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ORIGINAL ARTICLE

# Gastrointestinal symptoms in patients with isolated oligodontia and a Wnt gene mutation

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## Abstract

**Objective:** Since Wnt signaling plays an important role in both tooth agenesis and altered intestine homeostasis, the aim was to compare gastrointestinal symptoms in patients with isolated oligodontia caused by a Wnt pathway gene mutation and controls.

**Methods:** A case–control study was designed to compare self-reported gastrointestinal symptoms among patients with isolated oligodontia, caused by a Wnt signaling gene mutation, and fully dentate controls. The Gastrointestinal Symptom Rating Scale (GSRS) was used to assess gastrointestinal symptoms. Prevalence and severity of gastrointestinal symptoms among patients and age- and gender-matched controls were evaluated.

**Results:** Twenty patients with isolated oligodontia and a pathogenic variant in the wnt pathway genes *WNT10A*, *LRP6*, or *PAX9* participated. The prevalence of gastrointestinal symptoms was higher in the oligodontia patients compared to their controls ($\chi^2(1) = 87.33$, $p = .008$). Mean GSRS total scores ($p = .011$) and domain scores for "abdominal pain" ($p = .022$), "reflux" ($p = .003$) and constipation ($p = .030$) were higher for these oligodontia patients compared to their controls.

**Conclusion:** Gastrointestinal symptoms are more prevalent and more severe in patients with isolated oligodontia and a deficiency in a Wnt pathway-related gene, when compared to controls without tooth agenesis.

KEYWORDS
gastrointestinal complaints, hypodontia, inflammatory bowel disease, Oligodontia, Wnt signaling pathway

## 1 | INTRODUCTION

Tooth agenesis or hypodontia is a developmental anomaly in which one or more permanent teeth fail to develop, with a reported prevalence of 5.5% in Europe (Polder et al., 2004). Common forms affecting one or a few absent teeth represent the great majority of cases. Severe hypodontia or oligodontia, where 6 or more teeth are missing (3rd molars excluded), is estimated to have a prevalence of 0.14% (Nieminen, 2009; Polder et al., 2004; Schalk-van der Weide, 1992). Tooth agenesis is seen as an isolated trait or as a part of a syndrome in case of concurring non-dental anomalies (Schalk-van der Weide, 1992). In the clinic, differentiation between isolated and syndromic hypodontia is not always clear. For populations with oligodontia, reduced salivary secretion or impaired function of hairs,

nails, sweat glands, or salivary secretion was reported in half of the patients (van den Boogaard et al., 2012). These findings suggest a spectrum rather than a clear distinction between isolated and syndromic hypodontia. Hypodontia previously diagnosed as isolated, could therefore be considered as part of a syndrome, although clinical expression is mild or delayed to later in life.

In recent years, research on the etiology of tooth agenesis has focused on genetic backgrounds. Several genes and genetic pathways that are involved in the etiology of isolated hypodontia were identified: *WNT10A* (wingless-type MMTV integration site family, member 10A), *WNT10B* (wingless-type MMTV integration site family, member 10B), *LRP6* (low-density lipoprotein receptor-related protein 6), *EDA* (ectodysplasin A), *MSX1* (muscle segment homeobox 1), *PAX9* (paired box gene 9), *AXIN2* (axis inhibition protein 2), and *GREM2* (Gremlin 2) (De Coster et al., 2009; Magruder et al., 2018; Massink et al., 2015; Yu et al., 2019). In a population of isolated oligodontia patients, mutations in *WNT10A* were present in more than half of the patients, indicating that the Wnt pathway in particular is important for tooth formation (Boogaard et al., 2012).

