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## **WNT10A mutation results in severe tooth agenesis in a family of three sisters**

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## Abstract

**Objectives:** To identify the genetic basis of severe tooth agenesis in a family of three affected sisters. **Patients and Methods:** A family of three sisters with severe tooth agenesis were recruited for whole exome sequencing to identify potential genetic variation responsible for this penetrant phenotype. The **unaffected** father was tested for specific mutations using Sanger sequencing. Gene discovery was supplemented with *in situ* hybridization to localise gene expression during human tooth development. **Results:** We report a nonsense heterozygous mutation in exon 2 of *WNT10A* (RS121908119) **c.321C>A[p.Cys107\*]** likely to be responsible for the severe tooth agenesis identified in this family through the creation of a premature stop codon, resulting in truncation of the amino acid sequence and therefore loss of protein function. *In situ* hybridization showed expression of *WNT10A* in odontogenic epithelium during the early and late stages of **human primary** tooth development. **Conclusions:** *WNT10A* has previously been associated with both syndromic and non-syndromic forms of tooth agenesis and this report further expands our knowledge of genetic variation underlying non-syndromic forms of this condition. We also demonstrate expression of *WNT10A* in the epithelial compartment of human tooth germs during development.

Keywords      gene mutation, hypodontia, whole exome sequencing, nonsense mutation

## Introduction

Tooth agenesis is a common developmental anomaly seen in human populations. It is often associated with the permanent dentition, has a female preponderance and overall prevalence ranging from 1-10 per cent <sup>1,2</sup>. Significant variation in patterns of tooth agenesis are seen, with the third molar most commonly absent in up to 30 per cent of subjects <sup>3</sup>, followed by mandibular second premolars in 1-6 per cent and maxillary lateral incisors in 1-4 per cent <sup>4,5</sup>. The mandibular anterior teeth are absent in around 1 per cent, whilst absence of the maxillary central incisors, canines and first permanent molars is rare <sup>5</sup>. Tooth agenesis is often associated with other dental developmental anomalies, including microdontia, delayed tooth formation, primary tooth retention and delayed eruption <sup>6</sup>. Hypodontia is often used as the generic term to describe tooth agenesis affecting less than six permanent teeth, excluding third molars; whilst oligodontia describes an absence of more than six permanent teeth (excluding third molars). Tooth agenesis can have consequences for facial morphology, particularly associated with the upper and lower jaws. Although some research has reported only limited affects <sup>7</sup>, other work has found associations with reduced cranial base angle and length, mandibular and maxillary incisor retroclination, greater inter-incisal angle, protrusive mandible <sup>8</sup> and reduced lower anterior facial height <sup>9</sup>.

In recent years, progress has been made in understanding the molecular genetics of tooth agenesis with the identification of mutations in several human genes in association with this condition, including *PAX9* [Online Mendelian Inheritance in Man (OMIM) \*167416] <sup>10</sup>, *MSX1* [\*142983] <sup>11</sup>, *AXIN2* [\*604025] <sup>12</sup>, *EDA* [\*300451] <sup>13</sup>, *EDARADD* [\*606603] <sup>14</sup> and *WNT10A* [\*606268] <sup>15</sup>. In an attempt to further understand the molecular genetics of tooth agenesis, we have employed whole exome sequencing (WES) to investigate a family with three sisters demonstrating a highly penetrant and severe form of this condition.

## **Patients and methods**

Clinical and radiographic examination of three Caucasian sisters referred to the Department of Orthodontics at King's College London Dental Institute (Guy's and St Thomas' NHS Foundation Trust) revealed a penetrant form of tooth agenesis, characterized by absence of 14-23 permanent teeth, excluding third molars (Figure 1, Table 1). A full medical and dental history was obtained in addition to a physical examination by a clinical geneticist, none of which revealed any other developmental anomalies, dysmorphic features or significant family history. The family pedigree indicated that the father was not affected, while the deceased mother had been similarly affected with tooth agenesis, suggesting autosomal dominant transmission of the trait. There was no confirmed family history of cancer.

