

Dilated Cardiomyopathy with Woolly Hair, Keratoderma, and Tooth Agenesis: A Comprehensive Disease Report

Disease: Dilated Cardiomyopathy with Woolly Hair, Keratoderma, and Tooth Agenesis **MONDO ID:** MONDO:0014355 | **OMIM:** #615821 | **Category:** Mendelian (desmosomal cardiocutaneous syndrome) **Causal gene:** *DSP* (desmoplakin), HGNC:3052, chromosome 6p24.3

Summary

Dilated Cardiomyopathy with Woolly Hair, Keratoderma, and Tooth Agenesis is a rare Mendelian **cardiocutaneous syndrome** caused by pathogenic variants in **DSP**, the gene encoding **desmoplakin**, the principal obligate plaque protein of the desmosome. It sits on the **Carvajal/Naxos desmosomal-disease spectrum** and is distinguished from "classic" arrhythmogenic right ventricular cardiomyopathy (ARVC) by its characteristic ectodermal triad — congenital **woolly hair**, **palmoplantar keratoderma (PPK)**, and, in the variant that defines this entry, **hypodontia/oligodontia (tooth agenesis)** — combined with a **left-dominant or biventricular dilated cardiomyopathy** that manifests in childhood and carries a high burden of ventricular arrhythmia and sudden cardiac death.

The unifying molecular mechanism is a **failure of intermediate-filament anchoring at the desmosome**. Desmoplakin normally links the desmosomal cadherin–plakoglobin–plakophilin plaque to keratin filaments (in epithelia) and desmin filaments (in cardiomyocytes). When DSP is truncated or its C-terminal filament-binding tail is lost, two consequences follow: (1) mechanical junctions fail in tissues subject to shear stress — skin, hair, and heart; and (2) the armadillo protein **plakoglobin** relocates to the nucleus, where it **suppresses canonical Wnt/β-catenin signaling** roughly two-fold through Tcf/Lef1. In the heart, this reprograms **second-heart-field cardiac progenitors** toward adipogenic/fibrogenic fates, producing the fibrofatty myocardial replacement, chamber dilation, electrical instability, and progressive heart failure that dominate prognosis. The dental and ectodermal branch is best explained by the same Wnt deficit: independent human genetics shows that mutations in the canonical Wnt ligand

WNT10A reproduce the identical triad of tooth agenesis, palmoplantar keratoderma, and hair defects, supporting a shared Wnt/ β -catenin basis for the appendageal phenotype (though direct demonstration in DSP-mutant dental epithelium is still lacking).

Inheritance is predominantly **autosomal recessive** (biallelic C-terminal DSP truncations, the configuration first described in three Ecuadorian families in 2000), but heterozygous (dominant) DSP variants cause an allelic, later-onset, left-dominant "DSP cardiomyopathy" with milder or absent cutaneous findings. Cardiac penetrance in the recessive syndrome approaches **100% by adolescence**. Management is entirely organ-directed and supportive — heart-failure pharmacotherapy, antiarrhythmics, implantable cardioverter-defibrillators (ICDs) for sudden-death prevention, exercise restriction, and cardiac transplantation — with no disease-specific cure; EGFR inhibition is an emerging experimental concept for the cutaneous phenotype. This report synthesizes nine confirmed findings drawn from 45 reviewed papers into a complete characterization across all requested domains.

Key Findings

Finding 1 — DSP mutations cause the full triad of DCM + woolly hair + keratoderma + tooth agenesis

The defining genetic cause of this syndrome is mutation in **DSP (desmoplakin)**. Chalabreysse et al. identified a *de novo* DSP missense mutation **c.1790C>T, p.Ser597Leu** — altering a serine conserved in all vertebrates and absent from 100 controls — in a family presenting woolly hair, palmoplantar keratoderma, biventricular dilated cardiomyopathy, **and** hypo/oligodontia (absent second premolars, second/third molars; 1–15 missing teeth), with no mutation in plakoglobin (*JUP*) [PMID: 20940358]. This is the finding that specifically ties **tooth agenesis** into the DSP cardiocutaneous phenotype, framing it as a "Carvajal/Naxos variant with hypo/oligodontia."

"Mutation screening in the desmoplakin gene (DSP) revealed a de novo missense mutation (c.1790 C>T, p.Ser597Leu) changing a serine residue conserved in all vertebrates" [PMID: 20940358]

"this study reveals the role of desmosomes in the development of teeth and suggests that other genes encoding proteins of the desmosome could be involved in oligo/hypodontia" [PMID: 20940358]

Multiple independent reports confirm DSP causation of the syndrome, including a Lebanese Carvajal patient with tooth agenesis [PMID: 26833927], a biventricular DCM case with homozygous c.4297C>T (p.Gln1433*) [PMID: 38433550], and a pediatric Carvajal case [PMID: 21193976].