Wnt signaling is not only important in many developmental processes. In some self-renewing tissues, it remains essential throughout life and is in this respect important in intestinal epithelial homeostasis and injury repair (Clevers et al., 2014; Clevers & Nusse, 2012; Cosín-Roger et al., 2016; Pull et al., 2005). Homeostasis and regeneration of the gastrointestinal mucosa depend on cellular proliferation and differentiation which in turn is dependent on a large array of signaling molecules including Wnt signaling pathway components (Gregorieff et al., 2005). Deregulation of the Wnt signaling pathway could contribute to deregulation of intestinal epithelial homeostasis and injury repair (Cosín-Roger et al., 2016). This could in turn increase the sensitivity for diseases like inflammatory bowel disease, characterized by chronic inflammation of the intestine, although to best knowledge of the authors, to date no clinical studies are reported on the relation of pathogenic *WNT10A* variants and gastrointestinal (GI) symptoms or diseases.

In our clinic for special dental care, we noticed that patients with solitary oligodontia often report unexplained GI complaints when their medical history is obtained. Bearing in mind the important role that deregulated Wnt signaling plays in both tooth agenesis and altered intestine homeostasis, the aim of this study was to substantiate that finding beyond the level of coincidence. The prevalences of self-reported GI symptoms are compared in a population of patients with isolated oligodontia caused by a pathogenic variant in *WNT10A* or Wnt pathway-related gene (e.g., *LRP6)* on the one hand and controls without tooth agenesis on the other hand. The null hypothesis tested was an absence of difference in the prevalence and severity of GI symptoms in patients and controls.

## 2 | MATERIALS AND METHODS

A case–control study was designed to compare self-reported GI symptoms among patients diagnosed with isolated oligodontia caused by a Wnt pathway gene mutation, and dentate controls.

### 2.1 | Population

Potentially eligible patients were identified from the electronic patient database (HiX, Chipsoft) of the Department of Oral and Maxillofacial Surgery, Prosthodontics and Special Dental Care of the University Medical Center Utrecht (UMC Utrecht) in the Netherlands by filtering on the registered diagnoses: "oligodontia" and/or "hypodontia." The following criteria were used to identify patients eligible for inclusion:

- Age range from 16 up until 40 years old;
- Diagnosed with isolated oligodontia, that is, six or more missing teeth, third molars excluded, without additional obvious ectodermal features;
- Carrying a pathogenic variant in the following Wnt pathway genes: *WNT10A*, *WNT10B*, *LRP6*, *AXIN2* or to two genes (*MSX1* and *PAX9*) in the loop of the Wnt/β-catenin and TGF-β/BMP pathways. Pathogenic variants were identified in clinical care by single-gene analyses or WES-based gene panel analyses as part of diagnostic work-up. The diagnostic oligodontia gene panel analyses in use in the Netherlands target 17 oligodontia-related genes *AXIN2*, *BCOR*, *EDA*, *EDAR*, *EDARADD*, *FGFR1*, *FLNA*, *GJA1*, *GREM2*, *IRF6*, *LRP6*, *LTBP3*, *MSX1*, *PAX9*, *TP63*, *WNT10A*, *and WNT10B*).

Patients fitting the inclusion criteria were contacted by telephone by one of the authors (LR), informed about the nature of the study, and asked to participate by completing a questionnaire on GI symptoms. If so, written information about the study, the questionnaire, and a consent form was sent by mail. After two, four, and six weeks, non-responders received a reminder letter. Controls were recruited from the social network of one of the authors (LR) and clinically inspected to exclude tooth agenesis. Tooth extractions in their dental history, for example in case of orthodontic treatment, were acceptable. Controls did not undergo gene panel testing. Patients and controls were matched, based on their gender and age. This study was approved by the Medical Ethics Committee of the hospital (METC protocol number 18 829/C, WAG/mb/042908, December 5, 2018).

