Generate_G2P_document

Gene	***DSC2***
OMIM gene number	125645
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*DSC2*-related ARVC
MONDO ID	MONDO:0012506
Gene disease validity	DEFINITIVE
Inheritance	Autosomal recessive
Allelic requirement	Biallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice region variant, splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, inframe insertion, inframe deletion, splice acceptor variant NMD triggering, splice donor variant NMD triggering, frameshift variant NMD triggering, stop gained NMD triggering
PMIDs	31028357; 23911551; NBK1131; 21636032; 33831308; 26310507; 23863954; 24793512; 24070718; 34400560; 17033975; 17963498; 17186466; 20031616; 19863551; 31402444

Mechanism narrative

DSC2-related ARVC is due to decreased gene product level or altered gene product structure due to a variety of mechanisms (e.g. null alleles, trafficking defects, impaired proteolytic processing, absence of or impaired protein-protein interactions) (PMID: 31028357; 23911551; NBK1131).
Loss of function is the likely mechanism. ClinGen found there was some evidence to support haploinsufficiency as a mechanism. https://search.clinicalgenome.org/kb/gene-dosage/HGNC:3036
Autosomal dominant inheritance with incomplete penetrance is the most common mode of transmission (PMID: 21636032; 33831308). Homozygous and compound heterozygous variants have also been described associated with ARVC with or without cutaneous features (PMID: 26310507; 23863954; 24793512; 24070718; 34400560). In some cases, these appear to reflect autosomal recessive inheritance (PMID 24793512; 23863954, 33831308). Instances of digenic inheritance have been identified with *DSC2* variants along with other desmosomal gene pathogenic variants (PMID: 24070718).
A number of *DSC2* variants have been reported in the literature including nonsense, frameshift, splice, missense and in frame insertions and deletions (NBK1131; 17033975; 17963498; 17186466; 20031616; 19863551; 31402444).
DSC2-related ARVC appears to be characterised by an increased risk of biventricular involvement and heart failure when compared to PKP2-related ARVC (PMID: 34400560).

Gene	***DSG2***
OMIM gene number	125671
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*DSG2*-related ARVC
MONDO ID	MONDO:0012434
Gene disease validity	DEFINITIVE
Inheritance	Autosomal dominant
Allelic requirement	Monoallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, inframe insertion, inframe deletion, stop gained NMD triggering, stop gained NMD escaping
PMIDs	21636032; 33831308; 33917638; 34400560; 24070718; 30454721; 25616645; 30790397; 34400560; 16505173; NBK1131; 27532257; 16823493; 27170944

Mechanism narrative

DSG2-related ARVC is due to decreased gene product level or altered gene product structure due to a variety of mechanisms. Much of the underlying pathogenesis of *DSG2* pathogenic variants is still unknown; it is believed that loss of *DSG2* compromises cell-to-cell adhesion between cardiomyocytes (PMID:26085008; NBK1131). There is also work revealing that desmosomal variants can reduce canonical Wnt signalling and activating Wnt with a GSK3B inhibitor can block disease pathogenesis (PMID 16823493; 27170944).

The usual mode of inheritance is autosomal dominant characterized by reduced penetrance (PMID: 21636032; 33831308). Compound heterozygous and homozygous variants have been described. In some families, heterozygous carriers of these variants were not affected suggesting autosomal recessive inheritance (PMID: 33917638; 34400560; 24070718; 33831308; 30454721). Patients with >1 variant appear to have a more severe phenotype (PMID: 25616645; PMID: 30790397).

The majority of *DSG2* variants are rare missense variants with unknown significance/unknown mechanism of pathogenicity. In addition, nonsense, frameshift, insertions, deletions, and splice site variants have all been described (PMID: 16505173; NBK1131; 30790397; 27532257; 33917638).

DSG2-related ARVC appears to be characterised by an increased risk of biventricular involvement and heart failure when compared to PKP2-related ARVC (PMID: 34400560; 30790397).