Ethical approval for this study was provided by the South London Research Ethics Committee (reference 08/H0810/14). Venous blood was collected and genomic DNA isolated from peripheral blood cells using standard salt extraction. WES was performed to identify potential genetic variation responsible for this penetrant developmental anomaly. The resulting sequencing reads were aligned against the human reference genome hg-19 using Novocraft Technologies (Novoalign) software. Sequencing data (more than 5Gb) were generated for each individual with more than 90 per cent of the coding bases represented by at least 20 reads. Filtering of data was undertaken according to class and frequency of variant. Annotation was undertaken for previously reported specific variants and estimated population frequencies using the following public databases: 1000 Genomes ([www.1000genomes.org](http://www.1000genomes.org)), Exome Variant Server (EVS) (<http://evs.gs.washington.edu/EVS/>), Exome Accession Consortium (ExAC) (<http://exac.broadinstitute.org/>) and Database of Single Nucleotide Polymorphisms (dbSNP) (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). Variant pathogenicity was investigated using the following online bioinformatic tools: Combined Annotation Dependent Depletion (CADD) (<http://cadd.gs.washington.edu>) to investigate deleteriousness of single nucleotide

and insertion and deletion variants; Sorting Intolerant From Tolerant (SIFT) (<http://sift.bii.a-star.edu.sg>) to predict the effect of amino acid substitution on protein function and Polymorphism Phenotyping version 2 (PolyPhen-2) (<http://genetics.bwh.harvard.edu/pph2>) to predict the effect of amino acid substitutions on stability and function of human protein.

Sanger sequencing was also performed using DNA extracted from the father, with primers designed by the Primer3 tool: forward primer [5' CCAACACCAATTCAGGGACC 3'] and reverse primer [5' CTCTCGGAAACCTCTGCTGA 3']. Polymerase chain reaction (PCR) was performed and the products sequenced by BioScience (Source Bioscience).

Digoxigenin-labelled *in situ* hybridization was performed on embryonic tissue sections as previously described <sup>16</sup>, with cDNA clones for human *WNT10A* (687559) obtained from Source Bioscience. Human embryos were obtained at a variety of stages of gestation (approximately 12-15 weeks post-fertilization) from the Human Developmental Biology Resource Birth Defects Research Centre at the Institute of Child Health, University College London. All embryos were derived from elective termination of pregnancy and screened for gross chromosomal abnormalities. The general ethical approval is held by UCL Institute of Child Health; King's College London has a subscription to obtain embryos from this center for medical research. Embryos were stored in phosphate buffered saline, delivered immediately following retrieval via courier, fixed and decalcified, embedded in paraffin wax and sectioned at 8µm before mounting on microscope slides.

## **Results**

The pedigree and dental phenotype of the three sisters is detailed in Figure 1. Case A (proband-33 years old) had 14 missing permanent teeth (excluding third molars), including lower first

and second premolars, first permanent molars, upper lateral incisors, second premolars and second permanent molars. Case B (36 years old) had 23 missing permanent teeth (excluding third molars). Almost all teeth were missing, except the upper central incisors and lower right central incisor and canine. Case C (29 years old) had 17 missing permanent teeth (excluding third molars), including upper canines, premolars and second molars, lower central incisors, premolars and second molars.

