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Nonsyndromic Tooth Agenesis Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding the genetic causes of nonsyndromic tooth agenesis (NSTA), inform genetic counseling of at-risk family members, and review management options.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of nonsyndromic tooth agenesis (NSTA).

Goal 2

Review the genetic causes of NSTA.

Goal 3

Provide an evaluation strategy to identify the genetic cause of NSTA in a proband (when possible).

Goal 4

Inform genetic counseling of family members of an individual with NSTA.

Goal 5

Review management of NSTA following diagnosis: evaluations, treatment, and surveillance.

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1. Clinical Characteristics of Nonsyndromic Tooth Agenesis

Tooth agenesis is a developmental anomaly characterized by the absence of one or more permanent teeth (excluding third molars) due to failure at the early stages of tooth development. The term nonsyndromic tooth agenesis (NSTA) refers to the condition in which tooth agenesis of permanent teeth is the only clinical finding.

Nomenclature. Tooth agenesis is also commonly referred to as:

- **Congenitally missing teeth.** This term is not entirely adequate since development of permanent teeth continues after birth and diagnosis of tooth agenesis is only possible at around age six years.
- **Hypodontia.** Agenesis of five or fewer teeth (excluding third molars)
- **Oligodontia.** Six or more teeth are missing (excluding third molars)
- **Anodontia.** All permanent teeth are missing; this is found almost exclusively in syndromic cases (see Table 2) [Hennekam et al 2010].

Diagnosis requires thorough clinical and radiographic examination to exclude impacted teeth and missing teeth due to caries or dental trauma.

- Missing teeth in the primary dentition is rare, however, a missing deciduous tooth is usually an indicator of NSTA of the respective permanent tooth.
- The presence of unusual spacing in a child's dentition should lead the pediatrician and the dentist to suspect NSTA. Diagnosis of NSTA can be confirmed by panoramic radiograph after age six years, when all of the permanent tooth buds (excluding third molars) should be visible in the radiograph.
- In adults, consultation of dental records at younger ages in addition to careful evaluation of edentulous spaces are advisable to evaluate for missing teeth due to extractions or as a consequence of periodontal disease [Hennekam et al 2010].
- In general, tooth agenesis tends to manifest unilaterally, and affects the maxilla and mandible at similar rates. The most commonly missing teeth (excluding third molars) are permanent mandibular second premolars, followed by maxillary lateral incisors, and maxillary second premolars.
- Bilateral agenesis of maxillary lateral incisors is also more common than unilateral.
- A thorough medical history and physical examination to assess for syndromic features that lead to NSTA and/or premature loss of teeth is also required (see Table 2) [Hennekam et al 2010].

Note: NSTA is a common feature in individuals with nonsyndromic cleft lip with/without cleft palate. Careful examination and evaluation of medical history should help determine the nonsyndromic nature of both findings.

Prevalence. The prevalence of NSTA has been reported to vary between 1.6% and 36.5% depending on what population is being studied and whether third molars are included in the missing teeth count [Polder et al 2004].

- In most studies, the prevalence of NSTA ranges from 3% to 10% in the mild form (hypodontia) whereas the more severe forms (oligodontia) show a prevalence of 0.1%-0.5%, excluding third molars.
- Tooth agenesis may have variable prevalence according to the population studied, with Asians being more commonly affected, followed by individuals of northern European background and African Americans.
  - A meta-analysis investigating the prevalence of NSTA, which included 33 studies from different populations worldwide, showed that the prevalence of NSTA in Europe was 5.5% higher and in Australia was 6.3% higher compared to the prevalence in North America, which was 1% [Al-Ani et al 2017].
  - The prevalence in the Japanese population was reported to be 8.5% [Endo et al 2006].
- The most frequently missing tooth types also vary by population; agenesis of lower incisors is more frequent in Asians than in other populations [Polder et al 2004].
- Females are more frequently affected than males with a 3:2 ratio [Polder et al 2004].

2. Causes of Nonsyndromic Tooth Agenesis

The etiology of nonsyndromic tooth agenesis (NSTA) is attributed to mutation of genes involved in craniofacial and tooth development in about 80% of affected individuals. In the remaining 20%, NSTA is attributed to exogenous factors (e.g., chemotherapy, radiation therapy, maternal rubella virus infection, and exposure to medications such as thalidomide and antineoplastic agents) early in life while permanent tooth buds are developing [Hennekam et al 2010].

