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WNT10A, dermatology and dentistry

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What’s already known about this topic?

- WNT signalling pathways are fundamentally important in human embryogenesis, organogenesis and tissue homeostasis.
- One WNT family member, WNT10A, has special relevance to dermatologists and dentists regarding its impact on skin, its appendages and teeth.
- Germline mutations in the WNT10A gene have been implicated in developmental disorders of skin, hair and teeth, particularly in forms of ectodermal dysplasia.
- Variants in WNT10A also may be associated with other ectodermal derivative impairments.

What does this study add?

- This review provides an update on the role of WNT10A in skin and tooth biology
- The spectrum of WNT10A variants that underlie specific diseases or population traits is defined.
- Phenotype-genotype correlation is defined for patients with monoallelic or biallelic WNT10A mutations.
- The clinical impact of WNT10A gene pathology in dermatology and dentistry is presented.
Summary:
WNTs are secreted glycoproteins that are involved in signalling pathways critical to organ development and tissue regeneration. Of the 19 known WNT ligands, one member of this family, WNT10A, appears to have specific relevance to skin, its appendages and teeth. This review focuses on how variants in the WNT10A gene have been associated with various ectodermal disorders and how such changes may have clinical relevance to dermatologists and dentists. Germline mutations in WNT10A underlie several forms of autosomal recessive ectodermal dysplasia in which heterozygous carriers may also display some lesser ectodermal anomalies. Within the general population, multiple heterozygous variants in WNT10A can cause skin, hair, sweat gland or dental alterations, also known as ectodermal derivative impairments. WNT10A variants have also been implicated in hair thickness, male androgenetic alopecia, hair curl, acne vulgaris, lipodystrophy, keloids, wound healing, tooth size, tooth agenesis, hypodontia, taurodontism and oral clefting. Beyond dermatology and dentistry, WNT10A abnormalities have also been identified in kidney fibrosis, keratoconus, certain malignancies (particularly gastrointestinal), and neuropathic pain pathways. In this review, we detail how WNT10A is implicated as a key physiological and pathological contributor to syndromic and non-syndromic disorders, as well as population variants, affecting the skin and teeth, and document all reported mutations in WNT10A with genotype-phenotype correlation.

Introduction
WNT (Wingless and INT-1) signalling is fundamental to almost every aspect of embryogenesis, organ development, tissue regeneration, and homeostatic self-renewal in many adult tissues, including skin and teeth. These signalling pathways (involving 19 different WNT glycoproteins and 7 receptors) modulate cell proliferation, cell survival, cell behaviour and cell fate. Inherited or somatic mutations in several WNT family members or their receptors have been implicated in many human diseases (Table S1).
Of particular interest to dermatologists and dentists is the wingless-type MMTV integration site family member 10A (WNT10A) gene because of its contribution to the development and maintenance of the skin, teeth and other ectodermal structures, as well as observations that mutations therein have been shown to underlie a range of ectodermal dysplasias (EDs) and related abnormalities (Fig. 1).

An association between WNT10A and human disease was first highlighted in 2006, with genetic linkage analyses implicating WNT10A in cleft lip/palate.\(^2\) Shortly afterwards, homozygosity mapping studies identified a homozygous nonsense mutation in odonto-onychoderma-dysplasia (OODD; OMIM 257980), the first form of an ED syndrome to be shown to result from altered WNT signalling.\(^3\) EDs are a heterogeneous groups of disorders occurring in ~7 in 10,000 live births but initial analysis in an unselected ED cohort indicated that WNT10A mutations might underlie ~9% of all cases, indicating that WNT10A pathology was relatively common in this group of disorders.\(^14\) WNT10A mutations were also identified in isolated or non-syndromic oligodontia and Schöpf-Schulz-Passarge syndrome (SSPS; OMIM 224750).\(^4\) Moreover, this study also demonstrated that ~50% of heterozygotes had a phenotypic manifestation, mainly affecting teeth and nails, with a sex-biased manifestation pattern (tooth anomalies more common in males).\(^4\) Further diversity in the skin phenotype for WNT10A mutations was subsequently demonstrated,\(^5\) with hypodontia, microdontia, taurodontism, hair abnormalities and nail dystrophy noted as core pathologies alongside variable observations of benign hair follicle and adnexal tumours.\(^5\) Mutations in WNT10A were also demonstrated in hypohidrotic/anhidrotic ED, with similar clinical appearances to cases involving mutations in EDA1, EDAR and EDARADD.\(^6\) Indeed, mutations in these 4 genes were shown to account for 90% of all cases of hypohidrotic/anhidrotic ED.\(^6\) Bi-allelic WNT10A mutations were also demonstrated in non-syndromic tooth agenesis (NSTA).\(^6\)