WES was undertaken for these three individuals and identified more than 24000 non-reference alleles, including 16169 shared between the three sisters. These were filtered down to variants with a minor allele frequency of <0.01 predicted to be missense, nonsense, frameshift or splice-site variants, and resulting in 113 candidate heterozygous variants shared by each of the three siblings (Supplementary Table 1). Upon filtering of data, four candidate genes were identified (directly or indirectly related with dental anomalies). These variants were procollagen-lysine, 2-glutarate 5-dioxygenase 1 (*PLOD1*) c.2092C>T[p.Leu698Phe]; forkhead box F2 (*FOXF2*) c.1322C>T[p.Pro441Leu]; GLI family zinc finger 2 (*GLI2*) c.181C>A[p.61Leu] and WNT family member 10A (*WNT10A*) c.321C>A[p.Cys107\*]. Annotation of the first three variants predicted them to be non-pathogenic, which left only a single pathogenic variant of *WNT10A* [rs121908119] as a potential cause of the phenotype and predicted to create a premature stop codon.

Three-dimensional modelling of wild type and mutant protein using SWISS-MODEL online software (<https://swissmodel.expasy.org>) clearly showed the deleterious effect of this mutation on the amino acid sequence and truncation of the protein (Figure 2 A, B). Sanger sequencing on *WNT10A* was also carried out on DNA isolated from the father, which revealed an absence of the same variant (Figure 2C).

*In situ* hybridization for *WNT10A* during human tooth development showed strong expression in odontogenic epithelium during the bud and early cap stages (8-10 weeks), with

less significant expression in epithelium at the late cap stage (11-13 weeks). At the bell stage of development, expression continued in the epithelium and secondary enamel knots (14-15 weeks) (Figure 3A-E).

## **Discussion**

The three sisters in this pedigree demonstrated a severe form of tooth agenesis, with tooth absence ranging from 14-23 permanent teeth, excluding third molars with no clinical signs of ectodermal dysplasia. Several mutations have previously been described in *WNT10A* in association with syndromic and non-syndromic forms of tooth agenesis (Figure 2C). In a recent study of individuals with an average number of 8.2 missing teeth, 28 per cent had a pathogenic mutation in *WNT10A*<sup>17</sup>, whilst figures of up to 56 per cent have been demonstrated in cases affected by higher numbers of missing teeth (up to 14.6)<sup>15</sup>. In addition, seemingly less biologically significant missense mutations in *WNT10A* have been associated with absent maxillary permanent lateral incisors<sup>18</sup>. The mutation identified in this investigation (c.321C>A) has previously been described in association with several different types of syndromic ectodermal dysplasia and non-syndromic tooth agenesis. This included a family with severe tooth agenesis affecting up to 23 teeth in both the heterozygous and compound heterozygous states with mild ectodermal dysplasia<sup>19</sup> and the same mutation with non-syndromic tooth agenesis<sup>15,20</sup>. This variation in the penetrance of the phenotype in different subjects suggests the influence of different factors (environmental, genetics and epigenetics) on WNT signaling and developmental outcome.

WES is a powerful tool for discovering alleles underlying rare Mendelian disorders. *WNT10A* mutations have been strongly associated with oligodontia in up to 50 per cent of patients referred to dental specialist clinics<sup>20</sup>. Mutations in this gene are usually associated with tooth agenesis affecting the upper and lower premolars and molars, interestingly all



heterozygous mutations in *WNT10A* patients have intact central incisors, including those in our study, which indicates that these teeth have a potentially different developmental program <sup>21</sup>. In this family, we found tooth agenesis of the upper permanent canines, which has been previously reported to be associated with microdontia of the permanent lateral incisors <sup>22</sup> and in cases with syndromic tooth agenesis <sup>23</sup>. *WNT10A* mutations have also been reported to be associated with autosomal recessive syndromic forms of ectodermal dysplasia, including Schopf–Schulz–Passarge syndrome (SPSS) (OMIM \*224750), odonto-onycho-dermal dysplasia (OODD) (OMIM \*257980) and autosomal dominant severe tooth agenesis <sup>15,24</sup> (Table 2). In addition, marginally significant interactions exist between the proportion of calories from saturated fat and *WNT10A* polymorphism <sup>25</sup>, whilst both *WNT10A* and *WNT6* are strongly co-expressed in SW480 colorectal cancer cell line <sup>26</sup> and *WNT10A* is upregulated in primary gastric cancer <sup>27</sup>. WNT/beta-catenin signaling is critical for organogenesis of many tissues including the teeth, with *WNT10A* a key mediator of WNT signaling in tooth morphogenesis. *WNT10A* has four exons, encoding 417 amino acids with 10 putative  $\alpha$ -helices and 7  $\beta$ -strands and it demonstrates wide expression during embryonic development, including the skin <sup>28</sup>, limb <sup>29</sup> and hair follicle <sup>30</sup>.