Gene	***DSG2***
OMIM gene number	125671
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*DSG2*-related ARVC
MONDO ID	MONDO:0012434
Gene disease validity	DEFINITIVE
Inheritance	Autosomal recessive
Allelic requirement	Biallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, inframe insertion, inframe deletion, stop gained NMD triggering, stop gained NMD escaping
PMIDs	21636032; 33831308; 33917638; 34400560; 24070718; 30454721; 25616645; 30790397; 34400560; 16505173; NBK1131; 27532257; 16823493; 27170944

Mechanism narrative

DSG2-related ARVC is due to decreased gene product level or altered gene product structure due to a variety of mechanisms. Much of the underlying pathogenesis of *DSG2* pathogenic variants is still unknown; it is believed that loss of *DSG2* compromises cell-to-cell adhesion between cardiomyocytes (PMID:26085008; NBK1131). There is also work revealing that desmosomal variants can reduce canonical Wnt signalling and activating Wnt with a GSK3B inhibitor can block disease pathogenesis (PMID 16823493; 27170944).

The usual mode of inheritance is autosomal dominant characterized by reduced penetrance (PMID: 21636032; 33831308). Compound heterozygous and homozygous variants have been described. In some families, heterozygous carriers of these variants were not affected suggesting autosomal recessive inheritance (PMID: 33917638; 34400560; 24070718; 33831308; 30454721). Patients with >1 variant appear to have a more severe phenotype (PMID: 25616645; PMID: 30790397).

The majority of *DSG2* variants are rare missense variants with unknown significance/unknown mechanism of pathogenicity. In addition, nonsense, frameshift, insertions, deletions, and splice site variants have all been described (PMID: 16505173; NBK1131; 30790397; 27532257; 33917638).

DSG2-related ARVC appears to be characterised by an increased risk of biventricular involvement and heart failure when compared to PKP2-related ARVC (PMID: 34400560; 30790397).

Gene	*DSP*
OMIM gene number	125647
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*DSP*-related ARVC
MONDO ID	MONDO:0011831
Gene disease validity	DEFINITIVE
Inheritance	Autosomal dominant
Allelic requirement	Monoallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, inframe insertion, inframe deletion, splice donor variant NMD triggering, frameshift variant NMD triggering, stop gained NMD triggering
PMIDs	32372669; 23137101; 21636032; 33831308; 31319917; 20716751; 23810894; 24503780; 27532257; 31514951; 27761164; 21636032; 32808748; 33275305; 11063735; 27761164; 20940358; 22795705; 26604139; 30382575

Mechanism narrative

DSP-related ARVC is due to decreased gene product level or altered gene product structure.
The disease mechanism is loss of function via haploinsufficiency, dominant negative or both (PMID 32372669; 23137101; 16917092; NBK1131).
DSP-related ARVC is inherited in an autosomal dominant manner characterized by reduced penetrance (PMID: 21636032; 33831308). However, *DSP* is associated with multiple phenotypes which are heterogeneous and often overlapping (including DCM, DCM with cutaneous features, ARVC, and Carvajal syndrome) and autosomal recessive inheritance has been reported. There does not appear to be distinct mechanisms leading to different phenotypes
https://search.clinicalgenome.org/kb/gene-dosage/HGNC:3052.
The initial variant description in *DSP* was done in Carvajal syndrome characterized by woolly hair, keratoderma and ARVC. In 2000 three families from Ecuador were found to be homozygous for the variant 7901delG in *DSP* which produces a premature stop codon leading to a truncated desmoplakin protein missing the C domain of the tail region (PMID 11063735). Since then both autosomal dominant and autosomal recessive patterns of inheritance have been described in Carvajal syndrome (PMID: 27761164; 20940358; 22795705; 26604139; 23137101). This was followed by the description of a heterozygous variant in *DSP* in an Italian family with ARVC with co-segregation of the variant with disease. There have been reports of digenic inheritance with other desmosomal pathogenic variants.
In a retrospective multicentre study, curly hair and/or thick skin on the palms or soles (palmoplantar keratoderma) was commonly present in *DSP* patients (54/98, 55pct) but not in PKP2 patients (1/46, 2pct) (PMID: 32372669). Maruthappu et al 2019 also describe 38 patients with arrhythmogenic cardiomyopathy who were carriers of a dominant loss-of-function (nonsense or frameshift) variants in *DSP*. Nearly all were found to have curly hair and palmoplantar keratoderma. However, there was one family described where the majority did not demonstrate a curly hair/cutaneous phenotype. The variant in this family was located in a fragment (c.3585–5379, (p.1195–1793)) only included in isoform 1 of *DSP* (it has previously been shown that isoform 2 is the major isoform regulating keratinocyte adhesion (PMID: 30382575).
Both truncating (stop gained, frame shift, splice site) and non truncating variants in *DSP* have been reported in the literature associated with ARVC (PMID 31319917; 20716751; 23810894; 24503780; 27532257; 31514951; 27761164; 21636032; 32808748). Pathogenic truncating variants are more common.
Grondin et al 2020 re-evaluated reported missense variants and found an enrichment localizing to the spectrin repeat domain (SRD) in cases vs gnomAD. A similar hot spot location (amino acid residues 250-604) was reported by Kapplinger et al in 2011 (PMID: 32808748; 21636032). Smith E et al 2020 report that *DSP* variants are associated with a distinct type of cardiomyopathy with a high prevalence of LV inflammation, fibrosis, and systolic dysfunction, and *DSP* cardiomyopathy should be considered in the differential diagnosis for myocarditis and sarcoidosis (PMID: 32372669).