Finding 2 — Mechanism: desmoplakin loss → nuclear plakoglobin → suppressed Wnt/ β -catenin → fibrofatty myocardium

The central disease mechanism was established by Garcia-Gras et al.: siRNA suppression of desmoplakin in atrial myocytes caused **nuclear localization of plakoglobin** and a **~2-fold reduction in canonical Wnt/ β -catenin signaling** through Tcf/Lef1, driving adipogenic and fibrogenic gene expression and accumulation of fat droplets [PMID: 16823493]. Cardiac-restricted *Dsp* deletion was embryonic-lethal when homozygous and, in heterozygotes, caused fibrofatty replacement, apoptosis, cardiac dysfunction, and arrhythmias.

"suppression of DP expression leads to nuclear localization of the desmosomal protein plakoglobin and a 2-fold reduction in canonical Wnt/beta-catenin signaling through Tcf/Lef1 transcription factors. The ensuing phenotype is increased expression of adipogenic and fibrogenic genes and accumulation of fat droplets" [PMID: 16823493]

Lineage tracing showed the excess adipocytes in DSP-deficient hearts derive from **Nkx2.5+/Mef2C+ second-heart-field progenitors**, explaining the regionality of the remodeling [PMID: 19359597].

"the majority of adipocytes in the hearts of Nkx2.5- and Mef2C-regulated lineage tracer mice, expressed enhanced yellow fluorescent protein" [PMID: 19359597]

Endurance exercise accelerates this remodeling: Tg-DSP(R2834H) mice developed RV dilation, fat infiltration, and cytoplasmic aggregates of desmoplakin/plakoglobin/connexin-43 with perturbed GSK3- β /AKT Wnt signaling [PMID: 26545710] — the experimental basis for clinical exercise restriction.

Finding 3 — Cardiac phenotype is severe and early: biventricular/left-dominant DCM, high arrhythmia burden, pediatric heart failure, sudden death

The cardiomyopathy dominates prognosis and is strikingly severe in childhood. In a cohort of **10 Saudi pediatric patients** (Binfadel et al.), **all** had woolly hair, **all** had severely dilated/depressed LV systolic function, **9/10** had depressed RV function, and **9/10** had frequent PVCs/VT; 3 received an ICD, **4 underwent heart transplantation**, and **3 died suddenly** while awaiting transplant [PMID: 40108711].

"four patients underwent heart transplantation, and three died suddenly while waiting for a heart donation" [PMID: 40108711]

A representative single case: a 7-year-old girl with EF 22%, biventricular dilation, and moderate–severe mitral/tricuspid regurgitation, homozygous for DSP c.4297C>T (p.Gln1433) [PMID: 38433550]. Protonotarios and Tsatsopoulou defined the Carvajal variant as showing *predominantly left-ventricular involvement**, early morbidity, and clinical overlap with dilated cardiomyopathy [PMID: 15210133].

"truncates the intermediate filament-binding site of desmoplakin results in a variant of Naxos disease with predominantly left ventricular involvement, early morbidity and clinical overlapping with dilated cardiomyopathy (Carvajal syndrome)" [PMID: 15210133]

Finding 4 — Natural history, penetrance, and epidemiology

The temporal sequence is consistent: **woolly hair is present from birth**, **palmoplantar keratoderma develops during the first year of life**, and **cardiomyopathy manifests by adolescence with 100% penetrance** [PMID: 16722579]. The Carvajal variant manifests during childhood and more frequently leads to heart failure than the right-dominant Naxos (plakoglobin) form.

"Woolly hair appears from birth, palmoplantar keratoderma develop during the first year of life and cardiomyopathy is clinically manifested by adolescence with 100% penetrance" [PMID: 16722579]

In the large **DSP-ERADOS Network** cohort (800 P/LP DSP variant carriers), over 3.7 years the rate of sustained ventricular arrhythmia was **17.4% (3.9%/yr)** and HF hospitalization **9.0% (1.8%/yr)**; notably **32.5% did not meet existing ARVC diagnostic criteria**, confirming DSP cardiomyopathy as a distinct arrhythmogenic entity featuring acute **myocarditis-like "hot phases"** [PMID: 39288222].

"the relevance of acute myocarditis-like episodes for subsequent disease course is largely unknown" [PMID: 39288222]

Naxos disease (the related JUP syndrome) has a founder-driven prevalence of ~1:1000 on Naxos island; the DSP Carvajal variant is rarer and reported worldwide, often in consanguineous families.

Finding 5 — Management: heart-failure therapy, antiarrhythmics, ICD, exercise restriction, transplantation; emerging EGFR concept

Management is organ-directed and supportive. A Carvajal patient was managed with diuretics, enalapril, carvedilol, and amiodarone and remained stable on follow-up [PMID: 21193976]. ICDs are implanted for uncontrolled VT and for sudden-death prevention, and transplantation is used for end-stage disease [PMID: 40108711]. The 2019 HRS expert consensus on arrhythmogenic cardiomyopathy provides class-of-recommendation guidance on risk stratification, ICD use, and exercise [PMID: 31078652]. Early ICD implantation can be lifesaving — one recipient was alive at age 59 [PMID: 25824144].