Following on from the observations of ectodermal anomalies in some heterozygous carriers of WNT10A mutations,\(^4\) attention then turned to whether WNT10A variants might be linked to phenotypic traits in the population. WNT10A variants were shown to be associated with hair curl,\(^7\) isolated hypodontia,\(^8\)-\(^10\) and non-syndromic oral cleft.\(^11,12\) Further phenotypic associations were demonstrated for variability in tooth morphology and hair shape,\(^13,14\) as well as misshapen molar crowns and roots,\(^15\) taurodontism,\(^16\) and keratoconus.\(^17\) Heterozygous
mutations in \textit{WNT10A} also underlying autosomal dominant agenesis of maxillary permanent canines.\textsuperscript{18} Of note, mutations in \textit{WNT10A} preferentially affect the permanent dentition rather than the primary dentition.\textsuperscript{19}

Further clinical observations showed that \textit{WNT10A} variants were frequently present in individuals with oligodontia associated with minor signs of ED,\textsuperscript{20} and that several individuals with minor ectodermal anomalies, termed ectodermal derivative impairments, had underlying heterozygous mutations in \textit{WNT10A},\textsuperscript{13} with the amino acid substitution p.Phe228Ile representing a common recurrent finding. Indeed, this variant is not uncommon in the general population with an allele frequency of 0.0137 (https://gnomad.broadinstitute.org/variant/2-219755011-T-A?dataset=gnomad_r2_1).

Regarding hair biology, \textit{WNT10A} has been shown to have a role in stem cell activation in the hair cycle,\textsuperscript{21} as well as being identified as a genetic risk locus for male androgenetic alopecia,\textsuperscript{22} but not in females.\textsuperscript{23} Variants in \textit{Wnt10a} have also shown to be involved in the quality of Cashmere wool production in goats.\textsuperscript{24} Moreover, \textit{WNT10A} has also been implicated in genetic susceptibility to severe acne vulgaris,\textsuperscript{25} and in aspects of wound healing and fibrosis, regulating collagen synthesis,\textsuperscript{26} contributing to keloid proliferation by regulating telomerase,\textsuperscript{27} and being involved in kidney fibrosis and acute interstitial nephritis,\textsuperscript{28} as well as diffuse systemic sclerosis.\textsuperscript{29} With regards to malignancy, certain \textit{WNT10A} variants have been associated with colorectal adenoma risk.\textsuperscript{30} \textit{WNT10A} has been shown to contribute to chemotherapy-induced neuropathic pain pathways.\textsuperscript{31}

Thus, over the last 15 years or so, several diseases and phenotypic traits have been associated with \textit{WNT10A} gene variants and mutations, many of which are relevant to dermatological and dental practice. This review therefore examines genotype-phenotype correlation for \textit{WNT10A} variation focusing on skin and teeth, particularly ED and NSTA.

