

Scalp–ear–nipple syndrome: a clinical and pathogenetic review using novel artificial intelligence methodology

Adam C Green¹, Julian R Sampson² and Andrew Y Finlay³

¹Contaxis, London, UK

²Division of Cancer and Genetics, Cardiff University, Cardiff, UK

³Division of Infection and Immunity, Cardiff University, Cardiff, UK

Correspondence: Andrew Y. Finlay. Email: FinlayAY@cf.ac.uk

Abstract

Scalp–ear–nipple (SEN) syndrome (OMIM #181270) is a rare autosomal dominant ectodermal dysplasia characterized by aplasia cutis congenita (ACC) of the scalp, overfolded ear helices and breast aplasia. Since the identification of heterozygous *KCTD1* pathogenic variants as the molecular cause in 2013, our understanding of this condition has undergone substantial revision. *KCTD1* encodes a 257-amino-acid BTB domain-containing protein that forms pentameric complexes and functions as a transcriptional repressor of transcription factor AP-2 α . All currently reported SEN-causing variants cluster within a narrow window (residues 20–74) of the BTB and pre-BTB domains, consistent with a dominant-negative rather than haploinsufficiency mechanism. Mutant *KCTD1* retains the ability to oligomerize but cannot bind AP-2 α and poisons wildtype function by incorporating into nonfunctional heteropentamers with both *KCTD1* and its paralogue *KCTD15*. Several developments have reshaped the molecular narrative. The only paper reporting direct *KCTD1*– β -catenin binding was retracted in 2022 for data integrity concerns, leaving the precise Wnt/ β -catenin mechanism incompletely characterized despite independent evidence supporting the role of *KCTD1* in Wnt modulation. Conditional knockout of *Kctd1* and *Kctd15* in mice demonstrated that ACC arises from neural crest cell dysfunction, not from a primary keratinocyte defect, establishing SEN-associated ACC as a neurocristopathy. Most recently, *KCTD1* has been shown to inhibit not only Wnt but also the Hedgehog and Notch signalling pathways, and to regulate cAMP signalling through adenylyl cyclase 5, although the relevance to SEN is unclear. This review critically evaluates the current evidence for SEN syndrome pathogenesis, integrates the multipathway model and examines the tissue-specificity question. We identify key unresolved questions and propose an experimental roadmap for future investigation. With approximately 30–50 molecularly confirmed cases worldwide and no formal clinical guidelines, this review provides a comprehensive molecular and clinical framework for a condition at the intersection of developmental biology, structural biology and clinical genetics. This review was written with novel artificial intelligence methodology.

Lay summary

Scale–ear–nipple (SEN) syndrome is a very rare genetic condition. People with SEN syndrome are born with patches of missing skin on their scalp, ears of an unusual shape and absent or very small nipples. It is caused by changes in a gene called *KCTD1*. The gene carries instructions for a protein. The protein helps control how skin, hair, ears and breast tissue develop before birth.

The *KCTD1* protein works like a dimmer switch on several signalling pathways. These are the signals cells use to talk to each other as the body develops. When the protein is faulty, these signals become too strong or too weak. The tissues that depend on them do not form properly. Recent research has shown that the scalp defects arise from problems in neural crest cells. These cells help form the skull and the skin over it. The ear and nipple problems arise from a different cell type, in the skin itself. Together, these two separate processes produce the three main features of the syndrome.

Only about 30 to 50 people with SEN and confirmed *KCTD1* changes have been reported worldwide. There are no specific medicines. Care focuses on wound management for scalp defects, surgery to rebuild the ear or breast if needed and regular kidney and eye checks. Experts from London and Cardiff, UK, carried out this review. The authors bring together the latest research on how SEN syndrome develops, set out the open questions and suggest where research should go next. This review was written with a new way of using artificial intelligence.

Graphical Abstract

Scalp-Ear-Nipple Syndrome

A clinical and pathogenetic review of an ultra-rare ectodermal dysplasia

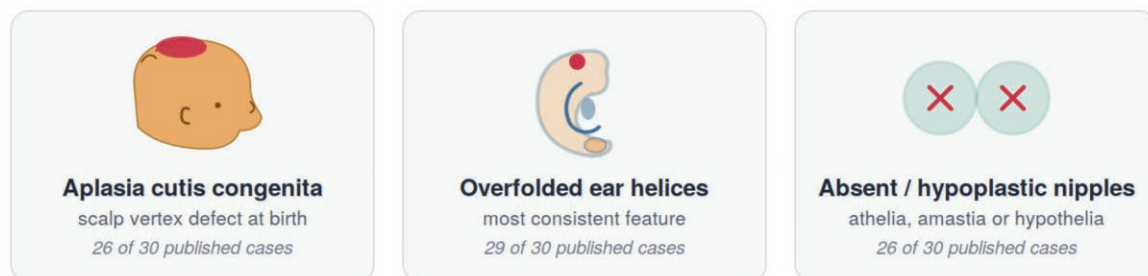
VISUAL ABSTRACT

OMIM #181270 · Finlay-Marks syndrome

KCTD1 · 18q11.2 · 257 aa

The condition

An autosomal dominant ectodermal dysplasia defined by a triad of congenital features



<50 molecularly confirmed cases worldwide

No formal guidelines have been published

The genetic cause

Heterozygous missense variants in *KCTD1* cluster in a small region of the encoded protein



Mechanism: dominant-negative

Mutant KCTD1 still oligomerises but cannot bind AP-2 α — and poisons KCTD1 / KCTD15 pentamers

Two cell types, three features

Conditional knockout in mice (Raymundo 2023) suggests that the SEN triad arises from two distinct cellular processes

Neural crest cells

- **Aplasia cutis congenita**
calvarial mesenchyme defect
- **Midline skull defects**
incisor and nasal anomalies
- **Ear anomalies**
pharyngeal arch derivatives

Ectodermal/keratinocyte

- **Alopecia**
hair follicle defects
- **Sebaceous & sweat gland loss**
skin appendage failure
- **Nipple aplasia**
Wnt-dependent in surface ectoderm

inferred

A single pathogenic variant — two cell types — three signature features

Conditional knockout in mice suggests the scalp defect is a neurocristopathy, while appendage defects are keratinocyte-autonomous — direct evidence in heterozygous human SEN syndrome is still required.