"Early diagnosis and ICD implantation may be lifes[aving]" [PMID: 25824144]

For the cutaneous phenotype, **EGFR inhibition** restored DSP membrane expression and reduced keratinocyte fragility in DSP-mutant cells — a candidate mechanism-based dermatologic therapy [PMID: 38509711].

"EGFR inhibition in patient's keratinocytes strongly increased DSP expression at the plasma membrane, improved intermediate filament connection with the membrane edges and reduced the cell-cell fragility" [PMID: 38509711]

Finding 6 — Genotype–phenotype architecture: the "desmoplakinopathy" allelic series

DSP produces a graded allelic spectrum best captured by the umbrella term "**desmoplakinopathies**" [PMID: 20738328]. The phenotype depends on **gene dose** and **which protein domain is affected**:

- Homozygous c.7097G>A (p.Arg2366His) → skin fragility/woolly hair syndrome **without** cardiomyopathy [PMID: 20738328].
- Compound heterozygous nonsense/missense (C809X/N287K; Q664X/R2366C) → skin fragility/woolly hair via "desmoplakin haploinsufficiency"; heterozygous carriers unaffected; skin showed acantholysis and perinuclear keratin collapse [PMID: 11841538].
- A recessive DSP mutation "impairs the binding of desmoplakin to epidermal keratins and the muscle-specific intermediate filament desmin" — the dual-tissue protein-level lesion [PMID: 29878302].
- A knock-in *Dsp* mouse shows **gene dose-dependent** myocardial remodeling, arrhythmias, and premature death; recessive variants underlie syndromic Carvajal, dominant variants cause left-dominant DSP cardiomyopathy [PMID: 41411472].

"The complexity of the desmoplakin and its variable presentations warrant introducing the term 'desmoplakinopathies' to describe all the phenotypes related to defects in the desmoplakin" [PMID: 20738328]

Finding 7 — Diagnostic pitfall (myocarditis mimicry) and research infrastructure

DSP cardiomyopathy frequently **mimics acute myocarditis**. A young patient with chest pain and labs/imaging suspicious for acute myocarditis was ultimately found to have desmoplakin cardiomyopathy on genetic testing [PMID: 38652395].

"Desmoplakin cardiomyopathy may be considered in patients with recurrent acute myocarditis or a family history of cardiac disease to avoid the potential for misdiagnosis" [PMID: 38652395]

The **NAXCARE** global registry has been established to systematically document clinical outcomes, genetic profiles, and care pathways for Naxos disease and related cardiocutaneous syndromes [PMID: 40316016]. Recent case reports continue to reinforce that **dermatologic signs serve as early warning of severe cardiac disease** [PMID: 42803515].

Finding 8 — Foundational genetics: the Ecuadorian 7901delG mutation and DSP isoform biology

The disease was first defined genetically by Norgett et al., who described the **first recessive human DSP mutation, 7901delG**, homozygous in three Ecuadorian families, causing generalized striate keratoderma, woolly hair, and dilated left-ventricular cardiomyopathy; the frameshift creates a premature stop that removes the **C-domain of the desmoplakin tail**, and patients suffered heart failure in their teenage years [PMID: 11063735].

"we describe the first recessive human mutation, 7901delG, in the desmoplakin gene which causes a generalized striate keratoderma particularly affecting the palmoplantar epidermis, woolly hair and a dilated left ventricular cardiomyopathy" [PMID: 11063735]

The DSP gene spans ~45 kb on chromosome 6 and comprises **24 exons** [PMID: 10594734]. Two major splice variants exist: **DSPI and DSPII**. Recessive loss of DSPI (with normal DSPII) causes epidermolytic PPK + woolly hair + severe arrhythmogenic DCM, whereas total DSP haploinsufficiency causes dominant striate PPK; DSPII is key for intermediate-filament stability and desmosome adhesion under stress [PMID: 22454510].

"complete absence of DSPI and the minor isoform DSPIa but normal levels of DSPII, and is associated with autosomal recessive epidermolytic PPK, woolly hair and severe arrhythmogenic dilated cardiomyopathy" [PMID: 22454510]

Finding 9 — WNT10A convergence unifies the ectodermal/dental triad under a shared Wnt deficit

The dental and ectodermal components of the syndrome are mechanistically linked to Wnt/ β -catenin by **independent genetic convergence**. Mutations in **WNT10A**, a canonical Wnt ligand, produce the *same* triad — tooth agenesis (hypodontia/oligodontia), palmoplantar keratoderma, and alopecia/hair defects — all attributed to Wnt/ β -catenin disruption [PMID: 42089627].