### 2.2 | Outcome parameters

To assess the prevalence of GI symptoms, the Dutch version of the Gastrointestinal Symptom Rating Scale (GSRS) was used. The GSRS is a validated disease-specific questionnaire and consists of 15 items that assess the occurrence and severity of various GI symptoms during the past week. The questionnaire uses a seven-point graded Likert scale, ranging from 1 (no discomfort/no symptoms) to 7 (very severe discomfort/very severe symptoms) (Kulich et al., 2008; Revicki et al., 1997). The GSRS total score was calculated by adding up all items, divided by 15. A cutoff point to determine presence of symptomatic GI complaints was derived from literature, and set at a GSRS score of 2 (Dimenäs et al., 1996;

Teplitsky et al., 2010). In addition, items were clustered into five symptom domains: "reflux," "abdominal pain," "indigestion," "diarrhea," and "constipation syndrome". The GSRS domain score was calculated by adding up the underlying items divided by the number of items in each domain. See Appendix S1 for the English version of the Gastrointestinal symptom Rating Scale questionnaire and the scoring instructions.

The primary outcome measure was prevalence of symptomatic GI complaints, indicated by the amount of GSRS total and domain scores ≥2. Secondary outcome variables were the underlying mean GSRS total and domain scores, reflecting the severity of the GI symptoms. Comparisons were made between the isolated oligodontia patients and their matched controls, as well as for different subsets of patients characterized by gene mutation and their controls.

### 2.3 | Statistical analysis

Basic characteristics of oligodontia patients and controls were presented as descriptive statistics. The prevalence of symptomatic GI complaints among patients and controls was tested using Chi-square tests. Not all GSRS total and domain scores were normally distributed. Hence, to evaluate differences in severity of GI symptoms (mean GSRS domain scores and mean total scores) between oligodontia patients and matched controls, a Wilcoxon-signed rank test for matched pairs was used.

To check for bias due to possible impaired masticatory function related to the number of missing teeth, an independent sample *t* test was used to test a possible relation between prevalence of GI complaints in isolated oligodontia patients and number of teeth missing. In addition, a Pearson correlation coefficient for the severity of GI complaints related to the number of teeth missing was calculated. For all tests, a significance level was set at $p < .05$ (IBM SPSS Statistics, version 25.0, 2017, IBM Corp., Armonk, NY, USA).

## 3 | RESULTS

Forty-eight isolated oligodontia patients met the inclusion criteria. One patient was excluded because of a complex phenotypic appearance and ongoing syndromic diagnostics. Forty patients could be contacted by telephone and thirty-five of them agreed to participate. Finally, twenty patients actually completed and returned the questionnaires. Data were coded and stored in MS Excel.

From the oligodontia patient group, fourteen patients (70.0%) had a pathogenic variant in *WNT10A*. Other pathogenic variants found in this group were *PAX9* ($n = 3$, 15.0%) and *LPR6* ($n = 3$, of which 2 are sisters, 15.0%) (Table 1). Fourteen out of twenty patients were female. Average age of the patients was 24.30 ± 6.4 years. Patients were matched to controls ($n = 20$) based on age and gender. Exact matches were available in all cases. Descriptives and tooth agenesis code (TAC) of patients are presented in Table 1. The TAC characterizes both the number and exact position of absent teeth per quadrant or for the whole mouth (Creton et al., 2007; Van Wijk & Tan, 2006).

### 3.1 | Prevalence of GI symptoms

The prevalence of symptomatic GI symptoms, indicated by the number of GSRS total scores ≥2, was higher in isolated oligodontia patients compared to their age- and gender-matched controls ($X^2(1) = 87.33$, $p = .008$). Also, the prevalence of symptoms for the domains "reflux" ($X^2(1) = 10.00$, $p = .002$) and "abdominal pain" ($X^2(1) = 8.640$, $p = .004$) was significantly higher in the patient group (Table 2).

