 1 | 0 | 2 |
## Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default | Range | Points Given | Max Score | PMID/Notes |
|---------------|------------------|-------------------|-------|--------------|-----------|------------|
| Autosomal dominant disease, OR X-linked disease, affected males | Variant is deleterious | 2 | 0-3 | 0 | 0 | 0 | 12 |
| Autosomal recessive disease, OR X-linked disease, affected males | Two variants in cases, at least one is LQD or null | 2 | 0-3 | 0 | 0 | 0 | 12 |
| Autosomal recessive disease, OR X-linked disease, affected males | Two non-LQD variants in case | 1 | 0-15 | 0 | 0 | 0 | 7 |

### Segregation Evidence

| Total LOD Score | Evidence of Segregation in one or more families | Candidate Gene Sequencing |
|----------------|-----------------------------------------------|--------------------------|
| 2-2.98         | 0.5                                           | 1                        |
| 3-4.98         | 1                                             | 2                        |
| >5             | 1.5                                           | 3                        |

### Case-Control Study Type

| Case-Control Quality Criteria | Suggested points/study | Points Given | Max Score |
|-------------------------------|------------------------|--------------|-----------|
| Variant Detection Methodology  | 0-6                    | 0            | 0         |
| Power                          |                        | 0            | 0         |
| Bias and Confounding Factors   | 0-6                    | 0            | 0         |
| Statistical Significance       |                        | 0            | 0         |

Total Genetic Evidence Points (Maximum 12): 0 0 0 12

### Experimental Evidence Summary

| Evidence Type | Suggested Default | Range | Points Given | Max Score |
|---------------|-------------------|-------|--------------|-----------|
| Function      | 0.5               | 0-2   | 0 | 12 |
| Protein Interaction | 0.5           | 0-2   | 0 | 0 |
| Expression    | 0.5               | 0-2   | 0 | 0 |
| Functional Alteration | 1                | 0-2   | 0 | 2 |
| Patient Cells | 0.5               | 0-2   | 0 | 0 |
| Non-Patient Cells | 0.5            | 0-2   | 0 | 0 |
| Models        | 2                 | 0-4   | 0 | 1 |
| Non-human model organism | 1               | 0-2   | 0 | 0 |
| Cell culture model | 1                | 0-2   | 0 | 0 |
| Rescue        | 2                 | 0-4   | 0 | 0 |
| Rescue in human | 2                | 0-4   | 0 | 0 |
| Rescue in non-human model organism | 1            | 0-2   | 0 | 0 |
| Rescue in cell culture model | 1              | 0-2   | 0 | 0 |

Total Experimental Evidence Points (Maximum 5): 0.5 0.5 1.5 5

Summary: 0.5 0.5 1.5
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default Range | Points Given | Max Score | PMIDs |
|---------------|------------------|-------------------------|--------------|-----------|-------|
| Autosomal dominant disease, OR X-linked disease, affected males | Variant is detected | 2 0-3 | 0 0 0 | 12 | |
| Autosomal recessive disease, OR X-linked disease, affected females | Two variants in trans, at least one is LOF or dominant | 2 0-3 | 0 0 0 | 12 | |
| | Two non-LOF variants in trans | 1 0-15 | 0.5 0 0 | 7 | 17224478 |

#### Segregation Evidence
- Evidence of Segregation in one or more families
- **Total LOD Score**: 3

#### Case-Control Study Type
- **Single Variant Analysis**
  - Variant Detection Methodology
  - Power
- **Aggregate Variant Analysis**
  - Bias and Confounding Factors
  - Statistical Significance

### Case-Control Quality Criteria
- **Suggested points/study**: 0-8
- **Points Given**: 0 0 0
- **Max Score**: 12

### Total Genetic Evidence Points (Maximum 12): 0.5 0 0 12

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested Default Range | Points Given | Max Score |
|-------------------|---------------|-------------------------|--------------|-----------|
| Function          | Biochemical Function | 0.5 0-2 | 0 0 0 | 2 |
|                   | Protein Interaction | 0.5 0-2 | 0 0 0 | |
|                   | Expression      | 0.5 0-2 | 0 0 0 | |
| Functional Alteration | Patient Cells | 1 0-2 | 0 0 0 | 2 17224478 |
|                   | Non-Patient Cells | 0.5 0-1 | 0.5 0 0 | |
| Models            | Non-human model organism | 2 0-4 | 0 0 0 | |
|                   | Cell culture model | 1 0-2 | 0 0 0 | |
| Rescue            | Rescue in human | 2 0-4 | 0 0 0 | |
|                   | Rescue in non-human model organism | 2 0-4 | 0 0 0 | |
|                   | Rescue in cell culture model | 1 0-2 | 0 0 0 | |
|                   | Rescue in Patient Cells | 1 0-2 | 0 0 0 | |