Gene	*DSP*
OMIM gene number	125647
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*DSP*-related ARVC
MONDO ID	MONDO:0011831
Gene disease validity	DEFINITIVE
Inheritance	Autosomal recessive
Allelic requirement	Biallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, inframe insertion, inframe deletion, splice donor variant NMD triggering, frameshift variant NMD triggering, stop gained NMD triggering
PMIDs	32372669; 23137101; 21636032; 33831308; 31319917; 20716751; 23810894; 24503780; 27532257; 31514951; 27761164; 21636032; 32808748; 33275305; 11063735; 27761164; 20940358; 22795705; 26604139; 30382575

Mechanism narrative

DSP-related ARVC is due to decreased gene product level or altered gene product structure.
The disease mechanism is loss of function via haploinsufficiency, dominant negative or both (PMID 32372669; 23137101; 16917092; NBK1131).
DSP-related ARVC is inherited in an autosomal dominant manner characterized by reduced penetrance (PMID: 21636032; 33831308). However, *DSP* is associated with multiple phenotypes which are heterogeneous and often overlapping (including DCM, DCM with cutaneous features, ARVC, and Carvajal syndrome) and autosomal recessive inheritance has been reported. There does not appear to be distinct mechanisms leading to different phenotypes
https://search.clinicalgenome.org/kb/gene-dosage/HGNC:3052.
The initial variant description in *DSP* was done in Carvajal syndrome characterized by woolly hair, keratoderma and ARVC. In 2000 three families from Ecuador were found to be homozygous for the variant 7901delG in *DSP* which produces a premature stop codon leading to a truncated desmoplakin protein missing the C domain of the tail region (PMID 11063735). Since then both autosomal dominant and autosomal recessive patterns of inheritance have been described in Carvajal syndrome (PMID: 27761164; 20940358; 22795705; 26604139; 23137101). This was followed by the description of a heterozygous variant in *DSP* in an Italian family with ARVC with co-segregation of the variant with disease. There have been reports of digenic inheritance with other desmosomal pathogenic variants.
In a retrospective multicentre study, curly hair and/or thick skin on the palms or soles (palmoplantar keratoderma) was commonly present in *DSP* patients (54/98, 55pct) but not in PKP2 patients (1/46, 2pct) (PMID: 32372669). Maruthappu et al 2019 also describe 38 patients with arrhythmogenic cardiomyopathy who were carriers of a dominant loss-of-function (nonsense or frameshift) variants in *DSP*. Nearly all were found to have curly hair and palmoplantar keratoderma. However, there was one family described where the majority did not demonstrate a curly hair/cutaneous phenotype. The variant in this family was located in a fragment (c.3585–5379, (p.1195–1793)) only included in isoform 1 of *DSP* (it has previously been shown that isoform 2 is the major isoform regulating keratinocyte adhesion (PMID: 30382575).
Both truncating (stop gained, frame shift, splice site) and non truncating variants in *DSP* have been reported in the literature associated with ARVC (PMID 31319917; 20716751; 23810894; 24503780; 27532257; 31514951; 27761164; 21636032; 32808748). Pathogenic truncating variants are more common.
Grondin et al 2020 re-evaluated reported missense variants and found an enrichment localizing to the spectrin repeat domain (SRD) in cases vs gnomAD. A similar hot spot location (amino acid residues 250-604) was reported by Kapplinger et al in 2011 (PMID: 32808748; 21636032). Smith E et al 2020 report that *DSP* variants are associated with a distinct type of cardiomyopathy with a high prevalence of LV inflammation, fibrosis, and systolic dysfunction, and *DSP* cardiomyopathy should be considered in the differential diagnosis for myocarditis and sarcoidosis (PMID: 32372669).