\textbf{Materials and methods}

A comprehensive review of the PubMed database was undertaken for reports in English language from 1 January 1990 to 1 September 2020. We used the (i) MeSH terms: “Wnt Pathway”, “Wnt Pathway, Canonical”, “Wnt beta-Catenin Signaling Pathway” and (ii) keywords “\textit{WNT10A}”, “Wnt Pathway”. Dermatology conference abstracts were also included in the review.
Titles and abstracts were reviewed, and both references and citations of relevant studies were also examined for additional cases. The available data from each publication were assessed to identify patients with a genetic diagnosis involving a mutation/variant in \textit{WNT10A}. Cases without a genetic diagnosis were excluded. Only \textit{WNT10A} mutations in humans were included. Corresponding authors of articles included in the review were contacted for further information regarding the clinical and/or genetic information of their patients. For each case, we recorded demographics, mutation and protein analysis, phenotypic features involved and their associated Online Mendelian Inheritance in Man (OMIM) catalogue reference if available.\textsuperscript{12} Digenic mutations involving \textit{WNT10A} were also reviewed and included separately. Acquired (somatic) \textit{WNT10A} mutations, e.g. in malignancies, were not included and are beyond the scope of this review.

Results

A total of 287 relevant articles involving \textit{WNT10A} mutations were identified. Articles comprised single case reports, family pedigree case series, other clinical studies, and genetic analyses, including genome-wide association studies (Fig. S1; see Supporting Information). A total of 83 novel bi-allelic \textit{WNT10A} mutation cases were identified with 50 cases presenting within the clinical spectrum of ED and 33 cases presenting with NSTA (Table S2 and S3; see Supporting Information). Bi-allelic mutations causing ED were located across all exons (1-4) whilst mutations causing NSTA were predominantly located within exon 2 and 3 (Fig. S2; see Supporting Information). There were 10 mutations that were associated with phenotypic overlap, present in both ED and NSTA presentations.

\textit{Bi-allelic WNT10A mutations causing ED:}

Among the ED cases, there were 59 missense, 27 nonsense, 10 frameshift and 2 intronic splice site mutations in \textit{WNT10A} identified (45 novel mutations). Mutations c.682T>A (p.Phe228Ile) and c.321C>A (p.Cys107*) had the highest frequency of involvement, present in 12/50 and 9/50 cases, respectively. Phenotypic features of dental abnormalities/hypo-/oligodontia were present in 48/49 (98.0%) cases. Disruption of hair growth with hypotrichosis +/- sparse hair were noted in 44/49 (89.8%) cases, whilst skin anomalies including palmoplantar
keratoderma, plaques and xerosis were present in 39/47 (83.0%) cases. Additional features of hypo-/hyperhidrosis and multiple eyelid cysts were present in 27/44 (61.4%) and 15/48 (31.3%) cases, respectively. Scattered cases of reduced/absent tongue papillae were noted in 4/47 (8.5%) presentations. No phenotypic differences were noted between males and females with either homozygous or compound heterozygous mutations.

**Bi-allelic WNT10A mutations causing NSTA:**

Between the NSTA cases with bi-allelic mutations, there were 55 missense, 9 nonsense and 4 frameshift mutations identified (28 novel mutations). The median (lower quartile (25%, Q1), upper quartile (75%, Q3)) of teeth agenesis was 13 (6, 18) indicating severe oligodontia. Amongst the 33 cases, maxillary permanent central incisors were present in almost all cases (30/31; 96.8%). In contrast, maxillary permanent lateral incisors and mandibular 2nd premolars were only present in 7/31 (22.7%) and 9/31 (29.0%) of cases, respectively. Symmetry of agenesis was present in approximately half of cases (51.6%), with a positive family history of tooth pathology or agenesis found in 21/25 (84.0%) cases. Once again, the mutation p.Phe228Ile had the highest frequency, present in 15/33 (45.5%) cases.