### Total Experimental Evidence Points (Maximum 6): 0.5 0 0.5 6

**Summary**: 1 0 0.5
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default | Points Given G1 | Points Given G2 | Points Given G3 | Max Score | PMID(s)/Notes |
|---------------|------------------|-------------------|-----------------|-----------------|-----------------|-----------|---------------|
| Autosomal dominant disease, DRX-linked disease, affected males | Variant is de novo | 2 | 0 | 0 | 0 | 2 | 1672946, 10940558, 25335986, 2103371, 29375809, 29415779, 29485588, 3187592; 15822882, 16893482, 25374815, 2103371, 3072575 |
| | Probands with predicted or proven null variant | 1.5 | 0.2 | 0 | 0 | 1 | |
| Autosomal recessive disease, DRX-linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 2 | 0.3 | 0 | 0 | 0 | |
| | Two non-LOF variants in trans | 1 | 0.1 | 0 | 0 | 0 | |
| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | Points Given G1 | Points Given G2 | Points Given G3 | Max Score |
|--------------------------|-----------------------------|-------------------|-----------------|-----------------|-----------|-----------|
| Single Variant Analysis  | Variant Detection Methodology | 0.6 | 0 | 0 | 0 | 2 |
| Aggregate Variant Analysis | Power | 0.6 | 0 | 0 | 0 | 2 |
| Aggregate Variant Analysis | Disease and Confounding Factors | 0.6 | 0 | 0 | 0 | 2 |
| Aggregate Variant Analysis | Statistical Significance | 0.6 | 0 | 0 | 0 | 2 |

#### Total Genetic Evidence Points (Maximum 12):

| Evidence Category | Evidence Type | Suggested Default | Points Given G1 | Points Given G2 | Points Given G3 | Max Score |
|-------------------|---------------|-------------------|-----------------|-----------------|-----------------|-----------|
| Function          | Biochemical Function | 0.5 | 0.2 | 0.5 | 0 | 0 | 2 |
| | Protein interaction | 0.5 | 0.2 | 0 | 0 | 0 | 2 |
| | Expression | 0.5 | 0.2 | 0.5 | 0.5 | 1 | 2 |
| Functional Alteration | Patient Cells | 1 | 0.2 | 15 | 0 | 1 | 2 |
| | Non-Patient Cells | 0.5 | 0.1 | 15 | 2 | 1 | 2 |
| Models            | Non-human model organism | 2 | 0.4 | 2 | 2 | 2 | 3 |
| | Cell culture model | 1 | 0.2 | 0 | 0 | 0 | 2 |
| | Rescue in human | 2 | 0.4 | 0 | 0 | 0 | 4 |
| | Rescue in non-human model organism | 2 | 0.4 | 0 | 0 | 0 | 4 |
| | Rescue in cell culture model | 1 | 0.2 | 0 | 0 | 0 | 4 |
| | Rescue in Patient Cells | 1 | 0.2 | 0 | 0 | 0 | 4 |

#### Total Experimental Evidence Points (Maximum 6):

| Summary | 12 | 11.5 | 12 |

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KCNH2
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default | Suggested Range | Points Given | Max Score | PMIDs |
|---------------|------------------|-------------------|----------------|--------------|-----------|--------|
| Autosomal dominant disease, X-linked disease, affected males | Variant is all male; Pedigree with predicted or proven null variant | 2 | 0-3 | 4 | 4 | 4 | 12 | 15761134, 23440103 |
| Autosomal recessive disease, X-linked disease, affected males | Two variants in trans, at least one is LOF or frameshift; Two non-LOF variants in trans | 2 | 0-3 | 0 | 0 | 0 | 12 | 2473485, 23615971, 23376527, 22155372 |