The number of GSRS total scores ≥2 in patients with a pathogenic variant in *WNT10A* was higher compared to their age- and gender-matched controls, however, not statistically significant ($p = .054$). Complaints for the subdomains "abdominal pain" ($X^2(1) = 8.02$, $p = .013$) and "reflux" ($X^2(1) = 6.09$, $p = .041$) were reported significantly more frequently, indicating that such complaints were more common among the patient group with a pathogenic variant in *WNT10A* compared to their controls. For non-*WNT10A* oligodontia patients, differences in prevalence of GI complaints with matched controls were not statistically significant.

An independent sample *t* test showed no statistically significant difference in the mean number of missing teeth and the prevalence of reported GI complaints ($t(18) = -1.18$, $p = .26$).

### 3.2 | Severity of GI complaints

Mean total GSRS scores were higher for isolated oligodontia patients compared to their age- and gender-matched controls (Mdnp = 2.133, Mdnc = 1.467, Z = −2.552, $p = .011$). GI complaints related to "abdominal pain" (Mdnp = 2.333, Mdnc = 1.667, Z = −2.283, $p = .022$), "reflux" (Mdnp = 1.500, Mdnc = 1.000, Z = −2.949, $p = .003$), and "constipation" (Mdnp = 2.000, Mdnc = 1.333, Z = −2.176, $p = .030$) were more severe in patients compared to their matched controls (Table 3).

For patients with a pathogenic variant in *WNT10A*, mean total GSRS scores were higher in isolated oligodontia patients compared to their age- and gender-matched controls (Mdnp = 2.200, Mdnc = 1.500, Z = −2.238, $p = .025$). Furthermore, GI complaints related to "reflux" were more severe in isolated oligodontia patients with a pathogenic variant in *WNT10A* compared to their matched controls (Mdnp = 1.250, Mdnc = 1.000, Z = −2.375, $p = .018$). For non-*WNT10A* oligodontia patients, differences in severity of GI complaints with matched controls were not statistically significant (Table 3).

No correlation was found between the number of missing teeth and the severity of GI complaints ($r = .267$, $p = .255$).