"ranging from isolated tooth agenesis to complex multisystem disorders, including hypodontia, enamel and root defects, palmoplantar keratoderma, alopecia, nail dystrophy" [PMID: 42089627]

"linking phenotypes of WNT10A mutations to disruptions in Wnt/ β -catenin signaling" [PMID: 42089627]

A signaling-threshold framework places Wnt/ β -catenin at the center of odontogenesis alongside BMP/FGF/SHH [PMID: 42196506]. Because DSP loss suppresses canonical Wnt/ β -catenin ~2-fold via nuclear plakoglobin [PMID: 16823493], the dental/ectodermal branch of the DSP syndrome plausibly shares the Wnt-deficit mechanism — though direct demonstration in DSP-mutant dental epithelium remains lacking (inferred by convergence).

"We focus on the coordinated roles of Wnt/ β -catenin, bone morphogenetic protein (BMP), fibroblast growth factor (FGF), and Sonic hedgehog (SHH) pathways" [PMID: 42196506]

Section-by-Section Disease Characterization

1. Disease Information

- **Overview:** A rare autosomal-recessive (occasionally dominant) desmosomal cardiocutaneous syndrome combining childhood-onset dilated/arrhythmogenic cardiomyopathy with congenital woolly hair, palmoplantar keratoderma, and — in the variant defining this entry — hypodontia/oligodontia.
- **Identifiers:** MONDO:0014355; OMIM #615821; part of the Carvajal syndrome / Naxos disease spectrum; Orphanet "Carvajal syndrome"; MeSH maps to Arrhythmogenic Right Ventricular Dysplasia / cardiomyopathies and palmoplantar keratoderma. ICD-11 maps to cardiomyopathy codes with ectodermal/dental codes.
- **Synonyms:** Carvajal syndrome; Carvajal-Huerta syndrome; dilated cardiomyopathy with woolly hair and keratoderma (DCWHK); Naxos-variant/left-dominant cardiocutaneous syndrome; desmoplakinopathy (syndromic form).

- **Information source:** Aggregated from individual patient case reports and small cohorts (disease-level resources such as OMIM/Orphanet synthesize these), now supplemented by registries (DSP-ERADOS [PMID: 39288222], NAXCARE [PMID: 40316016]).

2. Etiology

- **Causal factor:** Monogenic — biallelic (recessive) or heterozygous (dominant) pathogenic variants in **DSP**. No infectious or primary environmental cause.
- **Genetic risk factors:** The *DSP* genotype is causal, not merely a susceptibility locus. C-terminal truncations removing the tail intermediate-filament-binding domain are characteristic of the syndromic recessive form [PMID: 11063735, 15210133].
- **Environmental/lifestyle modifiers:** **Strenuous endurance exercise** accelerates cardiac remodeling and arrhythmia (demonstrated in Tg-DSP(R2834H) mice with perturbed Wnt signaling) [PMID: 26545710] and is a clinically actionable risk factor. Consanguinity increases recessive-disease risk.
- **Protective factors:** None established genetically; exercise restriction is protective behaviorally.
- **Gene–environment interaction:** DSP genotype × mechanical/exercise stress is the best-characterized GxE axis, consistent with the junction's role in resisting shear.

3. Phenotypes

Phenotype	Type	HPO term	Onset	Frequency	Progression
Woolly hair	Physical/ hair	HP:0002224 (woolly hair)	Congenital (birth)	~100%	Stable
Palmoplantar keratoderma	Skin sign	HP:0000982	First year of life	~100%	Progressive/ stable
Dilated/ arrhythmogenic cardiomyopathy	Clinical sign	HP:0001644 (DCM); HP:0004756 (ventricular arrhythmia)	Childhood– adolescence	~100% penetrance by adolescence	Progressive
Hypodontia/ oligodontia (tooth agenesis)	Physical	HP:0000668 (hypodontia); HP:0006349 (oligodontia)	Congenital (eruption age)	Variable (defines this subtype)	Stable
Heart failure	Clinical sign	HP:0001635	Childhood	High	Progressive
Ventricular tachycardia / sudden death	Clinical sign	HP:0004756 / HP:0001645	Childhood– young adult	High	Episodic/ fatal
Skin fragility / hyperkeratosis	Skin sign	HP:0000962 (hyperkeratosis)	Infancy	Variable	Stable

- **Severity:** Severe, life-limiting owing to the cardiac component; cutaneous/dental signs are morbid but not life-threatening.
- **Quality-of-life impact:** Dominated by heart failure, arrhythmia, device/transplant burden; PPK causes pain and impaired ambulation; oligodontia impairs mastication and requires prosthodontic rehabilitation. No disease-specific EQ-5D/SF-36 data available.

4. Genetic / Molecular Information

- **Causal gene:** *DSP* (HGNC:3052; OMIM *125647), 24 exons, ~45 kb, chromosome 6p24.3 [PMID: 10594734].