### Segregation Evidence

| Total LOD Score | LOD 1 | LOD 2 | LOD 3 | Max Score |
|----------------|-------|-------|-------|-----------|
| 0-3            | 0     | 0     | 0     | 3         |
| 2.00            | 0.5   | 1     |       |           |
| 3.00            | 1.5   | 3     |       |           |

### Case-Control Study Type

| Case-Control Quality Criteria | Suggested point | G1 | G2 | G3 | Max Score |
|-------------------------------|-----------------|----|----|----|-----------|
| Single Variant Analysis       |变异检测方法学| 0-6| 0  | 0  | 0         | 12     |
| Aggregate Variant Analysis    |偏倚和混杂因素 | 0-6| 0  | 0  | 0         |

Total Genetic Evidence Points (Maximum 12): 5 5.5 6.5 12

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested Default | Suggested Range | Points Given | Max Score |
|-------------------|---------------|-------------------|----------------|--------------|-----------|
| Function          | Biochemical Function | 0.5 | 0-2 | 1 | 0.5 | 2 | 19105627 |
|                   | Protein Interaction | 0.5 | 0-2 | 0 | 0 | 0 |

### Functional Alteration

| Models | Non-Human model organism | 2 | 0-4 | 0  | 0  | 0  | 2 | 19105627 |

### Rescue

| Models | Rescue in Human | 2 | 0-4 | 0  | 0  | 0  | 4 |
| Models | Rescue in Non-Human model organism | 2 | 0-4 | 0  | 0  | 0  |
| Models | Rescue in cell culture model | 1 | 0-2 | 0  | 0  | 0  |

Total Experimental Evidence Points (Maximum 6): 9 9.5 10.5

Summary: 9 9.5 10.5

35
### KCNQ1 Evidence Summary

#### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default | Range | Points Given | Max Score | PMIDs |
|---------------|------------------|-------------------|-------|--------------|-----------|-------|
| Variant Evidence | Autosomal dominant disease, DRX-linked disease, affected males | Variant is de novo | 2 | 0-3 | 6 | 6 | 6 | 12 | 16093888, 28491547 |
| | Proband with predicted or proven null variant | 15 | 0-2 | 0 | 0 | 0 | 10 | |
| | Proband with other variant type with some evidence of gene impact | 0.5 | 0-15 | 2.5 | 3 | 3.5 | 7 | 15593230, 24260499, 25974185, 26568993, 28346092, 26279181, 25409751 |
| | Autosomal recessive disease, DRX-linked disease, affected females | Two variants in trans, at least one is LOF or de novo | 2 | 0-3 | 0 | 0 | 0 | 12 | |
| | | Two non-LOF variants in trans | 1 | 0-15 | 0 | 0 | 0 | |

#### Segregation Evidence

- Evidence of Segregation in one or more families
- Total LOD Score: 3
- LOD Score: 2.38
- Sequence Method: 0.5
- Evidence: 0
- Gene: 0
- Segregation: 0.5

#### Case-Control Study Type

- Single Variant Analysis: Variant Detection Methodology
- Power: 0.6
- Points Given: 0 | 0 | 0 | 12
- Aggregate Variant Analysis: Bias and Confounding Factors
- Points Given: 0 | 0 | 0

#### Total Genetic Evidence Points (Maximum 12)

- 8.5 | 3 | 10 | 12

#### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested Default | Range | Points Given | Max Score | PMIDs |
|-------------------|---------------|-------------------|-------|--------------|-----------|-------|
| Function          | Biochemical Function | 0.5 | 0-2 | 1 | 0 | 0 | 2 | 15002593 |
| | Protein Interaction | 0.5 | 0-2 | 0 | 0.5 | 0 | 1 | 15026244 |
| | Expression | 0.5 | 0-2 | 0 | 1 | 1 | |
| | Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 2 | 15033230, 16093888, 26168993, 26346102, 28252224 |
| Functional Alteration | Non-Patient Cells | 0.5 | 0-1 | 2.5 | 2.5 | 2 | 15033230, 16093888, 26168993, 26346102, 28252224 |
| Models | Non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 4 | |
| | Cell culture model | 1 | 0-2 | 0 | 0 | 0 | 1 | |
| | Rescue in human | 2 | 0-4 | 0 | 0 | 0 | 2 | |
| | Rescue in non-human model organism | 2 | 0-4 | 0 | 0 | 0 | 2 | |
| | Rescue in cell culture model | 1 | 0-2 | 0 | 0 | 0 | 1 | |
| | Rescue in Patient Cells | 1 | 0-2 | 0 | 0 | 0 | 1 | |