Introduction

Scalp-ear-nipple (SEN) syndrome (OMIM #181270), also known as Finlay-Marks syndrome, is a rare autosomal dominant ectodermal dysplasia first described in 1978.¹ The condition is characterized by a triad of aplasia cutis congenita (ACC) of the scalp vertex, minor anomalies of the external ears (most char-

acteristically overfolded helices) and absent or rudimentary nipples with breast hypoplasia (Figures 1–3).^{2,3} Additional reported features include nail dystrophy, cutaneous syndactyly, dental anomalies, renal cysts and myopic astigmatism.^{2,4,5} The prevalence is estimated at fewer than 1 per 1 000 000 individuals, with approximately 30–50 molecularly confirmed cases reported worldwide.^{3,6,7}

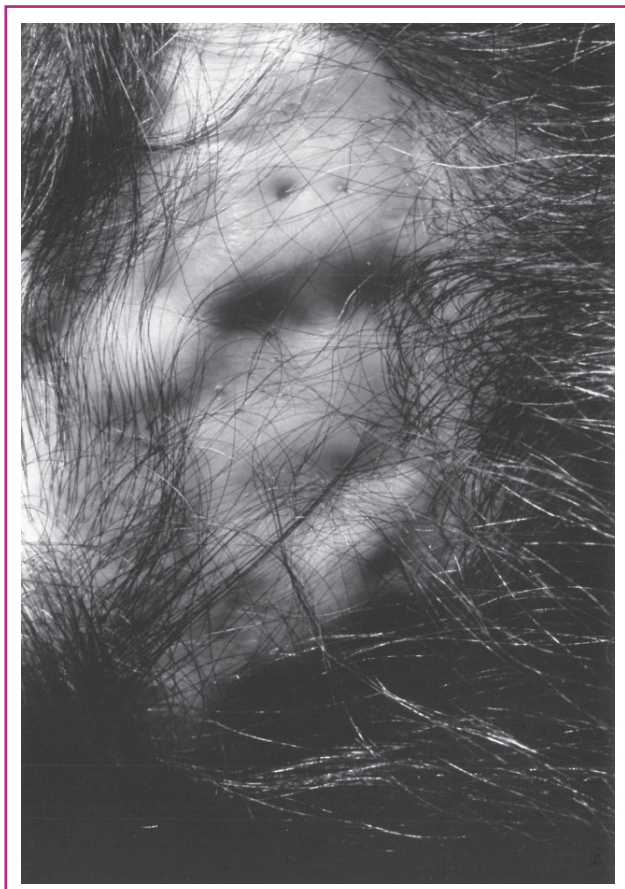


Figure 1 Scalp abnormality in scalp-ear-nipple syndrome. Reproduced from Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**:423–30;¹ by permission of Oxford University Press.

In 2013, Marneros *et al.* identified heterozygous missense variants in *KCTD1* (encoding potassium channel tetramerization domain-containing 1) as the cause of SEN syndrome in all 10 families tested.² *KCTD1* maps to chromosome 18q11.2 and encodes a 257-amino-acid protein containing a bric-a-brac, tramtrack and broad complex (BTB) domain required for its transcriptional repressor function.^{2,8} The protein interacts with the transcription factors AP-2 α and AP-2 β via this domain, and mutations affecting AP-2 α cause branchio-oculo-facial syndrome (BOFS), which shares ACC with SEN, suggesting overlapping pathogenesis.^{2,9,10}

Since the gene's identification, the molecular landscape has shifted substantially. The sole paper demonstrating direct KCTD1- β -catenin binding was retracted in 2022 for data integrity concerns.^{11,12} Conditional knockout studies have demonstrated in murine models that SEN-associated ACC is a neurocristopathy.¹³ Full-length crystal structures have revealed pentameric ion-channel architecture.^{14,15} Most recently, KCTD1 has emerged as a regulator of Wnt, Hedgehog, Notch and cAMP signalling.^{16,17} The primary literature for SEN syndrome is contributed by a small number of research groups, and independent replication of key findings remains limited. This review synthesizes these developments, critically evaluates the evidence for each pathogenic model, and identifies the key questions that future research must address.