This is the first study to identify expression of *WNT10A* during human odontogenesis at different embryological stages (8-15 weeks of gestation), showing clear expression of this gene in the epithelium. These results are consistent with data from mouse embryos, with these studies also finding high expression of *WNT10A* in the epithelium during the bud stage, in the enamel knot during the cap stage <sup>31</sup> and secondary enamel knots at the bell stage <sup>32</sup>.

## **Conclusions**

We report a *WNT10A* nonsense heterozygous mutation in a family of three sisters with an autosomal dominant form of severe tooth agenesis. These data expand phenotype-genotype

correlations associated with pathogenic variants in this gene and further emphasize the key role of *WNT10A* in human tooth development.

### **Disclosures**

The authors have nothing to disclose in relation to this work.

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## Figure legends

**Figure 1** Family pedigree and panoramic radiographic analysis for the three siblings. The upper diagram shows the family pedigree (square=male, circle=female, black circle=affected female, circle with slash=deceased female). The lower panel shows the dental panoramic radiographs of the siblings (A [proband] 14 missing teeth; B 23 missing teeth; C 17 missing teeth).

**Figure 2** *WNT10A* structure and amino acid construction. Three-dimensional model of amino acid construction showing the difference between (A) wild type and (B) mutant truncated protein; (C) The upper panel shows *WNT10A* structure and mutations in different exons. The grey box shows the mutation found in this study. The lower panel shows Sanger sequencing of DNA isolated from the father (mutant and wild type sequences).

**Figure 3** Expression of *WNT10A* using digoxigenin-labelled *in situ* hybridization on frontal sections of human primary tooth development. (A) expression at 8 weeks in epithelium of the bud stage lower canine; (B) at 9 weeks in epithelium of the bud stage upper first molar; (C) expression at 10 weeks in epithelium of the early cap stage upper canine; (D) expression at 11 weeks in epithelium of the late cap stage lower first molar; (E) expression at 12 weeks in epithelium of the late cap stage upper canine; (F) expression at 13 weeks in epithelium of the early cap stage lower canine; (G) expression at 14 weeks in epithelium (secondary enamel knot) of the bell stage lower second molar; (H) expression at 15 weeks in epithelium of the lower first molar at the late cap stage. (C, canine; M1 and M2, first and second primary molars, respectively). Scale bar in A=100 microns for A-G and in H=100 microns.

**Supplementary Table 1** Genetic variants shared by the three sisters

Figure 1.