Numerous genes and genetic variants have been implicated in the etiology of NSTA, most of which were suggested from syndromic forms or animal models (Table 1). Syndromic forms of tooth agenesis are commonly found in oral-facial cleft syndromes and ectodermal dysplasia syndromes [Phan et al 2016] (Table 2).

Traditionally, NSTA was considered a monogenic condition. Recently, several studies have suggested multilocus or oligogenic inheritance [Dinckan et al 2018b, Du et al 2018].

For many single genes associated with tooth agenesis, inter- and intrafamilial variability and reduced penetrance are common [Williams & Letra 2018]. Table 1 lists single genes in which at least two families have been identified to have NSTA after careful phenotyping. Some of these genes are associated with syndromic tooth agenesis (see Table 2) as well. It is likely that the genes that lead to apparent NSTA, but for which there is an allelic syndromic condition, are part of a spectrum with apparent NSTA at one end and syndromic features at the other end. However, it is important to realize that an individual with apparent NSTA can have a pathogenic variant in a gene that more traditionally has been associated with syndromic TA. Careful phenotyping for syndromic features after the identification of a pathogenic variant in one of these genes is recommended (see Management).

Table 1. Nonsyndromic Tooth Agenesis: Genes and Associated Dental Phenotypes

Gene	MOI	Dental Phenotype				Selected Allelic Syndromic Disorder(s) [1]
		Oligodontia	Hypodontia	Microdontia	Other	
AXIN2 [2]	AD		+			Oligodontia-colorectal cancer syndrome (OMIM 608615)
EDA	XL	+	+ (mandibular incisors, maxillary lateral incisors)			Hypohidrotic ectodermal dysplasia
EDAR	AD [3]	+	+ (mandibular second premolars)			
FGFR1	AD		+ (incisor & premolar agenesis)			Kallmann syndrome (See Isolated Gonadotropin-Releasing Hormone Deficiency.)
GREM2 [4]	AD		+	+	Taurodontism	
IRF6	AD		+ (incisor & premolar agenesis)			Van der Woude & popliteal pterygium syndromes (See *IRF6*-Related Disorders.)

Table 1. continued from previous page.

Gene	MOI	Dental Phenotype				Selected Allelic Syndromic Disorder(s) [1]
		Oligodontia	Hypodontia	Microdontia	Other	
LRP6 [5]	AD	+ (incisor & premolar agenesis)				AD coronary artery disease (OMIM 610947)
MSX1 [6]	(AD) [7]	+	+ (agenesis of permanent molars)			Witkop syndrome, Wolf-Hirschhorn syndrome, Pierre Robin syndrome
PAX9 [8]	AD	+	+ (agenesis of permanent 2nd molars followed by 2nd premolars)		Smaller tooth dimensions; agenesis of anterior teeth rarely reported	
WNT10A [9, 10]	(AD) [11] AR	+	+ (no particular preferential tooth type missing)		Taurodontism	Odonto-onycho-dermal dysplasia, Schöpf-Schulz-Passarge syndrome, hypohydrotic ectodermal dysplasia
WNT10B [12]	AD	+		+ (lateral incisor agenesis)		

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. See Table 2.

2. Haddaji Mastouri et al [2018]

3. Zeng et al [2017], Mumtaz et al [2020]; note that some forms of hypohidrotic ectodermal dysplasia are due to biallelic pathogenic variants in *EDAR* and are inherited in an autosomal recessive manner (see Table 2).

4. Kantaputra et al [2015], Magruder et al [2018], OMIM 617275

5. Massink et al [2015], Ockeloen et al [2016], Basha et al [2018], Ross et al [2019], Yu et al [2019], OMIM 616724

6. Paradowska-Stolarz [2014], OMIM 106600

7. Complex inheritance, mostly autosomal dominant

8. Murakami et al [2017], OMIM 604625

9. van den Boogaard et al [2012], Song et al [2014], Dinckan et al [2018b], Yuan et al [2017], OMIM 150400

10. The most common *WNT10A* pathogenic variant found in individuals with nonsyndromic tooth agenesis is c.682T>A (p.Phe228Ile), which is estimated to be present in about 3.43% of the general population [Vink et al 2014]. However, incomplete penetrance of the phenotype has been reported in heterozygotes with this variant [Yang et al 2015].