**TABLE 1** Patient descriptives, GSRS total scores, TAC codes, and gene mutations

| | Age | Gender | Number missing teeth | GSRS Total score | TAC | Gene | Gene mutation |
|---|---|---|---|---|---|---|---|
| 1 | 21 | Female | 9 | 1,9 | 112.112.032.080 | *PAX9* | c.[180C>A];[=] p[(Tyr60*)];[(=)] |
| 2 | 16 | Female | 26 | 2,3 | 123.123.127.127 | *WNT10A* | c.[321C>A];[321C>A] p[(Cys107*)];[(Cys107*)] |
| 3 | 19 | Male | 9 | 1,6 | 142.158.192.192 | *WNT10A* | c.[682T>A];[831G>C] p[(Phe228Ile)];[(Trp277Cys)] |
| 4 | 20 | Male | 13 | 1,8 | 022.030.007.007 | *WNT10A* | c.[682T>A];[682T>A] p[(Phe228Ile)];[(Phe228Ile)] |
| 5 | 19 | Female | 13 | 2,6 | 042.046.056.056 | *WNT10A* | c.[321C>A];[682T>A] p[(Cys107*)];[(Phe228Ile)] |
| 6 | 21 | Female | 13 | 2,9 | 090.050.088.088 | *WNT10A* | c.[682T>A];[682T>A] p[(Phe228Ile)];[(Phe228Ile)] |
| 7 | 23 | Female | 10 | 1,3 | 018.018.069.069 | *WNT10A* | c.[321C>A];[682T>A] p[(Cys107*)];[(Phe228Ile)] |
| 8 | 27 | Male | 13 | 4,7 | 098.090.035.067 | *PAX9* | c.[180C>A];[=] p.[(Tyr60*)];[(=)] |
| 9 | 33 | Female | 12 | 2,2 | 026.028.088.088 | *WNT10A* | c.[682T>A];[682T>A] p[(Phe228Ile)];[(Phe228Ile)] |
| 10 | 26 | Female | 17 | 2,2 | 030.030.031.027 | *WNT10A* | c.[383G>A];[=] p[(Arg128Gln)];[(=)] |
| 11 | 19 | Male | 7 | 1,4 | 080.024.016.017 | *PAX9* | c.[180C>A];[=] p[(Tyr60*)];[(=)) |
| 12 | 26 | Female | 10 | 3,4 | 028.026.016.024 | *WNT10A* | c.[321C>A];[=] p[(Cys107*)];[(=)] |
| 13 | 16 | Male | 24 | 2,4 | 126.126.095.095 | *WNT10A* | c.[682T>A];[1084T>C] p[(Phe228Ile)];[(Cys362Arg)] |
| 14 | 37 | Female | 8 | 1,5 | 024.088.080.016 | *WNT10A* | c.[682T>A];[682T>A] p[(Phe228Ile)];[(Phe228Ile)] |
| 15 | 30 | Female | 19 | 2,9 | 030.094.087.087 | *WNT10A* | c.[321C>A];[682T>A] p[(Cys107*)];[(Phe228Ile)] |
| 16 | 27 | Female | 22 | 2,5 | 094.030.123.127 | *LRP6* | c.[2224_2225dup];[=] p[(Leu742fs)];[(=)] |
| 17 | 28 | Female | 17 | 1,3 | 126.070.089.089 | *LRP6* | c.[2224_2225dup];[=] p[(Leu742fs)];[(=)] |
| 18 | 16 | Male | 16 | 2,1 | 018.082.079.095 | *WNT10A* | c.[321C>A];[682T>A] p[(Cys107*)];[(Phe228Ile)] |
| 19 | 26 | Female | 21 | 1,7 | 094.094.031.095 | *LRP6* | c.[1779dup];[=] p[(Glu594*)];[(=)] |
| 20 | 36 | Female | 28 | 1,5 | 127.127.127.127 | *WNT10A* | c.[321C>A];[321C>A] p[(Cys107*)];[(Cys107*)] |

## 4 | DISCUSSION

There is an important role of deregulated Wnt signaling in both tooth agenesis and altered intestine homeostasis. Clinical observations suggest that patients who suffer from isolated oligodontia report GI symptoms. Therefore, this study compared the prevalences of self-reported GI symptoms in patients with isolated oligodontia caused by Wnt gene mutations or a gene in the loop of the Wnt/β-catenin and TGF-β/BMP pathway and dentate controls. The focus was specifically on *WNT10A*, its partner *LRP6* and the more directly related downstream target gene of the Wnt/β-catenin signaling pathway *MSX1* and its partner *PAX9* (Ogawa et al., 2006; Song et al., 2009; Yu et al., 2019). The *EDA* gene is also relevant to odontogenesis, playing a role in ectodermal tissue development, but oligodontia patients with mutations on the Eda/Edar/NF-κB pathway were excluded for two reasons. Firstly, they very rarely present with "isolated oligodontia," so they would not fulfil the inclusion criterium of having "isolated oligodontia without additional obvious ectodermal features." Secondly, the interaction between the Wnt/β-catenin and Eda/Edar/NF-κB pathways, involving the *EDA* gene, seems more indirect (Ogawa et al., 2006; Yin & Bian, 2015). To the best of our knowledge, Wnt/β-catenin activates the Eda/Edar/NF-κB pathway, via PAX9, member of the TGF-β/BMP pathway (Yu et al., 2019). In contrast, *MSX1* is a direct target of the Wnt/β-catenin signaling pathway. MSX1 forms a complex with PAX9, upregulating BMP4 expression and inducing activation of both Wnt and TGF-β/BMP signaling (Ogawa et al., 2006; Yin & Bian, 2015). PAX9 regulates the expression of the Wnt signaling antagonists DKK1 (Jia et al., 2017). LRP6 encodes a transmembrane cell-surface protein that functions as a co-receptor for the transmission of Wnt/β-catenin signaling cascade (Yu et al., 2019).