**Mono-allelic WNT10A mutations causing a clinical phenotype:**

We noted several novel heterozygous WNT10A mutations (in trans with a wild-type WNT10A allele) that were responsible for the presentation of ED and/or NSTA (Table S4; see Supporting Information). NSTA, OOOD and SPSS presentations were noted in 27/39 (62.2%), 7/39 (17.9%) and 1/39 (2.6%) cases, respectively. Unclassified cases included additional findings such as delayed puberty, deafness, progressive scoliosis and clinodactyly, which may represent expansion of the clinical phenotype or unknown digenic inheritance patterns. Tooth agenesis was the most frequent finding, noted within 89.7% (35/39) of cases, followed by hair (33.3%), skin (30.8%) and nail (20.5%) involvement.

**Frequency of all known WNT10A mutations:**

In total, 564 cases of WNT10A mutations causing either OODD, SSPS, hypohidrotic/anhidrotic ED (HED/EDA) and/or NSTA were noted from published literature (Fig. 2). Mutational
hotspots included c.682T>A; p.Phe228Ile (173/564 cases; 30.7%), c.321C>A; p.Cys107* (76/564 cases; 13.5%) and c.637G>A; p.Gly213Ser (71/564 cases; 12.6%). Mutations causing NSTA were noted in 63.7% (359/564) of patients, followed by HED/EDA (16.1%), OODD (15.2%) and SSPS (5.0%). Of note, the highest frequency of mutations occurred in exons 2 and 3, whilst most single point mutations occurred in exon 4 (largest exon).

**WNT10A mutations in combination with mutations in other genes:**

Several reports also identified individuals having digenic inheritance involving WNT10A mutations and an additional gene mutation contributing to a complex phenotype. Digenic and modifier mutations and their associated clinical phenotype are presented in the Supporting Information (Table S5; see Supporting Information). Most presentations involved additional ED genes such as ectodysplasin A (EDA1; OMIM 305100), ectodysplasin A receptor (EDAR; OMIM 604095), or EDAR-associated death domain (EDARADD; OMIM 606603).

**Discussion:**

The data generated by this review highlight several key points. It is evident that bi-allelic mutations in WNT10A underlie several autosomal recessive forms of ED, as well as NSTA. The mutation data confirm that OODD and SSPS have both clinical and molecular overlap, in some cases with the same WNT10A mutations being documented in both disorders. Of note, p.Cys107* and p.Phe228Ile are the two most frequently seen mutations in each studied population, collectively accounting for ~20% of the total WNT10A pathology in these forms of ED, although neither have been reported in cases of hypohidrotic/anhidrotic ED. Furthermore, some of the same WNT10A mutations present in OODD/SSPS are also found in NSTA although, in general, the EDs tend to be associated with more nonsense mutations whereas missense mutations predominate in NSTA.

The study by Bohring *et al.* documented that ~50% of the heterozygous carriers of recessive WNT10A mutations had some clinical abnormalities, with hair/nail abnormalities more common in females and dental abnormalities more frequently seen in males. This sex-bias was also borne out in our literature review, although a much larger population study would be needed to confirm these findings. Notably, regarding the recurrent mutation p.Phe228Ile, the
gnomAD variant database (https://gnomad.broadinstitute.org) shows almost 3800 heterozygotes (out of 280,000 alleles), a frequency which provides an opportunity to assess penetrance and sex-bias to statistical depth. Nevertheless, p.Phe228Ile is just one of several heterozygous variants in \textit{WNT10A} which in some individuals could be manifesting with minor ectodermal anomalies or ectodermal derivative impairment. Based on ~50% penetrance, it is possible that 1 in every 400 or so people in the world could have such a phenotype, a statistic that has broad implications for accurate phenotyping of these and other dermatological and dental disorders. Indeed, we identified 27 cases in which \textit{WNT10A} variants might be contributing to or modifying the phenotype of another disorder – usually a form of ED, although this might be because of concomitant ED gene panel screening. These data have important implications for the accuracy of genotype-phenotype correlation in mutation screening in ED, i.e. there is a need to complete a comprehensive ED gene panel analysis before any conclusions on the precise molecular basis of ED in an individual case can be reached.