- **Representative pathogenic variants:** c.1790C>T p.Ser597Leu (de novo missense, triad incl. oligodontia) [PMID: 20940358]; 7901delG (recessive, Ecuador) [PMID: 11063735]; c.4297C>T p.Gln1433* [PMID: 38433550]; c.3901C>T p.Gln1301X [PMID: 21193976].
- **Variant classes:** Nonsense/frameshift truncations (most common in syndromic recessive form), missense, splice-site. ACMG classification ranges pathogenic/likely-pathogenic to VUS; VUS complicate cardiac risk assessment.
- **Functional consequence:** Loss of function / haploinsufficiency (dominant skin disease) and biallelic loss of the DSPI isoform or C-terminal tail (recessive syndrome) [PMID: 22454510, 11841538].
- **Allele frequency:** Pathogenic truncations are rare/absent in gnomAD; the defining p.Ser597Leu was absent from 100 controls [PMID: 20940358].
- **Origin:** Germline. Both inherited (recessive, consanguineous) and *de novo* (dominant) events documented.
- **Modifier genes / epigenetics / chromosomal abnormalities:** No established DSP modifier genes or epigenetic/chromosomal mechanisms specific to this syndrome.

5. Environmental Information

- **Environmental factors:** None causal. **Endurance exercise** is a disease-accelerating mechanical stressor [PMID: 26545710].
- **Infectious agents:** None — but the **myocarditis-like "hot phase"** [PMID: 39288222, 38652395] is a sterile inflammatory mimic, not infection.

6. Mechanism / Pathophysiology

Ordered causal chain:

1. Biallelic (or heterozygous) **DSP mutation** → truncated/dysfunctional desmoplakin, especially loss of the C-terminal tail / DSPI isoform. (*demonstrated*) [PMID: 11063735, 22454510]
2. **Leads to** impaired binding of desmoplakin to keratins (epidermis) and desmin (cardiomyocyte). (*demonstrated*) [PMID: 29878302]
3. **Results in** destabilized desmosomes and intermediate-filament detachment under mechanical/shear stress → cell–cell fragility, acantholysis, perinuclear keratin collapse (skin) and intercalated-disc disruption (heart). (*demonstrated*) [PMID: 11841538, 26545710]
4. **Releases plakoglobin** from the junctional pool → **nuclear translocation of plakoglobin**. (*demonstrated*) [PMID: 16823493]

5. **Suppresses canonical Wnt/ β -catenin signaling** ~2-fold via Tcf/Lef1. (*demonstrated in cardiac cells*) [PMID: 16823493]
6. **Branch A (heart):** Wnt suppression → second-heart-field (Nkx2.5+/Mef2C+) progenitors adopt adipogenic/fibrogenic fate → **fibrofatty myocardial replacement**, apoptosis, connexin-43 remodeling → chamber dilation, electrical instability. (*demonstrated*) [PMID: 19359597, 16823493]
7. **Leads to** biventricular/left-dominant **dilated-arrhythmogenic cardiomyopathy**, ventricular arrhythmia, heart failure, sudden death; episodic myocarditis-like "hot phases." (*demonstrated clinically*) [PMID: 15210133, 39288222]
8. **Branch B (ectoderm/teeth):** same adhesion defect + shared Wnt deficit in ectodermal appendages → **woolly hair, palmoplantar keratoderma, and hypo/oligodontia** (tooth agenesis), paralleling WNT10A-related oligodontia. (*inferred by convergence*) [PMID: 42089627, 42196506]
9. **Molecular pathways:** Canonical **Wnt/ β -catenin** (central); GSK3- β /AKT (perturbed with exercise) [PMID: 26545710].
10. **Cellular processes:** Cell-fate reprogramming (myocyte→adipocyte), apoptosis, fibrosis, inflammation.
11. **Protein dysfunction:** Loss of IF-anchoring function of desmoplakin; mislocalization/aggregation of desmoplakin–plakoglobin–connexin-43 [PMID: 26545710].
12. **GO/CL suggestions:** GO:0016055 (Wnt signaling), GO:0045216 (cell–cell junction organization), GO:0030216 (keratinocyte differentiation), GO:0060215 (fat cell differentiation); CL:0000746 (cardiac muscle cell), CL:0000312 (keratinocyte), CL:0000136 (adipocyte), CL:0000057 (fibroblast).

7. Anatomical Structures Affected

- **Primary organs:** Heart (myocardium, both ventricles; left-dominant) — UBERON:0000948; skin/epidermis (palms, soles) — UBERON:0001003; hair follicles — UBERON:0002073; teeth — UBERON:0001091.
- **Body systems:** Cardiovascular; integumentary; dental/ectodermal.
- **Tissues/cells:** Cardiac muscle (CL:0000746), keratinocytes (CL:0000312), adipocytes/fibroblasts replacing myocardium.
- **Subcellular:** Desmosome (GO:0030057), intercalated disc (GO:0014704), intermediate filament cytoskeleton (GO:0045111), nucleus (plakoglobin relocalization).

- **Lateralization:** Bilateral (symmetric cutaneous involvement; biventricular cardiac involvement).