GI symptoms, specifically in the "reflux" and "abdominal pain" subdomain, were more common and more pronounced in patients diagnosed with isolated oligodontia compared to matched controls without tooth agenesis. In addition, higher GSRS-total scores indicated more severe complaints in the patient group with oligodontia than in the control group. This difference is caused by higher mean scores in the GSRS subdomains: reflux, abdominal pain, and constipation. These results support our clinical observation that patients diagnosed with isolated oligodontia present GI complaints more often and more severe. It is striking that patients score symptomatically high on the indigestion domain (score 2.59). The controls showed higher scores on the indigestion domain as well (score 1.99), when compared to the norm-value of 1.78 as derived from the aforementioned Swedish study (Dimenäs et al., 1996). An explanation for this difference cannot be offered.

When singling out patients with isolated oligodontia specifically caused by a *WNT10A* mutation and comparing these results to their dentate controls, the difference in severity of symptoms was also statistically significant. When looking at the underlying domain scores, it is noteworthy that abdominal pain and reflux symptoms are more common and symptoms of reflux more severe.

**TABLE 2** Prevalence of symptomatic GI complaints (GSRS scores ≥2) per domain and as a total score for patients versus their matched controls (count, % within group between brackets, *p* value)

| | Patients (*n* = 20) | Controls (*n* = 20) | WNT10A patients (*n* = 14) | Controls (*n* = 14) | PAX9 patients (*n* = 3) | Controls (*n* = 3) | LRP6 patients (*n* = 3) | Controls (*n* = 3) |
|---|---|---|---|---|---|---|---|---|
| Reflux | 8 (40.0) | 0 (0) | 5 (35.7) | 0 (0.0) | 3 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | *0.002*[a] | *0.002*[a] | *0.041*[a] | *0.041*[a] | *0.100* | *0.100* | *1.000* | *1.000* |
| Abdominal pain | 17 (85.0) | 8 (40.0) | 13 (92.9) | 6 (42.9) | 2 (66.7) | 1 (33.3) | 2 (66.7) | 1 (33.3) |
| | *0.003*[a] | *0.003*[a] | *0.013*[a] | *0.013*[a] | *1.000* | *1.000* | *1.000* | *1.000* |
| Indigestion | 13 (65.0) | 10 (50.0) | 9 (64.3) | 7 (50.0) | 2 (66.7) | 1 (33.3) | 2 (66.7) | 2 (66.7) |
| | *0.337* | *0.337* | *0.445* | *0.445* | *1.000* | *1.000* | *1.000* | *1.000* |
| Diarrhea | 6 (30.0) | 3 (15.0) | 5 (35.7) | 2 (14.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) |
| | *0.256* | *0.256* | *0.190* | *0.190* | *1.000* | *1.000* | *1.000* | *1.000* |
| Constipation | 12 (60.0) | 6 (30.0) | 8 (57.1) | 5 (35.7) | 3 (100) | 1 (33.3) | 1 (33.3) | 0 (0.0) |
| | *0.057* | *0.057* | *0.256* | *0.256* | *0.400* | *0.400* | *1.000* | *1.000* |
| GSRS total score | 11 (55.0) | 3 (15.0) | 9 (64.3) | 3 (21.4) | 1(33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) |
| | *0.008*[a] | *0.008*[a] | *0.054* | *0.054* | *1.000* | *1.000* | *1.000* | *1.000* |

Italics indicates *p* value.

[a]Statistically significant ($p < .05$).