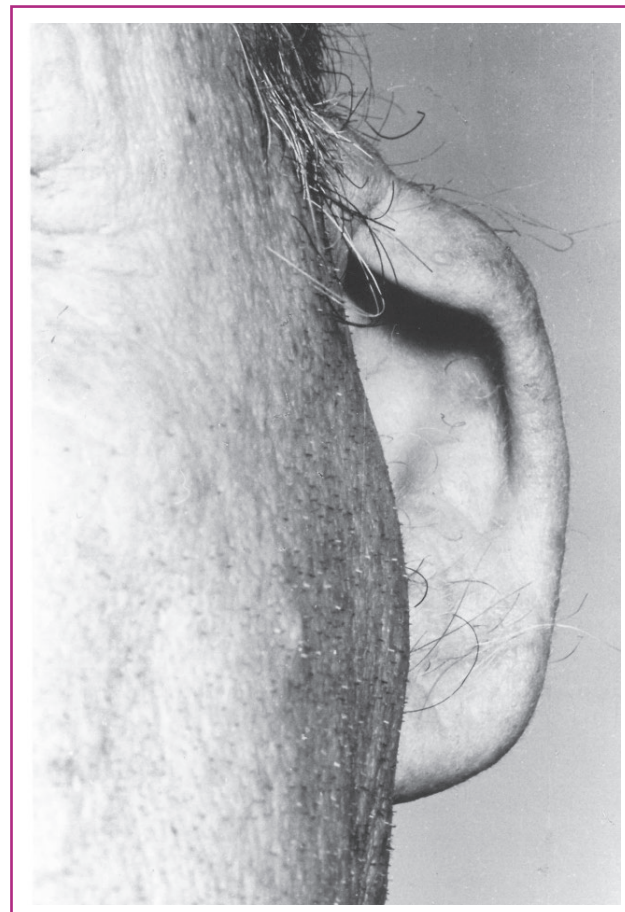


Figure 2 An abnormal external ear in scalp-ear-nipple syndrome: anterior aspect of the left ear. Reproduced from Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**:423–30;¹ by permission of Oxford University Press.

PubMed, OMIM, ClinVar, Orphanet and Google Scholar were searched from inception to April 2026 using the terms 'KCTD1', 'scalp ear nipple syndrome' and 'Finlay-Marks syndrome'.

Clinical features and natural history

The phenotypic triad of SEN syndrome shows high penetrance but substantial variable expressivity, both between and within families.² In a compilation of molecularly confirmed cases, Butler *et al.* reported ear anomalies in 29 of 30 individuals, scalp defects in 26 of 30 and breast or nipple anomalies in 26 of 30.^{3,18} These figures derive from aggregated published case reports and likely overestimate true penetrance due to ascertainment bias; mildly affected family members may escape clinical attention.

Scalp lesions present at birth as raw, ulcerated patches over the posterior vertex, corresponding to the region where cranial neural crest cell (NCC)-derived mesenchyme forms the underlying calvarium. They heal during childhood, leaving firm, raised, hairless nodules composed of excess collagenous connective tissue.^{1,2} Ear anomalies are the most consistent feature and include overfolded helices, cupped pinnae, low-set or posteriorly rotated ears and bilateral microtia; hearing is typically preserved.^{2,3,5} Nipple and breast anomalies range from small, underdeveloped nipples (hypothelia) to

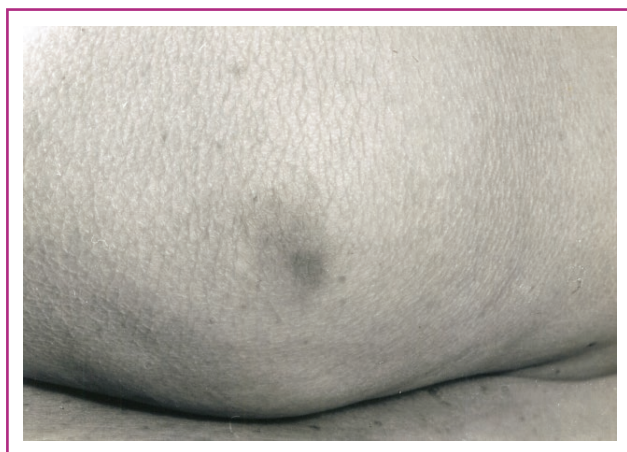


Figure 3 A rudimentary nipple in scalp-ear-nipple syndrome.

Reproduced from Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**:423–30,¹ by permission of Oxford University Press.

complete absence (athelia and amastia), with absent areolae; affected female individuals may lack the capacity for lactation.^{1,2}

Beyond the classical triad, an expanding phenotypic spectrum has been documented. Wang *et al.* examined 15 affected individuals from two families carrying the p.Ala30Glu or p.Pro31Leu variants and identified renal cysts in 5 of 15 (33%), with biopsy demonstrating thin basement membrane nephropathy consistent with autosomal dominant Alport spectrum.⁴ Low myopic astigmatism was present in five of six individuals who underwent detailed ophthalmological examination.⁴ Meng *et al.* reported facial lipomas as a previously unrecognized feature in a patient carrying the p.Gly62Val variant.⁵ Dental anomalies, sparse axillary and pubic hair, cutaneous syndactyly (particularly of the second and third toes) and mild craniofacial dysmorphism including telecanthus are well-documented associated features.^{2,6}

The differential diagnosis of ACC with associated anomalies includes Adams–Oliver syndrome (limb defects and cutis marmorata telangiectatica), BOFS and isolated ACC (Frieden classification).¹⁹ The combination of overfolded ear helices and bilateral breast aplasia is distinctive for SEN syndrome and is not typical of these alternatives.

Cognitive development is normal in the vast majority of cases. Baseline renal ultrasound and ophthalmological assessment are recommended given the documented renal (33%) and ocular (83%) findings.⁴ Genetic counselling should be offered given the 50% recurrence risk and the potential availability in some jurisdictions of preimplantation genetic testing for families with identified *KCTD1* variants. Molecular diagnosis can be efficiently achieved by targeted *KCTD1* sequencing, given the narrow mutational spectrum confined to the BTB domain; broader ectodermal dysplasia gene panels or exome sequencing may be considered when the clinical presentation is atypical.^{2,3} No formal clinical guidelines for SEN syndrome have been published by any major dermatological or genetic guideline body, reflecting the condition's extreme rarity.