11. Complex inheritance has also been proposed (see Genetic Risk Assessment).

12. Yu et al [2016], Kantaputra et al [2018], OMIM 617073

Table 2. Disorders to Consider in the Differential Diagnosis of Apparent Nonsyndromic Tooth Agenesis

Gene	Disorder	MOI	Dental Phenotype	Other Features
Selected allelic disorders (i.e., disorders assoc w/genes also known to be involved in nonsyndromic tooth agenesis)				
AXIN2	Oligodontia-colorectal cancer syndrome [1] (OMIM 608615)	AD	Oligodontia (agenesis of molars, lower incisors & upper lateral incisors), odontomas	Osteomas, colorectal cancer
EDA *EDAR* *EDARADD* [2]	Hypohidrotic ectodermal dysplasia [3]	XL AR AD	Oligodontia, hypodontia, microdontia, anodontia, taurodontism, tooth malformation	Hypotrichosis, anhidrosis, hypohidrosis, possible mammary agenesis, frontal bossing, periorbital wrinkling & hyperpigmentation, depressed nasal bridge, prominent lips

Table 2. continued from previous page.

Gene	Disorder	MOI	Dental Phenotype	Other Features
FGFR1	Kallmann syndrome [4] (See Isolated Gonadotropin-Releasing Hormone Deficiency.)	AD	Oligodontia, hypodontia	Cleft lip/palate, anosmia, hypogonadism
IRF6	Van der Woude & popliteal pterygium syndromes (PPS) [5] (See *IRF6*-Related Disorders.)	AD	Hypodontia	In PPS, webbed skin of the legs, genital malformations, lip pits, orofacial clefts
MSX1 [6]	Wiktop syndrome [7] (Witkop type ectodermal dysplasia 3) (OMIM 189500)	AD	Oligodontia (2nd premolars & molars more affected), hypodontia	Nail dysgenesis, orofacial clefts
WNT10A	Odonto-onycho-dermal dysplasia [8] (OMIM 257980)	AR	Oligodontia, hypodontia, microdontia	Smooth tongue w/marked ↓ of fungiform & filiform papillae, keratoderma & hyperhidrosis of palms & soles, hyperkeratosis of the skin, onychodysplasia
	Schöpf-Schulz-Passarge syndrome [9] (OMIM 224750)	AR	Oligodontia, hypodontia, microdontia	Eyelid cysts, sparse & dry hair, dystrophic nails, dry skin, hyperkeratotic hand papules
	Hypohidrotic ectodermal dysplasia [3]	AD AR	Oligodontia, hypodontia, microdontia, anodontia, taurodontism, tooth malformation	Hypotrichosis, anhidrosis, hypohidrosis, possible mammary agenesis, frontal bossing, periorbital wrinkling & hyperpigmentation, depressed nasal bridge, prominent lips
Genes that preliminary research data suggest may also be assoc w/isolated nonsyndromic tooth agenesis (but insufficient data to state this definitively)				
ANTXR1	Optic atrophy syndrome [10] (GAPO) (OMIM 230740)	AR	Oligodontia, hypodontia, failure of tooth eruption (pseudoanodontia)	Delayed growth, alopecia, optic atrophy
COL17A1 [11]	Junctional epidermolysis bullosa [12]	AR	Oligodontia (no preferential tooth type missing), hypodontia	Extensive blistering, nail dystrophy, atrophic alopecia, amelogenesis imperfecta, dental caries
Genes assoc w/syndromic disorders involving ectodermal findings (Note: Listed disorders are limited to those w/o characteristic dysmorphic features &/or cognitive impairment.)				
EVC *EVC2*	Weyers acrofacial dysostosis [13] (OMIM 193530)	AD	Hypodontia, malocclusion, conical teeth, supernumerary teeth	Mild short stature, postaxial polydactyly, dystrophic nails
FGF10	Lacrimoauriculodentodigital (LADD) syndrome [14] (OMIM 149730)	AD	Hypodontia (maxillary incisors), microdontia, delayed eruption, enamel dysplasia, caries	Digital anomalies, hearing loss, lacrimal & salivary gland hypoplasia & aplasia, auricular anomalies
FGFR2		AD	Hypodontia, microdontia, agenesis of maxillary incisors, delayed eruption, enamel dysplasia	Lacrimal duct aplasia, deafness, digital anomalies
GRHL2	Ectodermal dysplasia / short stature syndrome [16] (OMIM 616029)	AR	Hypodontia, enamel hypoplasia, developmental delay of dentition	Short stature, nail dystrophy &/or loss, focal hyperkeratosis of hands & feet, hyperpigmentation of oral mucosa &/or tongue