#### Total Experimental Evidence Points (Maximum 6)

- 4 | 2.5 | 3 | 6

### Summary

- 12.5 | 11.5 | 13
### Genetic Evidence Summary

| Evidence Type                        | Case Information                              | Suggested Points Given | Max Score |
|-------------------------------------|-----------------------------------------------|------------------------|-----------|
|                                      |                                               | Default                | G1  | G2  | G3  |          |           |
|                                      |                                               | Range                  |     |     |     |          |           |
| Autsomal dominant disease, OR X-linked disease, affected males | Proband with predicted or proven null variant | 2 | 0-3 | 0   | 0   | 0   | 12       |
|                                      | Proband with other variant type with some evidence of gene impact | 1.5 | 0-2 | 0   | 0   | 0   | 10       |
| Autsomal recessive disease, OR X-linked disease, affected males | Two variants in cases, at least one is LCR or de novo | 2 | 0-3 | 0   | 0   | 0   | 12       |
|                                      | Two non-LCR variants in cases                 | 1 | 0-15 | 0   | 0   | 0   |          |

#### Segregation Evidence
- Evidence of Segregation in one or more families
- Total LOD Score
  - 0-3 | 0 | 0 | 0 | 3

#### Case-Control Study Type
| Case-Control Study Type                          | Case-Control Quality Criteria | Suggested Points/Study | Points Given | Max Score |
|------------------------------------------------|------------------------------|------------------------|--------------|-----------|
| Single Variant Analysis                          | Variant Detection Methodology  | 0-5                    | 0 | 0 | 0 | 12 |
| Aggregate Variant Analysis                       | Power                         | 0-5                    | 0 | 0 | 0 |          |

| Total Genetic Evidence Points (Maximum 12)       | 0 | 0 | 0 | 12 |

### Experimental Evidence Summary

#### Evidence Category

| Evidence Type                        | Suggested Default | Suggested Range | Points Given | Max Score |
|-------------------------------------|-------------------|-----------------|--------------|-----------|
| [Function]                          | 0.5               | 0-2             | 0.5          | 0 | 0 | 0 | 2 | 1303546 |
| [Protein Interaction]               | 0.5               | 0-2             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| [Expression]                        | 0.5               | 0-2             | 0.5          | 0 | 0 | 0 | 2 | 1303546 |
| Patient Cells                       | 1                 | 0-2             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Non-Patient Cells                   | 0.5               | 0-1             | 0.25         | 0 | 0 | 0 | 2 | 1303546 |
| Non-human model organism            | 2                 | 0-4             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Cell culture model                  | 1                 | 0-2             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Rescue                              | 2                 | 0-4             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Rescue in non-human model organism  | 2                 | 0-4             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Rescue in cell culture model        | 1                 | 0-2             | 0            | 0 | 0 | 0 | 2 | 1303546 |
| Rescue in Patient Cells             | 1                 | 0-2             | 0            | 0 | 0 | 0 | 2 | 1303546 |

| Total Experimental Evidence Points (Maximum 6) | 125         | 0 | 0 | 0 | 6 |

Summary: 1.25 | 0 | 0
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default Value | Con | Int | Hol | Max Score | PMIDs |
|---------------|------------------|-------------------------|-----|-----|-----|-----------|-------|
| Variant Evidence | Autosomal dominant disease, CHX-linked disease, affected males | Variant is disease causing | 2 | 0 | 0 | 0 | 12 | 2915747 |
| | | Proband with predicted or proven null variant | 15 | 0 | 0 | 0 | 10 | 2915747 |
| | | Proband with other variant types with some evidence of gene impact | 0.5 | 0.5 | 1 | 2 | 7 | 2915747 |
| | Autosomal recessive disease, CHX-linked disease, affected females | Two variants in frame, at least one is LOP or deleted | 2 | 0 | 0 | 0 | 12 | 2915747 |
| | | Two non-LOP variants in family | 1 | 0 | 0 | 0 | 12 | 2915747 |