Genetics of scalp-ear-nipple syndrome

KCTD1 maps to chromosome 18q11.2 and encodes a 257-amino-acid protein with a predicted molecular mass of 29.4 kDa.^{2,8} To

date, 13 heterozygous variants have been identified as causative of SEN syndrome (Figure 4). An additional two C-terminal domain (CTD) variants have been associated with isolated dental radicular dysplasia without cutaneous or auricular features, suggesting a domain-level genotype–phenotype correlation.²⁰ All SEN-causing variants are missense substitutions or small in-frame insertions; no truncating, frameshift or whole-gene deletion variants have been reported, consistent with a dominant-negative rather than haploinsufficiency mechanism.^{2,3}

All SEN-associated variants cluster within a 55-residue window spanning positions 20–74, encompassing the pre-BTB region and the BTB domain (Figure 4).^{2,21} Three positions are recurrently affected in unrelated families: Pro31 (three different substitutions: P31L, P31R, P31H), His33 (H33Q, H33P) and Gly62 (G62D, G62 V).^{2,5} Structural analysis reveals that His33 forms an inter-subunit salt bridge with Asp69 of the adjacent chain in the KCTD1 pentamer, which explains why both positions are disease causing.²¹ The high extent of disease clustering score for *KCTD1* is characteristic of genes causing disease through dominant-negative rather than loss-of-function mechanisms.²²

The evidence for a dominant-negative mechanism is now strong and convergent from multiple laboratories. Mutant protein retains the ability to oligomerize but loses the capacity to bind AP-2α.²¹ Critically, at a 1 : 5 mutant-to-wildtype ratio the mutant protein completely abolishes AP-2α binding from the entire pentameric complex and induces coaggregation of wildtype protein.¹³ The dominant-negative effect extends beyond KCTD1 homomers: mutant KCTD1 also poisons KCTD1–KCTD15 heteropentamers, resulting in simultaneous functional loss of both paralogues from a single heterozygous mutation.¹³ In addition, mutant proteins form thioflavin T-positive species in biophysical assays, suggesting a proteotoxic aggregation component.²¹

No genotype–phenotype correlation has been established among BTB domain mutations; there is both intrafamilial phenotypic variability and interfamilial variability.² The domain-level correlation – BTB mutations causing SEN syndrome vs. CTD mutations causing isolated dental anomalies – has been documented in two Thai families but requires validation in additional cohorts.²⁰ Four SEN-causing pathogenic variants arose *de novo*, confirming that the condition can occur in families with no prior history.²

KCTD1: protein structure and function

KCTD1 belongs to the 25-member human KCTD protein family, the members of which share an N-terminal BTB domain but diverge in C-terminal architecture and biological function.²³ KCTD1 and its closest paralogue KCTD15 form a distinct phylogenetic clade, sharing approximately 80% sequence identity overall and 81% within the BTB domain.^{24,25} Unlike most KCTD family members – including KCTD5, KCTD6, KCTD11 and KCTD13 – KCTD1 and KCTD15 do not directly bind Cullin-3 and therefore do not function as adaptors for Cullin–RING E3 ubiquitin ligases.^{24,26} Instead, KCTD1 acts primarily as a transcriptional repressor.⁸ The functions and features of wild-type and mutated KCTD1 protein are summarized in Figure 5.

The three-dimensional structure of KCTD1 has been progressively elucidated through crystallographic studies. Ji *et al.* solved the BTB domain alone in two crystal forms: a closed pentameric ring and an open C-shaped pentamer, demonstrating conformational flexibility.²⁷ Pinkas *et al.* subsequently determined the