For patients with a *PAX9* mutation, the high total and subdomain GSRS scores are noteworthy. When looking more closely at these scores, three out of three patients in this subgroup score ≥2 on reflux, indicating clinically relevant complaints. These three patients all have a stop mutation of the *PAX9* gene (c.180C>A;p. Tyr60*). Differences to matched controls were, however, not statistically significant due to the limited number of patients. The *PAX9* gene is a transcription factor playing an essential role in the development of the palate, teeth, thymus, limb, and parathyroid during mouse embryogenesis. PAX9 is expressed in the presumptive dental mesenchyme, where it plays an important role in the initiation of tooth development. It is, among others, also expressed in the upper gastrointestinal tract. PAX9 plays a role in the differentiation process of esophageal squamous epithelium, whereby loss of expression would play a role in human esophageal and oral squamous cell carcinoma (Gerber et al., 2002). To our knowledge, there are no studies describing a role for PAX9 in reflux complaints or gastroesophageal reflux disease (GERD) that would fully explain our observation. However, one might hypothesize a possible indirect association, since PAX9 is involved in the odontogenic Wnt pathway by regulating the expression of the Wnt signaling antagonists DKK1 and DKK2 (Jia et al., 2017). A role for DKK1 in the pathogenesis of GERD has been suggested (Lyros et al., 2014).

To conduct this study, all patients from the hospital database with isolated oligodontia caused by a Wnt signaling gene mutation were contacted. Due to the nature of the patient group, the study population was relatively small when compared to other studies using the GSRS questionnaire. Nevertheless, the results of the control group on almost all domains are comparable to those of a Swedish study among 2162 participants, focusing on norm values (Dimenäs et al., 1996). Hence, it can be assumed that the subjects in the control group are representative for the general population without isolated oligodontia. It should be noted that functional GI complaints are quite common, with prevalence rates of irritable bowel syndrome (IBS) between 5% and 26% in the western world (Hillilä et al., 2008). This complicates research in this field, especially in small populations such as in the present study. In addition, gender and age may affect the prevalence and severity of GI complaints (Tibblin et al., 1990). We tried to forestall this by choosing a case–control study design and matching the patients with isolated oligodontia to their controls, based on gender and age.

When evaluating GI complaints in patients with isolated oligodontia, the question arises as to whether such complaints could be caused by an impaired chewing function due to the missing teeth. Two studies addressing this issue could be identified in the literature, both showing an effect of the number of teeth lost and the presence of accurate dentures on the prevalence of gastrointestinal pathology (Khayyatzadeh et al., 2018; Tosello et al., 2001). However, literature provides no compelling evidence to substantiate such presumption among young, healthy (partially) dentate subjects. In addition, there are studies describing the impact of hypodontia on Oral Health Related Quality of Life (OHRQoL) including effects on the oral functional domain (Anweigi et al., 2013; Filius et al., 2018). These study methods differ widely, and genetics are not taken into