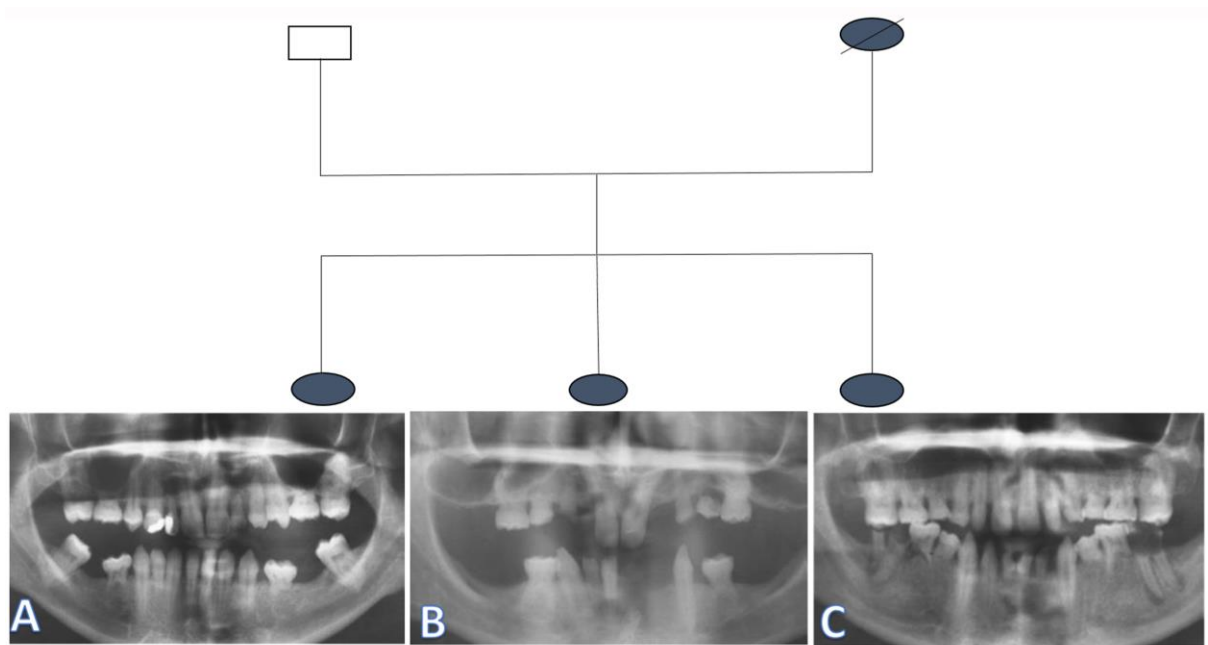


Figure 2.