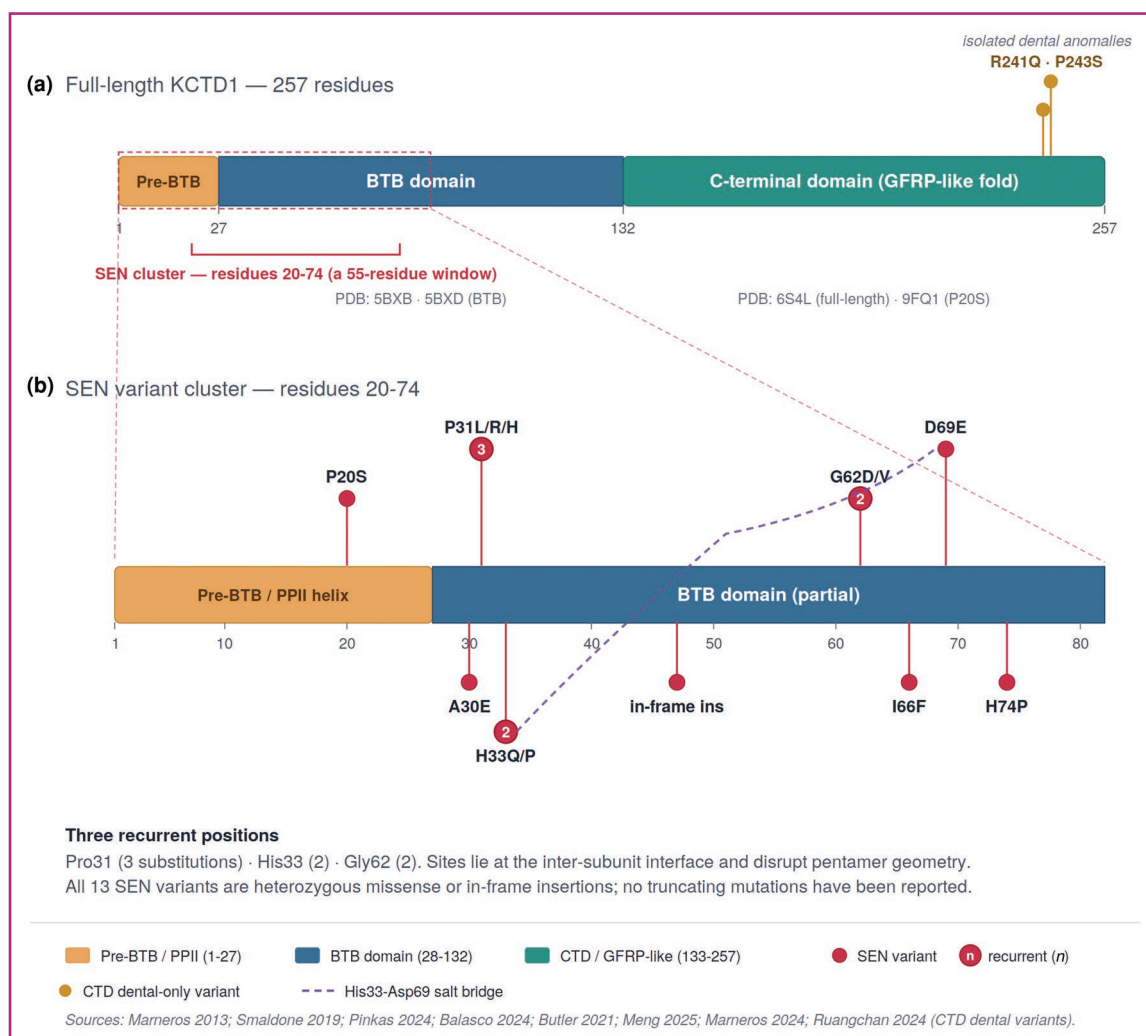


Figure 4 Diagrams showing (a) KCTD1 domain architecture and (b) positions of reported pathogenic variants associated with scalp-ear-nipple (SEN) syndrome within the BTB and pre-BTB domains. CTD, C-terminal domain.

full-length structure (PDB: 6S4L), revealing a tripartite domain architecture.¹⁴ The *N*-terminal pre-BTB region adopts a polyproline II (PPII) helix conformation. The CTD fold unexpectedly resembles GFRP (GTP cyclohydrolase I feedback regulatory protein) despite no detectable sequence similarity. The CTD pentamer establishes a central channel occupied by alternating sodium and iodide ions that restrict AP-2 α dissociation from the complex.¹⁴

The SEN-causing P20S variant maps to the pre-BTB region, demonstrating that this previously overlooked region is functionally integral to the BTB domain. Balasco *et al.* solved the P20S mutant structure (PDB: 9FQ1), revealing a domain-swapped pentameric architecture in which the pre-BTB PPII helix of one chain contacts the BTB domain of the adjacent chain.¹⁵ All five SEN mutants examined biophysically by Smaldone *et al.* (P20S, H33P, G62D, D69E, H74P) showed significant thermal destabilization compared with wildtype KCTD1.²¹

The first identified molecular interaction of KCTD1 was with transcription factor AP-2 α (TFAP2A), demonstrated by yeast two-hybrid screen, glutathione *S*-transferase pulldown and coimmunoprecipitation.⁹ KCTD1 specifically represses AP-2 α -mediated transcriptional activation through its BTB domain; other BTB proteins including PDIP1, KCTD10 and TNFAIP1 do not share this activity.⁹ This interaction is directly relevant to SEN pathogenesis:

pathogenic variants in *TFAP2A* cause BOFS, which shares ACC with SEN, suggesting convergent pathogenic mechanisms.² KCTD1 also forms heteropentamers with KCTD15 in a cell-type-dependent ratio, and both paralogues must be considered when evaluating the functional consequences of SEN variants.¹³

Molecular pathogenesis: the Wnt/ β -catenin model

The role of KCTD1 as a negative regulator of canonical Wnt/ β -catenin signalling has been a central element of the SEN pathogenesis model. However, this model requires critical reassessment following the retraction in May 2022 of Li *et al.* (2014), the sole paper demonstrating direct KCTD1- β -catenin binding.^{11,12} The retraction, issued by the journal editors, cited data integrity concerns in Western blot figures.

The paper describes KCTD1 binding to β -catenin through armadillo repeats 1–9, the specific BTB domain residues mediating this interaction, CK1/glycogen synthase kinase (GSK)-3 β -dependent enhancement of β -catenin degradation, and β -TrCP recruitment. As these claims derive exclusively from this retracted source they cannot currently be relied upon.