Gene	***PKP2***
OMIM gene number	602861
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*PKP2*-related ARVC
MONDO ID	MONDO:0012180
Gene disease validity	DEFINITIVE
Inheritance	Autosomal dominant
Allelic requirement	Monoallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	Typified by reduced penetrance
Disease-associated variant consequence	decreased gene product level, altered gene product structure
Variant classes reported with evidence of pathogenicity	splice region variant, splice acceptor variant, splice donor variant, frameshift variant, stop gained, missense variant, splice acceptor variant NMD triggering, splice donor variant NMD triggering, frameshift variant NMD triggering, stop gained NMD triggering
PMIDs	33831308; 21636032; 23736219; 34120153; 30830208; 25616645; 24070718; 17010805; NBK1131; 30619891; 24704780; 28740174; 22781308; 20301310; 17041889

Mechanism narrative

PKP2 pathogenic variants cause ARVC through decreased gene product level or altered gene product structure. *PKP2* encodes plakophilin-2 which is a protein of the desmosome and provides structural and functional integrity to adjacent cells. Mechanism in ARVC is loss of function (LoF). Rasmussen et al showed that truncating variants in *PKP2* resulted in *PKP2* transcript and protein levels reduced to around 50pct (PMID: 24704780). Cerrone et al showed that loss of *PKP2* in adult myocytes was sufficient to generate an arrhythmogenic cardiomyopathy of RV predominance in mice (PMID: 28740174)
PKP2 is the major causative gene for ARVC and accounts for 34pct-74pct of cases (PMID: 20301310).
Inheritance is predominantly autosomal dominant characterised by variable expression and incomplete penetrance (PMID: 34120153; 21636032; 17010805).
Both recessive and digenic inheritance (with one pathogenic variant in *PKP2* and a second in another desmosomal gene) have been reported (including a recessive cryptic splice variant PMID 17041889) and appear to confer a more severe phenotype (PMID: 30830208; 25616645; 24070718; NBK1131). The expert panel noted instances where *PKP2* LoF variants on both alleles had resulted in neonatal lethality.
There are over 250 *PKP2* variants listed in ClinVar for ARVC (nonsense, frameshift, splice, missense, deletions, duplications and complex rearrangements (PMID: 30619891; 25616645; 21636032; 34120153).
Dries et al report that *PKP2* truncating variants explain a large proportion of ARVC but there is no clear relationship between their transcript position and their likelihood of disease association (PMID: 30619891). Although missense variants are associated with disease and validated with functional studies (PMID 22781308), their mechanism and overall impact in ARVC is not completely understood. The majority of missense variants on ClinVar are classified as variants of uncertain significance.

Gene	***TMEM43***
OMIM gene number	612048
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*TMEM43*-related ARVC
MONDO ID	MONDO:0011459
Gene disease validity	DEFINITIVE
Inheritance	Autosomal dominant
Allelic requirement	Monoallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	
Disease-associated variant consequence	altered gene product structure
Variant classes reported with evidence of pathogenicity	missense variant
PMIDs	20301310; 18313022; 21214875; 23812740; 24598986; 33831308; 21391237; 29980933; 25343256; 22725725; 32062046