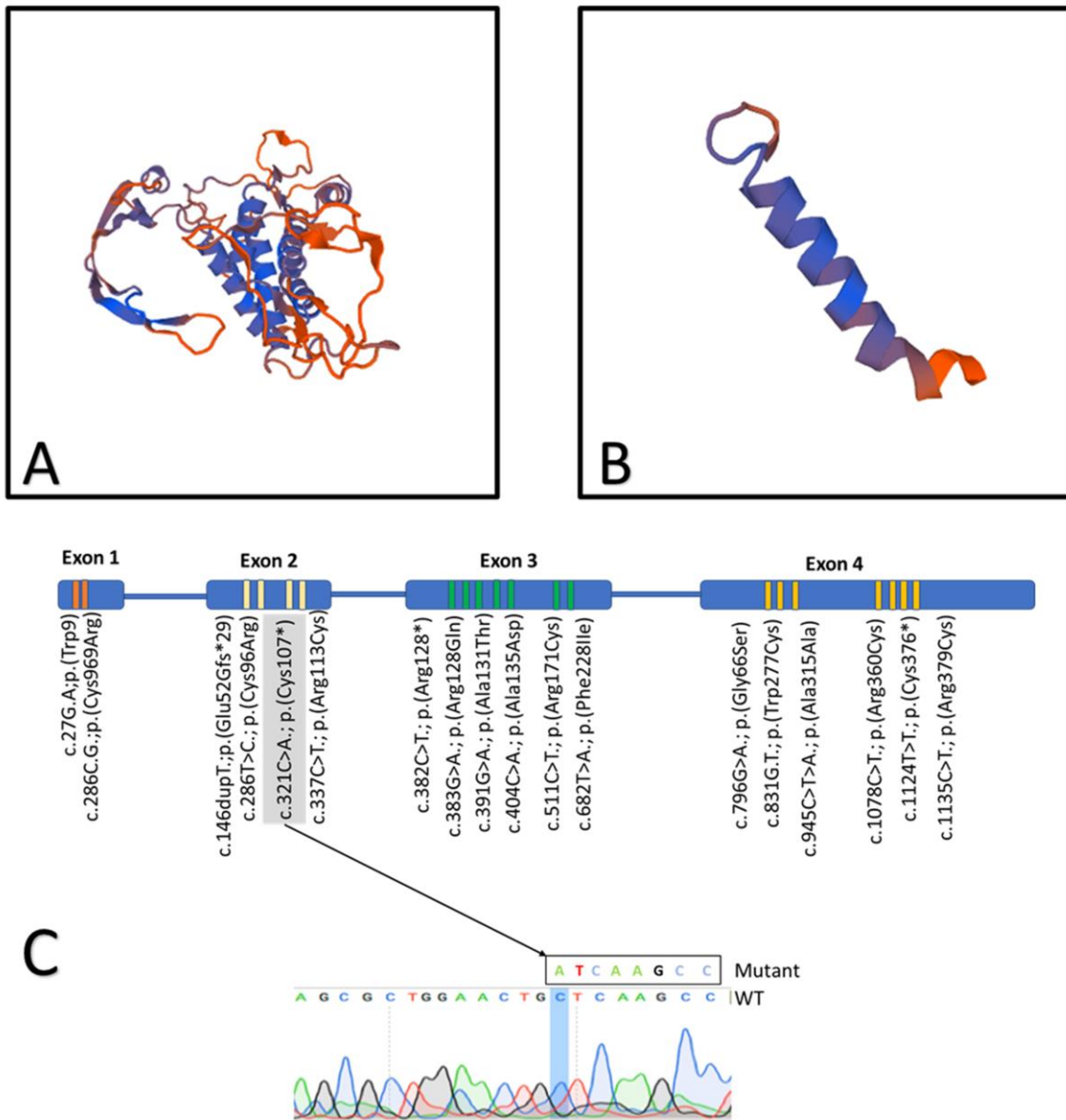
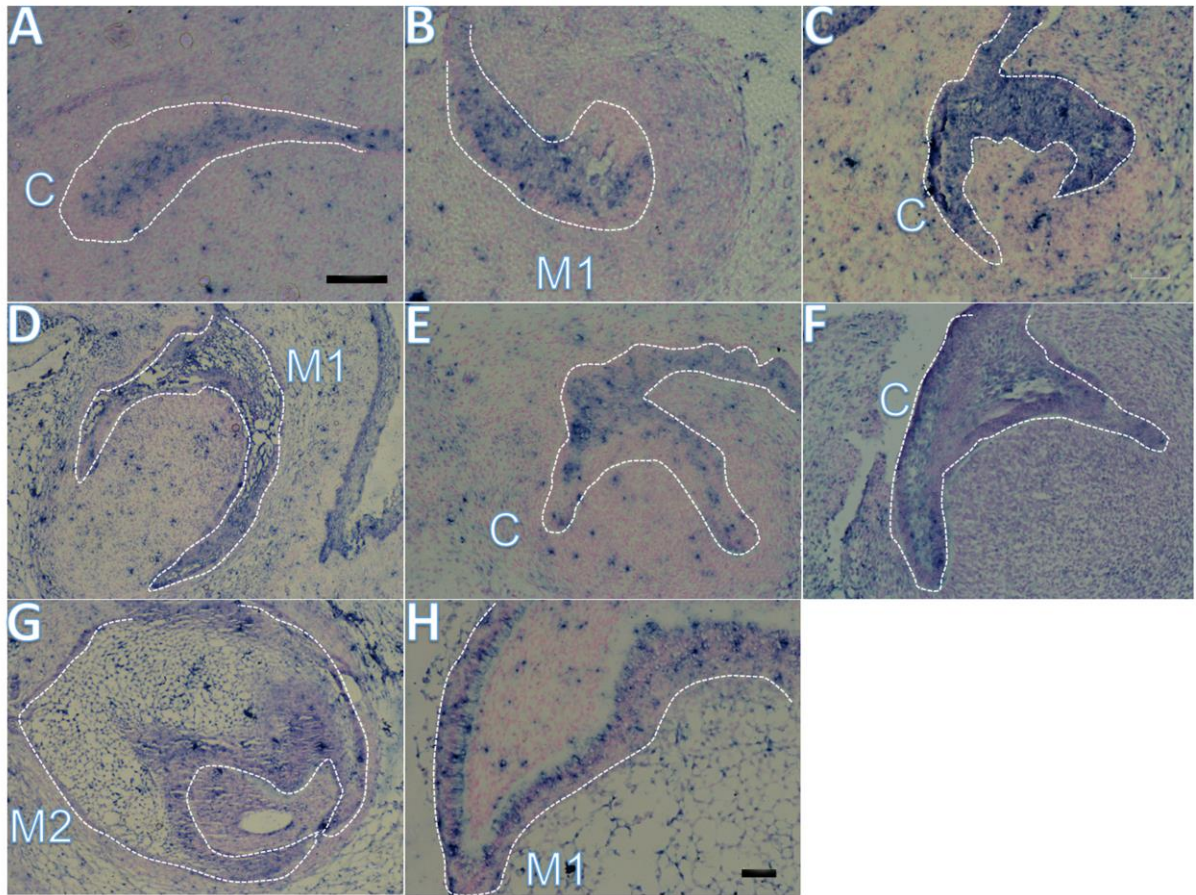