### Segregation Evidence
- Evidence of Segregation in one or more families
  - Total LOD Score: 3
  - LOD: 2.289
  - LOD: 3.499
  - LOD: >5

### Case-Control Study Type
- Single Variant Analysis
  - Variant Detection Methodology: Power
  - Power: 0.5
- Aggregate Variant Analysis
  - Bias and Confounding Factors: Statistical Significance
  - Statistical Significance: 0.5

### Experimental Evidence Summary

| Evidence Category | Evidence Type | Suggested Default Value | Range | Points Given | Max Score | PMIDs |
|-------------------|--------------|-------------------------|-------|-------------|-----------|-------|
| Function          | Biochemical Function | 0.5 | 0.2 | 0 | 0 | 0.5 | 2915747 |
| | Protein interaction | 0.5 | 0.2 | 0 | 0 | 0 | 2915747 |
| | Transcriptional expression | 0.5 | 0.2 | 0 | 0 | 0 | 2915747 |
| Functional Alteration | Patient Cells | 1 | 0.2 | 0 | 0 | 0 | 2915747 |
| | Non-Patient Cells | 0.5 | 0.1 | 1 | 0 | 0.5 | 2915747 |
| Models             | Non-human model organism | 2 | 0.4 | 1 | 2 | 2 | 2915747 |
| | Cell culture model | 1 | 0.2 | 0 | 0 | 0 | 2915747 |
| Rescue             | Rescue in human | 2 | 0.4 | 0 | 0 | 0 | 2915747 |
| | Rescue in non-human model organism | 2 | 0.4 | 2 | 0 | 2 | 2915747 |
| | Rescue in cell culture model | 1 | 0.2 | 0 | 0 | 0 | 2915747 |
| | Rescue in Patient Cells | 1 | 0.2 | 0 | 0 | 0 | 2915747 |

### Total Evidence Points
- Total Genetic Evidence Points (Maximum 12): 3.5, 4, 5, 12
- Total Experimental Evidence Points (Maximum 5): 3.5, 4, 4, 6

**Summary**
- Total: 9
### Genetic Evidence Summary

| Evidence Type | Case Information | Suggested Default | Can | kA | Hol | Max Score | PMIDs |
|---------------|------------------|-------------------|-----|----|-----|-----------|-------|
| Autosomal dominant disease, DRX-linked disease, affected males | Proband with predicted or proven null variant with some evidence of gene impact | 15 | 0 | 0 | 0 | 10 | |
| Autosomal recessive disease, DRX-linked disease, affected males | Two variants in trans, at least one is LOF or frameshift | 2 | 0 | 0 | 0 | 3 | |

#### Case-Level Data

**Segregation Evidence**
- Evidence of Segregation in one or more families
- Candidate Gene Sequencing

#### Case-Control Study Type

| Case-Control Study Type | Case-Control Quality Criteria | Suggested points/study | Points Given | Max Score |
|-------------------------|-----------------------------|------------------------|--------------|-----------|
| Single Variant Analysis | Variant Detection Methodology | 0-6                    | 0            | 12        |
| Aggregate Variant Analysis | Base and Con founding Factors | 0-6                    | 0            | 0         |

**Total Genetic Evidence Points (Maximum 12):** 0 0 0 12

### Experimental Evidence Summary

#### Evidence Category

| Evidence Type | Suggested Default | Range | Points Given | Max Score |
|---------------|-------------------|-------|--------------|-----------|
| Function      | Biochemical Function | 0.5   | 0-2          | 2         |
|               | Protein Interaction | 0.5   | 0-2          | 2         |
|               | Expression        | 0.5   | 0-2          | 2         |
| Functional Alteration | Patient Cells | 1     | 0-2          | 2         |
|               | Non-Patient Cells | 0.5   | 0-1          | 2         |
| Models        | Non-human model organism | 2     | 0-4          | 4         |
|               | Cell culture model | 1     | 0-2          | 4         |
| Rescue        | Rescue in Human | 2     | 0-4          | 4         |
|               | Rescue in non-human model organism | 2     | 0-4          | 4         |
|               | Rescue in cell culture model | 1     | 0-2          | 4         |
|               | Rescue in Patient Cells | 1     | 0-2          | 4         |

**Total Experimental Evidence Points (Maximum 6):** 0 0 0 6

**Summary:** 0 0 0