Mechanism narrative

TMEM43-related ARVC is due to altered gene product structure.
Pathogenic variants in *TMEM43* are a rare cause of ARVC (PMID: 20301310).
The majority of genetic evidence comes from one founder missense variant, S358L (PMID 18313022; 21214875; 23812740; 20301310; 24598986; 33831308). This was originally identified on Newfoundland but subsequently was also found in other countries, USA, Germany, Denmark (PMID: 33831308; 18313022; 23812740). The variant occurs on "a common haplotype with those from Newfoundland, USA, and Denmark, suggesting that the mutation originated from a common founder. Examination of 40 control chromosomes revealed an estimated age of 1300-1500 years for the mutation, which proves the European origin of the Newfoundland mutation." (PMID 24598986)
Molecular mechanism is largely unknown. There is no evidence currently for haploinsufficiency (https://search.clinicalgenome.org/kb/gene-dosage/HGNC:28472).
Although ARVC is known to display variable penetrance, this particular founder variant appears to be more penetrant.
TMEM43-related ARVC is associated with a high risk of sudden cardiac death and characteristic clinical and electrocardiographic features (PMID: 32062046). Ventricular ectopy on Holter monitoring is commonly seen and can occur early in the natural history (PMID: 22725725).
PMID 21391237 described two patients with *TMEM43* heterozygous missense variants in Emery Dreifuss Muscular Dystrophy-related Myopathy. Other missense variants have been reported but their pathogenicity is debated.

Gene	*JUP*
OMIM gene number	173325
Referral indication	ARVC
Disease grouping	Arrhythmogenic Right Ventricular Cardiomyopathy
Disease name	*JUP*-related Naxos disease
MONDO ID	MONDO:0011017
Gene disease validity	STRONG
Inheritance	Autosomal recessive
Allelic requirement	Biallelic autosomal
Inheritance modifiers	
Cross cutting modifiers	
Disease-associated variant consequence	altered gene product structure
Variant classes reported with evidence of pathogenicity	missense variant, inframe deletion, frameshift variant NMD escaping
PMIDs	10902626; 32966140; 17924338; 2582031520031617; 25705887; 21673311; 11691526; 28098346; 15851108; 31402444; 20130592; 21320868; 8954745; 8858175

Mechanism narrative

JUP-related Naxos disease (ARVC, woolly hair and palmoplantar keratoderma) is due to altered gene product structure causing loss of function of *JUP* (PMID: 25705887; 21673311; 11691526; 10902626). *JUP* encodes the protein plakoglobin. Kaplan et al found that in 4 Naxos patients, Connexin43 expression at intercellular junctions was significantly reduced and mutant plakoglobin was expressed but failed to localize normally at intercellular junctions (PMID:15851108)

Inheritance is autosomal recessive. The initial nine patients described ranged in age from 7 to 41 years. Since then, more patients have been discovered carrying the disease with an estimate of 1:1000 in the population of the Greek islands. The disease has also been diagnosed in other countries (PMID: 32966140).

A homozygous 2bp deletion in plakoglobin (*JUP*), c.2157delTG, causing a frameshift and premature termination of the protein and expression of a truncated plakoglobin lacking 56 residues from the C terminus was described in 2000 (PMID:10902626). The truncated protein was identified on western blot. In 2017, a homozygous missense variant was described in 7 unrelated French Canadian individuals. All had typical hair and skin findings; 4/7 had ARVC presenting after 28 years (PMID: 28098346). The effect of this variant in the heterozygous state was not investigated. Two siblings of consanguineous parents were found to have a homozygous 3bp deletion in *JUP* c.901 903delGAG (p.Glu301del). Both had woolly hair and skin findings, only the older sister had ARVC and neither had palmoplantar keratoderma (PMID: 28098346).

In OMIM there have been reports of other types of homozygous variants (nonsense, splice, missense) in *JUP* causing overlapping phenotypes and segregating with disease. Data on biallelic LoF variants are sparse. In mice, generation of a null mutation of the plakoglobin gene by homologous recombination results in embryonic lethality (PMID: 8954745; 8858175). 2 reports in humans who had skin features but no obvious cardiomyopathy (PMID: 20130592; 21320868). In one, *JUP* expression in the skin was absent. Cardiac *JUP* expression was not directly measured to establish the consequence in the heart - not known whether variant allele was expressed, degraded, or rescued by alternate splicing.

To note dominant pathogenic variants in *JUP* have also been rarely described in association with ARVC. Asimaki et al reported a dominant variant in *JUP* in a German family with ARVC and no obvious cutaneous abnormalities (PMID: 17924338). Other studies have identified heterozygous missense variants however their pathogenicity is still debated (PMID 25820315; 20031617; 31402444).