Table 2. continued from previous page.

Gene	Disorder	MOI	Dental Phenotype	Other Features
KREMEN1	Ectodermal dysplasia, hair/tooth type [17] (OMIM 617392)	AR	Oligodontia, hypodontia	Thin sparse hair, eyelashes & eyebrows, protruding lips, depressed nasal bridge, broad nose w/hypertelorism, down slanting palpebral fissures
LTBP3 [18]	Dental anomalies & short stature (OMIM 601216) [19]	AR	Oligodontia (no preferential tooth type missing), hypodontia	Short stature, mitral valve prolapse
OFD1	Oral-facial-digital syndrome type I [20]	XL	Hypodontia (lateral incisors), canine malposition	Micrognathia, lobulated tongue, tongue nodules, cleft lip/palate, accessory gingival frenula, hypoplastic alae nasi, syndactyly, polycystic kidney disease
PITX2	Axenfeld-Rieger syndrome, type 1 [21] (OMIM 180500)	AD	Oligodontia (upper lateral incisors & upper 2nd premolars), hypodontia, microdontia, enamel hypoplasia	Eye anomalies, glaucoma, maxillary hypoplasia, umbilical anomalies
PVRL1	Cleft lip/palate-ectodermal dysplasia [22] (OMIM 225060)	AR	Hypodontia, microdontia	Cleft lip & palate, sparse scalp hair, syndactyly
TP63	Ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3; orofacial cleft 8; Rapp-Hodgkin syndrome [23] (See *TP63*-Related Disorders.)	AD	Hypodontia, microdontia, extensive dental caries, enamel hypoplasia, prominent marginal ridges of permanent maxillary incisors, round-shaped permanent molars, barrel-shaped permanent maxillary central incisors	Cleft lip & palate, sparse/brittle/dry hair (trichodysplasia), ectodermal dysplasia, minor limb anomalies, tear duct anomalies, ankyloblepharon, nail abnormalities, T-cell lymphopenia

Table 2. continued from previous page.

Gene	Disorder	MOI	Dental Phenotype	Other Features
TSPEAR	Ectodermal dysplasia [24] (OMIM 618180)	AR	Hypodontia, microdontia	Scalp hypotrichosis; skin, hair, & limb defects

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Lammi et al [2004], Paranjyothi et al [2018]
2. Emerging evidence exists that mutation in this gene could cause isolated nonsyndromic tooth agenesis, but data are insufficient to state this definitively.
3. Güven et al [2019]
4. Meczekalski et al [2013], Phan et al [2016]
5. Phan et al [2016]
6. Larger deletions of the chromosome 4p16.2 region that include *MSX1* and surrounding genes may lead to Wolf-Hirschhorn syndrome, depending on the deletion size and gene content. Individuals with Wolf-Hirschhorn syndrome can have hypodontia in addition to syndromic features including seizures, intellectual disability, muscular hypotonia, congenital heart defects, and cryptorchidism [Ozcan et al 2017].
7. Paradowska-Stolarz [2015]
8. Kantaputra & Sripathomsawat [2011]
9. Williams & Letra [2018]
10. Dinckan et al [2018a], Williams & Letra [2018]
11. Mutation of this gene also leads to dystrophic epidermolysis bullosa (AD and AR) and epithelial recurrent erosion dystrophy (OMIM 122400; AD) but tooth agenesis is not a reported feature of these other phenotypes.
12. Smith et al [2017], Dinckan et al [2018b], Adorno-Farias et al [2019]
13. Katti et al [2019], Öz & Kirzioglu [2020]
14. Hajianpour et al [2017], Rodrigues et al [2020]
15. Williams & Letra [2018]
16. Petrof et al [2014]
17. Issa et al [2016]
18. Mutation of this gene also leads to geleophysic dysplasia (AD) but tooth agenesis is not a reported feature of this phenotype.
19. Dugan et al [2015]
20. Klein et al [2013]
21. Fan et al [2019]
22. Williams & Letra [2018]
23. Basha et al [2018]
24. Peled et al [2016]