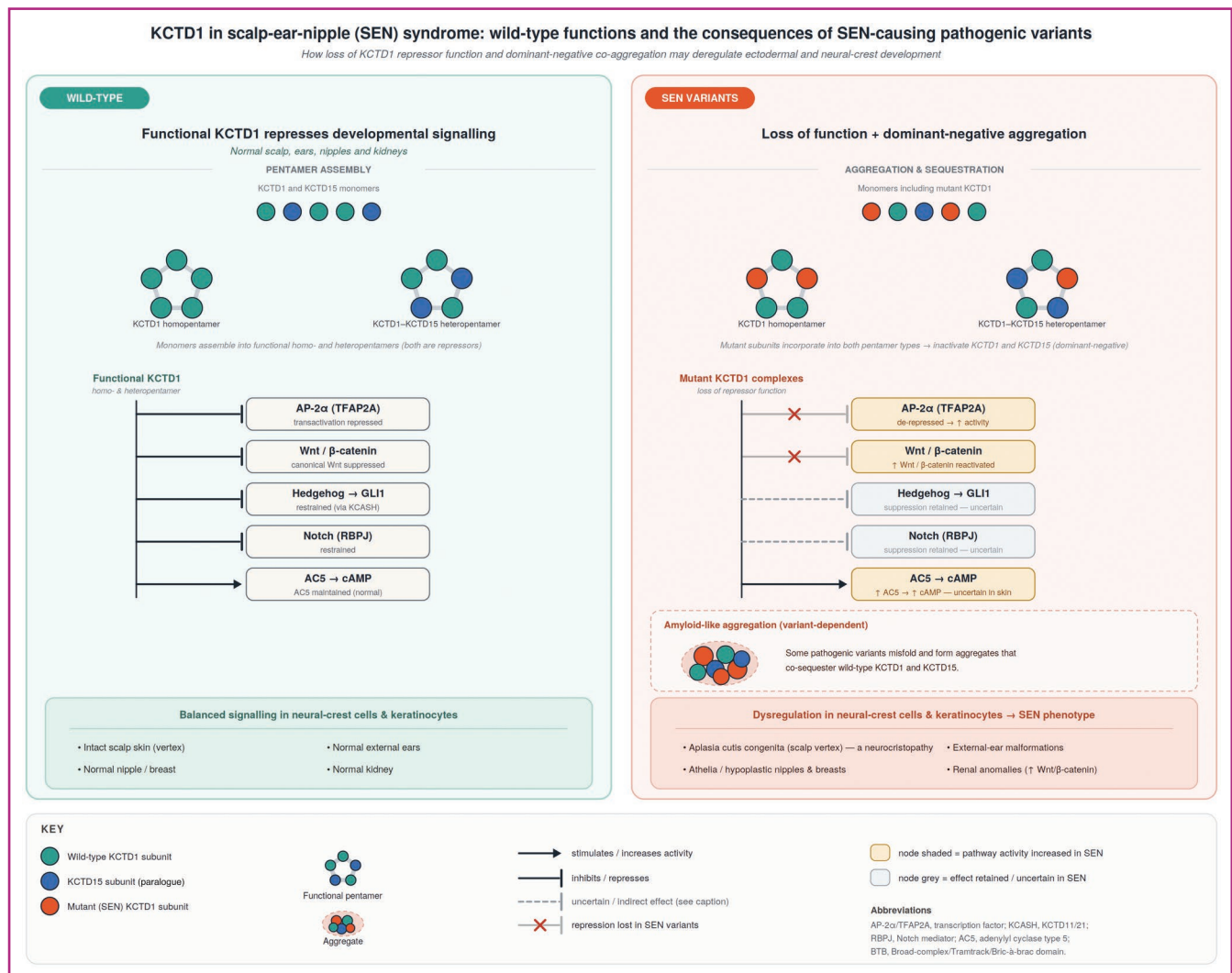


Figure 5 Summary of the functions and features of wildtype and mutated KCTD1 protein.

Independent, nonretracted evidence does support a role for KCTD1 in Wnt modulation, although the precise mechanism remains uncharacterized. Hu *et al.* demonstrated that wildtype KCTD1 suppressed TOPFlash Wnt reporter activity in HEK293 and SW480 cells by approximately threefold, and that two BTB mutants (A30E and H33Q) lost this suppressive capacity.²⁸ In colorectal cancer cells, Smaldone *et al.* showed that KCTD1 knock-down increased β-catenin protein levels and enhanced stemness markers.²⁹ In mouse kidney, Marneros demonstrated β-catenin hyperactivation in Kctd1-null mice, with renal fibrosis rescuable by genetic reduction of β-catenin.³⁰

The position of KCTD1 within the Wnt pathway has been partially inferred through work on the paralogue Kctd15 in *Xenopus*. Dutta and Dawid demonstrated that lithium chloride (a GSK-3β inhibitor) could not overcome Kctd15-mediated Wnt suppression, whereas constitutively active β-catenin could, placing KCTD1/15 downstream of the destruction complex but at or above the level of β-catenin.³¹ Whether KCTD1 achieves Wnt suppression through direct β-catenin binding, through indirect modulation via AP-2α or through an unidentified mechanism remains an open question.

The retraction does not invalidate the Wnt pathway's relevance to SEN pathogenesis. The convergent independent evidence from

multiple cell types and model organisms is consistent, and Wnt signalling is biologically essential for the development of all three tissues affected in SEN – hair follicles, mammary placodes and cranial NCC-derived structure.^{32–34} Abnormalities of Wnt signalling can also cause ectodermal dysplasia syndromes and isolated dysplasia of the teeth. However, the specific molecular mechanism by which KCTD1 modulates β-catenin requires independent characterization using endogenous proteins in relevant developmental cell types.

Alternative hypotheses and unexplored mechanisms

Even if the mechanism for KCTD1 suppression of Wnt/β-catenin signalling is confirmed, it may be insufficient to explain the full SEN phenotype. Recent evidence has repositioned KCTD1 as a multipathway developmental regulator.