Thus, from a clinical perspective, the key points are that (a) bi-allelic \textit{WNT10A} mutations may result in autosomal recessive forms of ED and NSTA; (b) mono-allelic \textit{WNT10A} mutations may result in minor forms of ED, some autosomal dominant forms of tooth agenesis, or ectodermal derivative anomalies that may be prevalent in the general population; and (c) \textit{WNT10A} mutations may act as modifiers or digenic contributors in some cases of ED.

In some forms of ED, such as hypohidrotic ED caused by mutations in \textit{EDA}, progress towards new treatments, such as the use of recombinant replacement protein therapy, is developing.\cite{33} However, for \textit{WNT10A}, therapeutic options are less advanced. The creation of WNT-based therapies have been hampered by challenges in developing soluble, potent, and selective WNT molecules.\cite{34} Though challenging, initial studies have shown the successful development of selective WNT surrogates that have receptor specificity via ligand activation and offer a new avenue to facilitate functional studies of Wnt signalling and the exploration of Wnt agonists for translational applications in regenerative medicine.\cite{34,35} At present, however, there are no specific inhibitors or modifiers of \textit{WNT10A} although modification of Wnt signalling pathways involving \textit{WNT10A} have been studied in mouse models. Wnt10a-deficient mice demonstrate a critical \textit{in vivo} role in wound healing by regulating collagen
expression/synthesis, and topical Wnt inhibitors can reduce fibrosis and promote regenerative cutaneous wound repair. Moreover, it has also been shown that inhibition of the β-catenin-dependent Wnt pathway with topical application of small molecules (XAV 939 or pyrvinium) reduces fibrosis and promotes regeneration in full-thickness excisional wounds. Thus, although not a key component of the ED or NSTA phenotypes, future targeting of WNT10A may have relevance to improving wound healing in humans.

Concerning tooth bioengineering, Wnt signalling pathways are implicated in healing of dental pulp after injury or dental caries. Furthermore, the topical use of the Wnt signalling activator lithium chloride and GSK3β inhibitor Tideglusib have been shown to promote the formation of tertiary dentin in vivo. Studies researching these agents may therefore provide preliminary data to promote dentin formation, one of the crucial steps in tooth development.

In conclusion, within the biological complexity of Wnt signalling, the discovery of WNT10A mutations has provided major new insights into the molecular pathology of a range of developmental disorders. In the future, it is hoped that a more detailed understanding of the pathobiology of these conditions will advance regenerative medicine efforts to improve clinical management of ED, NSTA and related dermatological and dental diseases.
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**Figure Legends:**

**Figure 1:** Phenotypic features of *WNT10A* mutations associated with ectodermal dysplasia and non-syndromic tooth agenesis. (a) thin, sparse and fragile hair with apocrine hidrocystomas of the eyelids, (b) fingernail dystrophy/ dysplasia, (c) plantar keratoderma, fissures and scaling, (d) oral cavity showing a normal complement of primary dentition in a 12-year-old, although primary
incisors are barrel-shaped and microdontia, (e) upper jaw and (h) lower jaw showing oligodontia with only a few secondary teeth present, alongside dental implants in the same patient as (f) at 22 years old. Clinical images (a-c) provided by Tziotzios et al., 2014 and Nagy et al., 2010.

Figure 2: **WNT10A mutation database and phenotypes.** Adapted from Tziotzios et al., 2014. SSPS, Schöpf–Schulz–Passarge syndrome; OODD, odonto-onycho-dermal dysplasia; HED/EDA, Hypohidrotic or anhidrotic ectodermal dysplasia; NSTA, Non-syndromic tooth agenesis. Note that most mutations underlying cases of HED/EDA are found in the *EDA, EDAR* and *EDARADD* genes, rather than *WNT10A*. 