3. Evaluation Strategies to Identify the Genetic Cause of Nonsyndromic Tooth Agenesis in a Proband

Establishing a specific genetic cause of NSTA:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical and dental history, physical examination, intra- and extraoral radiographs, family history, and genomic/genetic testing.

Physical Examination

A thorough physical exam should be completed to assess the presence of any extraoral features that may indicate a syndromic presentation.

A detailed oral exam and review of current and previous intra- and extraoral radiographs should then follow to identify exactly how many and which permanent teeth are absent and identify the presence of other dental anomalies in individuals with tooth agenesis.

Microdontia (which includes peg laterals), malocclusion, and retention of primary teeth are common findings in affected individuals.

Family History

A three-generation family history should be taken (when possible), with attention to relatives with manifestations of tooth agenesis and other dental anomalies, such as enamel defects or differences in tooth shape. Direct examination by a dental professional with specific expertise in tooth agenesis may need to be completed on all pertinent relatives due to the difficulty in diagnosing tooth agenesis vs other causes of tooth loss in adults. Review and documentation of medical and dental records and results of molecular genetic testing is recommended, when available.

Genomic/Genetic Testing

Molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing or multigene panel) and comprehensive genomic testing (exome sequencing or genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

Serial single-gene testing can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene are most likely (see Table 1) [van den Boogaard et al 2012, Williams & Letra 2018, Yu et al 2019].

- In individuals with posterior tooth agenesis, molecular genetic testing of *MSX1* and/or *PAX9* may be considered first.
- In individuals with hypodontia and oligodontia affecting both anterior and posterior dentition alike, molecular genetic testing of *AXIN2, IRF6*, and/or *WNT10A* may be considered first.
- In individuals with microdontia (peg laterals) or abnormally shaped teeth in addition to missing teeth, molecular genetic testing of *WNT10A* and/or *EDA* may be considered first.

A multigene panel that includes some or all of the genes listed in Tables 1 and 2 is most likely to identify the genetic cause of the tooth agenesis while limiting identification of variants of uncertain significance and pathogenic variants in genes that currently do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with tooth agenesis, some panels may not include all the genes mentioned in this overview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing, which does not require the clinician to determine which gene(s) are likely involved, may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The

following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nonsyndromic tooth agenesis (NSTA) caused by pathogenic variants in *AXIN2*, *EDAR*, *FGFR1*, *GREM2*, *IRF6*, *LRP6*, *MSX1*, *PAX9*, or *WNT10B* is inherited in an autosomal dominant manner.

NSTA caused by pathogenic variants in *EDA* is inherited in an X-linked manner.

NSTA caused by pathogenic variants in *WNT10A* is inherited in an autosomal dominant or autosomal recessive manner; however, both decreased penetrance and variable expressivity (even within individuals from the same family) has been reported for some variants [Yang et al 2015]. Complex inheritance has also been proposed (see Complex/Multifactorial Inheritance).

Note: This section provides genetic risk assessment information for individuals and families with a molecular diagnosis of NSTA (see Table 1). If an individual has tooth agenesis as part of known syndromic disorder (see Table 2), counseling for that disorder is indicated; for more information, see Klein et al [2013], Williams & Letra [2018], and Yu et al [2019].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Many individuals with a molecular diagnosis of autosomal dominant NSTA have an affected parent [Williams & Letra 2018, Yu et al 2019].
- Some individuals diagnosed with autosomal dominant NSTA have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with NSTA caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Though theoretically possible, no instances of germline mosaicism have been reported. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with NSTA may appear to be negative because of failure to recognize the disorder in affected family members, reduced penetrance, and variable expressivity. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Clinical manifestations may vary in heterozygous sibs; both reduced penetrance and intrafamilial variability are observed in autosomal dominant NSTA.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant NSTA has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with biallelic *WNT10A* pathogenic variants are presumed to be heterozygous for a *WNT10A* pathogenic variant, unless proven otherwise through molecular genetic testing of both parents.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *WNT10A* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes for a *WNT10A* pathogenic variant may appear to be asymptomatic or have hypodontia.