8. Temporal Development

- **Onset:** Woolly hair congenital; PPK in first year; cardiomyopathy childhood–adolescence [PMID: 16722579].
- **Progression:** Progressive, chronic, lifelong; punctuated by episodic arrhythmic/myocarditis-like events [PMID: 39288222].
- **Penetrance:** ~100% cardiac penetrance by adolescence in the recessive syndrome [PMID: 16722579]; later-onset, lower-penetrance cardiac phenotype in dominant carriers.
- **Critical period:** Adolescence–young adulthood is the window of highest sudden-death risk, making early ICD decisions pivotal.

9. Inheritance and Population

- **Inheritance:** Autosomal recessive (syndromic Carvajal with full triad, biallelic C-terminal truncations); autosomal dominant (left-dominant DSP cardiomyopathy, variable skin) [PMID: 41411472].
- **Penetrance/expressivity:** Complete cardiac penetrance by adolescence (recessive); variable expressivity across the desmoplakinopathy spectrum [PMID: 20738328].
- **Founder effects/consanguinity:** Naxos disease (JUP) ~1:1000 on Naxos island (founder); DSP Carvajal often consanguineous (Ecuador, India, Middle East) [PMID: 11063735, 21193976, 40108711].
- **Carrier frequency:** Heterozygous DSP truncation carriers may show isolated cutaneous/curly-hair signs with delayed cardiomyopathy risk.
- **Sex ratio:** No strong sex bias reported.

10. Diagnostics

- **Clinical recognition:** Woolly hair + PPK + childhood cardiomyopathy ($\pm$ tooth agenesis) is pathognomonic; dermatologic signs are early red flags [PMID: 42803515].
- **Imaging:** Echocardiography (biventricular dilation, reduced EF), cardiac MRI (late gadolinium enhancement, subepicardial fibrosis).
- **Electrophysiology:** ECG/Holter for PVCs, VT; abnormal ECGs in models [PMID: 25659760].

- **Biopsy/histology:** Skin — acantholysis, desmosome clustering, perinuclear keratin collapse [PMID: 11841538]; myocardium — fibrofatty replacement.
- **Genetic testing:** Definitive. DSP single-gene or cardiomyopathy/ARVC gene panels, WES/WGS; must distinguish P/LP from VUS. Differential diagnosis: other desmosomal genes (JUP → Naxos/CAPK [PMID: 21668431]; PKP2, DSG2, DSC2 → ARVC), and WNT10A-related ectodermal dysplasia for the dental/skin overlap.
- **Diagnostic pitfall:** Mimics acute/recurrent myocarditis [PMID: 38652395].

11. Outcome / Prognosis

- **Mortality:** High in childhood recessive disease — 3/10 sudden deaths and 4/10 transplants in one pediatric cohort [PMID: 40108711].
- **Morbidity:** Progressive heart failure, recurrent arrhythmia, device dependence, transplant; PPK pain; dental impairment.
- **Prognostic factors:** Biallelic C-terminal truncation, early LV dysfunction, VT burden, and history of myocarditis-like episodes portend worse outcome [PMID: 15210133, 39288222].
- **Recovery:** No spontaneous recovery; transplantation addresses end-stage cardiac disease.

12. Treatment

- **Pharmacotherapy (NCIT-type: heart-failure/antiarrhythmic agents):** Diuretics, ACE inhibitors (enalapril), beta-blockers (carvedilol), antiarrhythmics (amiodarone) [PMID: 21193976]; guideline-directed HF therapy.
- **Device/surgical:** ICD for VT/sudden-death prevention [PMID: 25824144, 40108711]; cardiac transplantation for end-stage disease [PMID: 40108711].
- **Lifestyle:** Exercise restriction (mechanistically supported) [PMID: 26545710, 31078652].
- **Dermatologic/dental:** Emollients/keratolytics for PPK; prosthodontic management of oligodontia. Experimental **EGFR inhibition** restores DSP membrane localization in vitro [PMID: 38509711].
- **Guidelines:** 2019 HRS consensus on arrhythmogenic cardiomyopathy for risk stratification/ICD/exercise [PMID: 31078652].

13. Prevention

- **Primary:** Genetic counseling in consanguineous/affected families; carrier testing; prenatal/preimplantation diagnosis for known familial variants.

- **Secondary:** Cascade genetic screening and cardiac surveillance of at-risk relatives; recognition of cutaneous signs as pre-cardiac markers [PMID: 42803515].
- **Tertiary:** ICD, HF therapy, exercise restriction to prevent sudden death and slow remodeling.