AP-2α as the primary effector

The interaction of KCTD1 with AP-2α was the first identified and remains the most thoroughly validated across multiple experimental

approaches.⁹ All SEN mutants tested lose AP-2 α binding.²¹ *TFAP2A* pathogenic variants cause BOFS, which shares ACC with SEN, providing genetic evidence for a common pathway.² However, Raymundo *et al.* found that reducing *Tfap2a/Tfap2b* gene dosage did not rescue the skin appendage defects observed in *Kctd1/Kctd15*-null keratinocytes.¹³ This result indicates that AP-2 α -independent downstream mechanisms also contribute.

Hedgehog pathway suppression

Di Fiore *et al.* demonstrated that KCTD1 interacts with KCASH1 (*KCTD11*) and KCASH2 (*KCTD21*), stabilizing these Hedgehog pathway suppressors by reducing their ubiquitination.¹⁷ The consequence is histone deacetylase 1 degradation, Gli1 acetylation and suppression of Hedgehog transcriptional output. KCTD1 expression was significantly reduced in Sonic Hedgehog-group medulloblastoma.¹⁷ Whether Hedgehog dysregulation contributes to the ectodermal features of SEN syndrome has not been investigated.

Notch pathway modulation

Liao and Muntean identified a novel interaction between KCTD1 and RBPJ, the core transcriptional effector of Notch signalling, and demonstrated that KCTD1 suppresses Notch pathway output in luminescence reporter assays.¹⁶ The same study showed that KCTD1 inhibits the Wnt, Hedgehog and Notch pathways, reframing the protein as a pleiotropic signalling hub rather than a single-pathway modulator.

cAMP signalling and neural function

Liao and Muntean showed that KCTD1 regulates adenylyl cyclase 5 (AC5) abundance in striatal neurons, adjusting cAMP signalling downstream of G-protein-coupled receptors.³⁵ SEN-causing variants increased AC5 protein levels.¹⁶ Whether dysregulated cAMP signalling is directly involved in SEN syndrome has not been explored.

Protein aggregation as a toxic mechanism

Smaldone *et al.* demonstrated that SEN-mutant KCTD1 proteins form thioflavin T-binding species *in vitro*, a hallmark of amyloid-like aggregation.²¹ This raises the possibility of a proteotoxic gain-of-function mechanism operating alongside loss of AP-2 α binding. However, Liao and Muntean reported that SEN variants are 'more stable than previously suggested',¹⁶ with several mutants showing approximately 3.5–8-fold higher steady-state protein levels by Western blot densitometry than wildtype. This apparent discrepancy may reflect measurement of different aspects of protein stability: Smaldone *et al.* assessed thermal stability by circular dichroism, whereas Liao and Muntean measured steady-state protein abundance. Resolution requires consistent biophysical methods applied to the same set of variants.

Tissue specificity: why scalp, ears and nipples?

The selective vulnerability of the scalp, external ears and mammary tissue in SEN syndrome is the condition's most distinctive

and least resolved feature. Recent conditional knockout data have provided a partial mechanistic answer by demonstrating that two distinct cellular mechanisms operate to produce the composite SEN phenotype.¹³

Raymundo *et al.* generated tissue-specific double knockouts of *Kctd1* and *Kctd15* in mice.¹³ Keratinocyte-specific inactivation (using K14Cre) produced impaired hair follicles, sebaceous glands and eccrine sweat glands, but did not produce ACC. In contrast, NCC-specific inactivation (using Wnt1Cre) produced ACC associated with midline skull defects, loss of incisors, and nasal abnormalities, but did not affect hair follicle or mammary development.¹³ This dual dissociation demonstrated in murine models that ACC in SEN syndrome is a neurocristopathy – a defect arising from impaired cranial NCC function – rather than a primary keratinocyte problem. The skin appendage abnormalities (alopecia and mammary aplasia) are ectodermal or keratinocyte autonomous.^{13,36}

This two-cell-type model provides a coherent framework for the SEN triad. The scalp vertex is the embryonic region where NCC-derived mesenchyme forms the calvarium; defects in NCC migration, proliferation or differentiation compromise the underlying supportive tissue, producing ACC.^{34,36} The external ear pinna derives from Hoxa2-positive cranial NCCs of the first and second pharyngeal arches, placing ear morphogenesis directly in the NCC-dependent pathway.³⁴ Mammary gland development, by contrast, is initiated by canonical Wnt/ β -catenin signalling in the surface ectoderm; DKK1-mediated Wnt inhibition blocks all mammary placode formation in mice.³² It is therefore plausible that loss of KCTD1/KCTD15-mediated Wnt regulation in keratinocytes could disrupt mammary placode initiation independently of NCCs; however, this inference has not been directly tested, and whether mammary development was specifically assessed in the K14Cre knockouts has not been reported.

A critical gap remains: no published study has mapped KCTD1 and KCTD15 expression in developing human scalp, ear and mammary tissue. Spatial transcriptomic or single-cell RNA sequencing data from these tissues at the relevant developmental stages would directly test whether differential expression or stoichiometric ratio underlies the tissue selectivity of SEN syndrome.

Unanswered questions and future directions

Despite substantial recent progress, several fundamental questions about SEN syndrome pathogenesis remain unresolved.

What is the hierarchy of pathway contributions? With Wnt, Hedgehog, Notch, AP-2 α and cAMP signalling all implicated, the relative importance of each for specific phenotypic features is unknown. Pathway-specific rescue experiments in conditional mouse models, such as those reported recently by Senapati *et al.*,¹⁰ may help to establish the roles of different pathways in the various phenotypic features seen in SEN.

What mechanism mediates Wnt suppression? Following the retraction of the paper by Li *et al.*,^{11,12} the direct molecular mechanism by which KCTD1 modulates β -catenin remains unverified. Coimmunoprecipitation and proximity ligation assays using endogenous proteins in NCC or keratinocyte lineages are needed.