Sibs of a proband

- If both parents are known to be heterozygous for a *WNT10A* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *WNT10A* pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither of the familial *WNT10A* pathogenic variants.
- While clinical manifestations of tooth agenesis vary among affected family members, sibs who inherit biallelic *WNT10A* pathogenic variants will often have oligodontia.
- Sibs who inherit one *WNT10A* pathogenic variant (heterozygotes) may be asymptomatic or have hypodontia.

Offspring of a proband. The offspring of an individual with biallelic *WNT10A* pathogenic variants are obligate heterozygotes for a pathogenic variant in *WNT10A* and may appear to be asymptomatic or have hypodontia.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *WNT10A* pathogenic variant.

Carrier (heterozygote) detection. Heterozygote testing for at-risk relatives requires prior identification of the *WNT10A* pathogenic variants in the family.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have *EDA*-related NSTA nor will he be hemizygous for the *EDA* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *EDA* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo EDA* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism. The frequency of *de novo EDA* pathogenic variants is unknown.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *EDA* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant will be heterozygotes and may have a range of clinical manifestations.
- If the proband represents a simplex case and if the *EDA* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *EDA* pathogenic variant to all of their daughters and none of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having an *EDA* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote detection. Identification of female heterozygotes requires prior identification of the EDA pathogenic variant in an affected family member.

Complex/Multifactorial Inheritance

Oligogenic inheritance due to multilocus variation has recently been proposed for nonsyndromic tooth agenesis. For example, pathogenic variants in *WNT10A* have been found to cosegregate with pathogenic variants in *GREM2*, *LAMA3*, and/or *BCOR* in individuals with nonsyndromic tooth agenesis [Kantaputra et al 2015, Dinckan et al 2018b, Du et al 2018].

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the nonsyndromic tooth agenesis-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Organization for Rare Disorders (NORD)**
  Tooth Agenesis

5. Management

There is no standard of care procedure or clinical practice guideline for management of nonsyndromic tooth agenesis (NSTA).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with NSTA, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Nonsyndromic Tooth Agenesis

System/Concern	Evaluation	Comment
Dental	Pediatric dental eval in children	• Clinical exam incl hard tissue exams & radiographs (bitewings, individualized periapicals, & orthopantomographs) [1] • Referral to orthodontic & prosthodontic providers
	Clinical assessment of feeding/chewing in children (in cases of oligodontia)	Consider referral to feeding specialist if clinical concerns based on severity of tooth agenesis.
	Orthodontics / general dentistry eval in adolescents & adults	Clinical & radiographic exam (e.g., panoramic, cepholometric radiographs, cone beam computed tomography)
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of NSTA to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

1. Dental Radiograph Guideline [2016]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Nonsyndromic Tooth Agenesis

Manifestation/Concern	Treatment/Recommendation	Considerations/Other
Oral hygiene	Standard treatment per dentist	Pediatric dentists typically treat patients from infancy to age 14 yrs; then, transition to an adult dentist should be considered.
Maintenance of existing dentition	Diet counseling	Nutritional counseling to incl non- or low-cariogenic foods & eliminate unhealthy habits
	Fluoride varnish	Biannual placement to prevent dental caries/cavities
	Fluoride sealants	Placed on deep pits & fissures to prevent caries/cavities
	Mouth guard	To prevent dental trauma & loss of additional permanent teeth
Preservation of primary teeth that are missing successor permanent teeth	Maintenance of dental arch length until growth is complete & implants can be placed	Arch length must be maintained until orthodontic appliances are complete or until implants are placed after growth is complete, age 6 to adulthood.
Prosthodontics	Adjustable appliance to accommodate normal craniofacial growth & development	• In those ages 6-18 yrs • Also serves psychological & functional purposes
	Prosthetic replacement of missing teeth following orthodontic treatment	• In those ages 12-18 yrs • Emphasis on functional & esthetic success
Space redistribution, alignment, bite correction	Standard treatment per orthodontist	Typically after age 12 yrs
Missing teeth	Implant placement [1, 2]	For single tooth implant, in adulthood / after growth is complete
	Implant retained prothesis [1, 2]	For multiple missing teeth, in adulthood / after growth is complete
	Orthognathic surgery	If skeletal discrepancies are present, in adulthood / after growth is complete

1. Implants should only be placed after the majority of skeletal growth is completed.
2. Extraction of primary teeth and/or bone augmentation procedures may be necessary before implant placement.