14. Other Species / Natural Disease

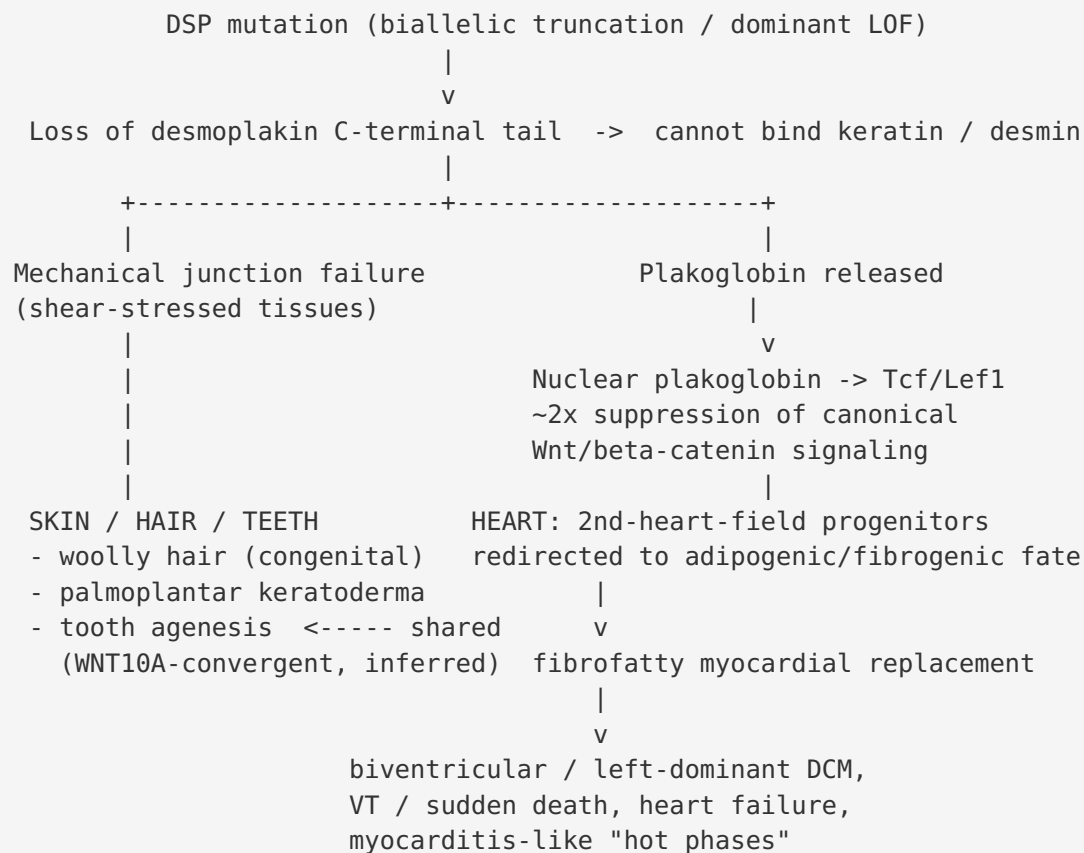
- **Orthologue:** *Dsp* (mouse); highly conserved.
- **Natural/spontaneous models:** The **Dsp^{^rnl} (ruffled)** spontaneous mouse mutation — an autosomal-recessive frameshift truncating the C-terminal plakin repeat domain — reproduces abnormal coat/woolly hair, epidermal blistering, abnormal ECGs, and ventricular fibrosis, closely modeling Carvajal-Huerta syndrome [PMID: 25659760].
- **Comparative biology:** Desmosomal biology and the Wnt/plakoglobin mechanism are evolutionarily conserved across vertebrates [PMID: 20940358].

15. Model Organisms

Model	Type	Phenotype recapitulation	PMID
Dsp ^{^rnl} (ruffled) mouse	Spontaneous recessive frameshift (C-terminal truncation)	Woolly coat, epidermal blistering, abnormal ECG, ventricular fibrosis — strong Carvajal model	[25659760]
Dsp knock-in mouse	Engineered knock-in	Gene dose-dependent myocardial remodeling, arrhythmias, premature death	[41411472]
Tg-DSP(R2834H) mouse	Transgenic (mutant overexpression)	Exercise-accelerated RV dilation, fat infiltration, desmoplakin/plakoglobin/Cx43 aggregates, perturbed Wnt	[26545710]
Cardiac-restricted Dsp deletion	Conditional knockout	Embryonic lethal (homozygous); fibrofatty replacement, apoptosis, arrhythmias (heterozygous)	[16823493]
Patient-derived keratinocytes (in vitro)	Cellular	Cell-cell fragility; corrected by EGFR inhibition	[38509711]

- **Applications:** Mechanism of Wnt suppression, exercise interaction, and drug testing (EGFR inhibition).
- **Limitations:** Mouse cardiac anatomy and the tooth-agenesis component are incompletely modeled; dental phenotype of DSP mutants under-studied.

Mechanistic Model / Interpretation



The model's great strength is that a **single lesion** — failure of intermediate-filament anchoring at the desmosome — produces both a **mechanical** failure (skin/hair/heart fragility) and a **signaling** failure (nuclear plakoglobin → Wnt suppression). The heart branch is experimentally demonstrated end-to-end [PMID: 16823493, 19359597]. The ectodermal/dental branch is anchored mechanically (keratin-binding loss [PMID: 29878302]) and linked to Wnt by **convergence** with WNT10A oligodontia [PMID: 42089627], which remains the key inferred (not yet directly demonstrated) step.