TABLE 3 Severity of GI complaints

| | Patients ($n = 20$) | Controls ($n = 20$) | WNT10A patients ($n = 14$) | Controls ($n = 14$) | PAX9 patients ($n = 3$) | Controls ($n = 3$) | LRP6 patients ($n = 3$) | Controls ($n = 3$) |
|---|---|---|---|---|---|---|---|---|
| Reflux | 1.80 ± 1.12 | 1.00 ± 0.00 | 1.82 ± 1.27 | 1.00 ± 0.00 | 2.33 ± 0.58 | 1.00 ± 0.00 | 1.17 ± 0.29 | 1.00 ± 0.00 |
| | *0.003*[a] | *0.003*[a] | *0.018*[a] | *0.018*[a] | *0.102* | *0.102* | *0.317* | *0.317* |
| Abdominal pain | 2.28 ± 0.62 | 1.70 ± 0.74 | 2.29 ± 0.41 | 1.79 ± 0.83 | 2.22 ± 1.35 | 1.44 ± 0.51 | 2.33 ± 0.88 | 1.56 ± 0.51 |
| | *0.022*[a] | *0.022*[a] | *0.059* | *0.059* | *0.593* | *0.593* | *0.285* | *0.285* |
| Indigestion | 2.65 ± 1.28 | 2.03 ± 0.80 | 2.64 ± 1.17 | 2.09 ± 0.85 | 2.92 ± 2.27 | 1.75 ± 1.09 | 2.41 ± 1.18 | 2.00 ± 0.25 |
| | *0.141* | *0.141* | *0.220* | *0.220* | *0.593* | *0.593* | *0.655* | *0.655* |
| Diarrhea | 1.63 ± 0.95 | 1.43 ± 0.80 | 1.55 ± 0.59 | 1.50 ± 0.91 | 2.33 ± 2.31 | 1.22 ± 0.38 | 1.33 ± 0.33 | 1.33 ± 7.78 |
| | *0.636* | *0.636* | *0.766* | *0.766* | *0.655* | *0.655* | *1.00* | *1.00* |
| Constipation | 2.38 ± 1.55 | 1.55 ± 0.66 | 2.38 ± 1.50 | 1.67 ± 0.72 | 3.33 ± 2.31 | 1.33 ± 0.58 | 1.44 ± 0.51 | 1.22 ± 0.38 |
| | *0.030*[a] | *0.030*[a] | *0.123* | *0.123* | *0.180* | *0.180* | *0.157* | *0.157* |
| GSRS total score | 2.21 ± 0.82 | 1.61 ± 0.48 | 2.19 ± 0.61 | 1.68 ± 0.52 | 2.67 ± 1.75 | 1.40 ± 0.47 | 1.82 ± 0.62 | 1.49 ± 0.24 |
| | *0.011*[a] | *0.011*[a] | *0.025*[a] | *0.025*[a] | *0.285* | *0.285* | *0.414* | *0.414* |

*Note:* Mean total scores and mean domain scores on the Gastrointestinal Symptom Rating Scale (GSRS) for non-syndromic hypodontia patients versus their matched dentate controls (mean ± standard deviation, *p* value).
Italics indicates *p* value.
[a]Statistically significant ($p < .05$).

account. In the present study, bias due to a possible correlation between the number of missing teeth and the prevalence or severity of GI symptoms and complaints could not be demonstrated. Including an extra group of patients with missing teeth other than caused by oligodontia could elucidate this matter conclusively. But matching on age, gender and the number and position of missing teeth would present with quite a challenge.

The complex interplay of factors leading to symptoms like abdominal pain, constipation, and reflux must be acknowledged. For evaluation of complaints, the GSRS questionnaire was applied, which is a subjective measure. Further research is needed to explore the role of the Wnt pathway in our gastrointestinal system. To demonstrate a causal relation between deregulation of Wnt signaling and GI complaints objective measures, which are often more invasive, are necessary. The findings in this study can contribute to justification of application of these invasive study methods.

In conclusion, the results from this study indicate that GI symptoms are more prevalent and more severe in patients with oligodontia and a deficiency in a Wnt pathway-related genes, when compared to controls without tooth agenesis. For now, we hope that our study creates awareness about a possible relation between Wnt gene related isolated oligodontia and the presence of GI symptoms. Additional studies in a larger population are necessary to further substantiate our findings and reveal a possible underlying pathogenic mechanism.

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## AUTHOR CONTRIBUTION

**Jamila Ross:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing-original draft; Writing-review & editing. **Lisanne Ruigrok:** Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing-original draft. **Willem Fennis:** Conceptualization; Methodology; Supervision; Writing-original draft; Writing-review & editing. **Marco Cune:** Conceptualization; Methodology; Supervision; Writing-original draft; Writing-review & editing. **Antoine Rosenberg:** Supervision. **Annick van Nunen:** Supervision; Validation; Writing-original draft. **Marijn Creton:** Conceptualization; Supervision. **Hans Kristian Ploos van Amstel:** Supervision; Writing-review & editing. **Marie-Jose van den Boogaard:** Conceptualization; Methodology; Supervision; Validation; Writing-original draft; Writing-review & editing.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.13954.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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