Prevention of Secondary Complications

It is recommended that individuals with (or suspected of having) nonsyndromic tooth agenesis be followed by a dentist at least every six months to ensure maintenance of remaining dentition. Oral health disease prevention for remaining dentition often includes dietary counseling, fluoride sealants, and mouth guards (see Table 4).

Surveillance

Table 5. Recommended Surveillance in Individuals with Nonsyndromic Tooth Agenesis

Age	Evaluation	Frequency
Childhood and adolescence	Hard tissue exams & radiographs (bitewings, individualized periapicals, & orthopantomographs)	Biannually or w/frequency based on individual factors
	Orthodontic eval to determine appropriate timing of orthodontic intervention	Prior to puberty
	Assessment of alveolar ridge	Prior to implant placement

Table 5. continued from previous page.

Age	Evaluation	Frequency
All ages after tooth eruption	Caries risk assessment	Every 6 mos or as recommended by dentist
	Assessment of deep pits & fissures treated w/sealants to evaluate for retention & efficacy	Biannually

Evaluation of Relatives at Risk

It is appropriate to clarify the clinical and/or genetic status (when possible) of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of dental treatment. Evaluations can include:

- Complete clinical intra- and extraoral examinations and radiographs (see Table 3);
- Molecular genetic testing if the pathogenic variant(s) in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Chapter Notes

Author Notes

Ariadne Letra is a dentist with additional formal training in Human Molecular Genetics and a Professor in the Department of Diagnostic and Biomedical Sciences and Center for Craniofacial Research at UTHealth School of Dentistry at Houston. Dr Letra has adjunct faculty appointments at the Pediatric Research Center, UTHealth McGovern Medical School, and at the University of Texas MD Anderson Cancer Center Graduate School of Biomedical Sciences. Dr Letra's research focuses on the cellular and molecular basis of complex oral traits and anomalies, particularly craniofacial and dental anomalies. Her work has identified numerous genes and gene variants associated with these conditions. Additional work in her lab focuses on identifying common molecular players linking oral and general health conditions. Dr Letra has published 98 peer-reviewed original articles, two invited book chapters, four invited review articles, and more than 180 abstracts related to craniofacial anomalies and oral diseases/conditions. Her research has been continuously supported by grants from the National Institutes of Health and additional funding agencies.

Brett Chiquet is a board-certified pediatric dentist and Associate Professor in the Department of Pediatric Dentistry at UTHealth School of Dentistry. Dr Chiquet treats all children, including patients with special health care needs. Dr Chiquet helps teach dental residents how to comprehensively treat all pediatric patients, including anticipatory guidance, prevention, restorative dentistry, growth and development, special health care needs, hospital dentistry, behavior guidance, trauma, and oral pathology. The resident clinic provides comprehensive care for children ages 0-21, including management of developing oral tissues and occlusion. Patients with tooth agenesis are monitored for treatment at appropriate time points, balancing growth and development of the oral structures and the developing psyche of the patient. Dr Chiquet's clinical and research interest is cleft lip and palate, which often co-occur with tooth agenesis.

Emily Hansen-Kiss is a board-certified genetic counselor and Assistant Professor in the Department of Diagnostic and Biomedical Sciences at UTHealth School of Dentistry. Ms Hansen-Kiss has served as the genetic counselor in the Cleft and Craniofacial Clinics at Shriners Hospitals for Children – Houston, and UTHealth/Memorial Herman Hospital for the last two years, where she has gained extensive experience counseling patients and families about syndromic and nonsyndromic orofacial conditions. Ms Hansen-Kiss has also been involved in teaching genetics with an orofacial focus to the UTHealth School of Dentistry and the UTHealth Genetic Counseling graduate program students.

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