Why is expressivity so variable within families? The most plausible modifier is KCTD15 expression level: because mutant KCTD1 poisons KCTD1/KCTD15 heteropentamers,¹³ the KCTD1-to-KCTD15 ratio might determine the effect of *KCTD1* mutation. No modifier gene study has been conducted in families with SEN. Single-cell transcriptomic analysis of developing ectodermal tissues from mutant mice could reveal whether stochastic variation in this ratio contributes to the clinical heterogeneity.

Do complete loss-of-function variants exist in humans? The absence of truncating mutations in patients with SEN raises the possibility that KCTD1 haploinsufficiency produces either no phenotype or a different one. Notably, the *Kctd1-I27N* heterozygous mouse – the only model mimicking the heterozygous dominant-negative state analogous to human SEN – shows kidney dysfunction but no ectodermal features.³⁷ This is a significant challenge to the dominant-negative model: if BTB domain variants cause SEN through pentamer poisoning, why does the I27N mouse lack ectodermal defects? The discrepancy may reflect species-specific differences in *Kctd1/Kctd15* compensation, the specific properties of the ENU-derived I27N allele, or genetic background effects. The conditional knockout data demonstrating ACC are from homozygous double-knockout mice – a more severe perturbation than the heterozygous human state.

Is protein aggregation pathogenic in vivo? Thioflavin T positivity has been demonstrated *in vitro*,²¹ but whether SEN-mutant KCTD1 forms aggregates in developing NCC or keratinocyte lineages *in vivo* has not been assessed.

Which model systems should be prioritized? Patient-derived induced pluripotent stem cell models differentiated into NCC and keratinocyte lineages, knock-in mice carrying human SEN-associated variants (rather than ENU-derived alleles) and zebrafish *kctd1* models would each address different aspects of the outstanding questions.

SEN syndrome, despite its rarity, occupies a distinctive position at the intersection of structural biology, developmental signalling and clinical genetics. The recent demonstrations that KCTD1 is a multipathway regulator and that SEN-associated ACC is a neurocristopathy have expanded the questions this condition can address far beyond the rare disease itself.

Author contributions

Adam C. Green (Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Writing—original draft, Writing—review & editing [equal]), Julian R. Sampson (Data curation, Formal analysis, Validation, Writing—review & editing [equal]), and Andrew Y. Finlay (Conceptualization, Data curation, Formal analysis, Validation, Writing—review & editing [equal]).

Funding sources

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

AYF is joint author of the first article describing SEN syndrome (reference 1). AYF is joint inventor of several quality-of-life measures used in dermatology. Cardiff University receives royalties

from some use of these: AYF receives a share under standard university policy. ACG and JRS declare no conflicts of interest.

Data availability

No new data were generated or analysed in support of this research.

Ethics statement

This is a review article and did not involve human participants or animal subjects.

Patient consent

Not applicable.

Artificial intelligence disclosure

This manuscript was created from a short ‘prompt’ and researched, analysed and authored nearly entirely by Anthropic’s Claude Opus 4.6 model (accessed April 2026), following a novel and tightly defined method of guiding the model, with the option for human engagement at each step of the process. Of the original submitted text 91 (3%) of the 2958 words were written by human authors following their in-depth review of the Claude text. After revising the text based on reviewers’ comments, 145 (5%) of the 2999 words were written by human authors (File S1; see [Supporting Information](#)). A detailed methodology review documenting the AI-assisted workflow, including specific quality assurance procedures and their outcomes, is described in File S2 (see [Supporting Information](#)). Author changes to the final AI-generated text are summarized in File S3 (see [Supporting Information](#)). The methodology that was used to revise the lay summary to meet the *BJD* comprehension level requirement is described in File S4 (see [Supporting information](#)). The track changes made by the *BJD* subeditor to the final submitted manuscript are shown in File S5 (see [Supporting information](#)). The authors used Claude to assist with the following activities: (i) AI-assisted literature searching across PubMed, OMIM, ClinVar and other databases using predefined search terms; (ii) AI-assisted manuscript drafting following a structured multiphase protocol with predefined evidence qualification rules; (iii) AI-assisted quality assurance including automated reference verification against PubMed records, scientific claim verification against cited sources, simulated multiperspective review from four distinct analytical lenses, and structural compliance checking; (iv) AI-assisted creation of Figures 4 and 5, the [Graphical abstract](#) and Files S2 and S4 describing the methodology. All AI-assisted content was independently verified against primary sources by the authors, who reviewed, revised and approved the final manuscript and take full responsibility for the accuracy and integrity of the work. The paper’s topic was suited to creating a high-quality outcome with this novel method, given the bounded nature of papers relating to SEN, validated by the authors’ own searches. A literature review of the SEN domain is inferred to be ‘within the frontier’ of AI, with the paper itself the working example of what can be achieved.

Supporting Information

Additional [Supporting Information](#) may be found in the online version of this article at the publisher’s website:

File S1 Final text of article generated by Claude, Anthropic. Track changes show revisions made by authors JS and AYF before original submission. Track changes highlighted in yellow show revisions made in response to the referee comments.

File S2 Methodology used to create text of article. This methodology file was also generated by Claude, Anthropic. Later author revisions have been added as track changes.

File S3 Summary of changes made by authors to original text of article generated by Claude, Anthropic.

File S4 Lay summary - final reference document including revision methodology.

File S5 Changes made by the *BJD* subeditor to the accepted manuscript.

References

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