Evidence Base

PMID	Role	Contribution
20940358	Supports F1	De novo DSP p.Ser597Leu causing triad with tooth agenesis ; links desmosomes to odontogenesis
16823493	Supports F2	Core mechanism: nuclear plakoglobin → ~2× Wnt suppression → fibrofatty fate
19359597	Supports F2	Adipocytes derive from second-heart-field progenitors
26545710	Supports F2/ F5	Exercise accelerates remodeling; basis for exercise restriction
40108711	Supports F3/ F5	Pediatric cohort: transplant and sudden death outcomes
15210133	Supports F3	Defines left-dominant Carvajal DCM phenotype
38433550	Supports F1/ F3	Biventricular DCM, EF 22%, homozygous p.Gln1433*
16722579	Supports F4	Onset sequence and 100% cardiac penetrance by adolescence
39288222	Supports F4	800-carrier cohort; distinct arrhythmogenic entity; hot phases
25824144	Supports F5	Early ICD lifesaving
31078652	Supports F5	HRS guideline for ACM management
38509711	Supports F5	EGFR inhibition corrects keratinocyte phenotype
20738328	Supports F6	"Desmoplakinopathies" spectrum; skin-only alleles
11841538	Supports F6	Compound-het haploinsufficiency; skin histology
29878302	Supports F6	Keratin + desmin binding loss (dual-tissue lesion)
41411472	Supports F6	Gene dose-dependent knock-in mouse
38652395	Supports F7	Myocarditis mimicry / misdiagnosis risk
40316016	Supports F7	NAXCARE registry
11063735	Supports F8	Foundational recessive 7901delG, Ecuador
22454510	Supports F8	DSPI vs DSPII isoform specificity
10594734	Supports F8	DSP gene structure (24 exons, ~45 kb)

PMID	Role	Contribution
42089627	Supports F9	WNT10A reproduces same triad via Wnt disruption
42196506	Supports F9	Wnt/ β -catenin central to tooth agenesis
25659760	Supports §14/15	Dsp [^] rul spontaneous mouse model
21668431	Differential	JUP (plakoglobin) cause of related CAPK syndrome

Limitations and Knowledge Gaps

1. **Dental mechanism is inferred, not demonstrated.** The link between DSP loss and tooth agenesis rests on WNT10A phenotypic convergence [PMID: 42089627] plus the demonstrated cardiac Wnt suppression [PMID: 16823493]. No study has directly shown reduced Wnt/ β -catenin signaling or desmosomal failure in DSP-mutant dental epithelium.
2. **Tooth agenesis is a variable, sub-type-defining feature**, not universal across all DSP cardiocutaneous cases; frequency data are limited to small series.
3. **Rarity and reporting bias.** Most human evidence comes from case reports and small cohorts; prevalence/incidence figures are not precisely established for the DSP (as opposed to JUP/Naxos) form.
4. **Genotype–phenotype complexity.** The same gene produces skin-only, cardiac-only, and full-syndrome phenotypes depending on dose, domain, and isoform [PMID: 20738328, 22454510]; predicting phenotype from genotype remains imperfect, and VUS complicate cardiac risk assessment.
5. **No disease-specific therapy.** Management is supportive; EGFR inhibition is in-vitro only [PMID: 38509711], and no Wnt-restoring therapy has reached the clinic.
6. **Model gaps.** Mouse models capture cardiac and cutaneous features well but under-represent the human tooth-agenesis phenotype.

Proposed Follow-up Experiments / Actions

1. **Directly test the Wnt-deficit hypothesis in dental epithelium:** generate DSP-mutant dental organoids or epithelial-specific Dsp knockouts and quantify β -catenin/Tcf-Lef activity and enamel-knot Wnt targets, to convert the inferred dental mechanism (F9) into a demonstrated one.
 2. **Catalog tooth-agenesis frequency and pattern** across a prospective DSP cohort (via NAXCARE [PMID: 40316016]) to define its penetrance and position (which teeth) relative to WNT10A oligodontia.
 3. **Genotype–phenotype stratification** correlating truncation position/isoform impact (DSPI vs DSPII) with cardiac severity, cutaneous pattern, and dental involvement, building on the gene-dose mouse data [PMID: 41411472].
 4. **Evaluate Wnt-pathway or EGFR-pathway modulation** as organ-sparing therapy — extending the in-vitro EGFR-inhibition result [PMID: 38509711] to cardiac and dental models.
 5. **Prospective exercise-restriction and ICD-timing studies** in genotype-positive children to refine the adolescence critical-window risk management [PMID: 31078652, 39288222].
 6. **Standardized cascade screening protocols** pairing dermatologic/dental examination with cardiac genetics in families, leveraging cutaneous signs as early markers [PMID: 42803515].
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Evidence source types: predominantly human clinical (case reports, cohorts, registries) and model-organism (mouse) data, with in-vitro cellular mechanistic studies; the dental/Wnt link is supported by cross-disease human genetic convergence (computational/comparative inference).