Figure 3.



Supplementary table 1.

**Table 1** Summary of permanent tooth number in the three sisters. 1=central incisor; 2=lateral incisor; 3=canine; 4=first premolar; 5=second premolar; 6=first molar; 7=second molar; 8=third molar. \*=missing teeth; +=present teeth+ L=left; R=right.

Subject	JAWS	8R	7R	6R	5R	4R	3R	2R	1R	1L	2L	3L	4L	5L	6L	7L	8L
Sibling A	Upper	*	*	+	*	+	*	*	+	+	*	*	+	*	+	*	*
	Lower	*	+	*	*	*	+	+	+	+	+	+	*	*	*	+	*
Sibling B	Upper	*	*	*	*	*	*	*	+	+	*	*	*	*	*	*	*
	Lower	*	*	*	*	*	+	*	+	*	*	-	*	*	*	*	*
Sibling C	Upper	*	*	+	*	*	*	+	+	+	+	*	*	*	+	*	*
	Lower	*	*	+	*	*	+	+	*	*	*	+	*	*	+	*	*

Supplementary table 2.

**Table 2** Overview of dental phenotypes associated with the same *WNT10A* mutation **c.321C>A[p.Cys107\*]**.

Author	Variant	Missing teeth	
Bohring et al <sup>24</sup> 2009	Compound heterozygous, homozygous	Most reported patients have 4-6 missing teeth including 3 <sup>rd</sup> molars. Two have 10 missing teeth	In 12 patients, the most consistent missing teeth were upper permanent lateral incisors and third molars.  Two patients had missing upper central incisors and 1 <sup>st</sup> permanent molars. Others had absent primary teeth and peg shaped lateral incisors.
Van den Boogaard et al <sup>15</sup> 2012	Heterozygous, compound heterozygous and homozygous	58 patients	Mean of 14-16 missing teeth, one patient had 26 missing teeth
Van Geel et al <sup>33</sup> 2010	Homozygous, compound heterozygous		No missing teeth
Mostowska et al <sup>20</sup> 2013	Heterozygous, compound heterozygous and homozygous		Seven patients (some are syndromic)  They have 1, 2, 3, 9, 12, 19, 22 missing teeth
Plaisancié et al <sup>34</sup> 2013	Heterozygous, compound heterozygous and homozygous		Number of missing teeth with the same mutation is not mentioned (mean is 13 teeth)

This study 2018	Heterozygous		14, 17, 23 missing teeth
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