Oral Health Status of Patients with 22q11 Deletion Syndrome

Thesis

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By

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Abstract

Purpose: The purpose of this study is to better describe and define the oral health status and orthodontic characteristics of patients formally diagnosed with 22q11.2 deletion syndrome (DS), which is one of the most common microdeletion syndromes.[1] 22q11 DS occurs from a deletion, usually a *de novo* deletion, of a small part of chromosome 22, near the middle of the chromosome at a location known as q11.2.[1,6,20] Prior to modern genetic testing, the 22q11 deletion syndrome population was classified according to phenotype rather than genotype. In this, the affected population was segmented into sub-categories including DiGeorge Syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, CATCH 22, and more.[1,2,3] More recently, the 22q11.2 deletion was found in all of the previously listed syndromes.[1] This study serves to provide a comprehensive and broad overview of the dental and orthodontic characteristics for patients with 22q11.2 deletion syndrome. Secondary objectives include identifying any oral health disparities that may be present in patients with 22q11.2 deletion syndrome in order to provide appropriate prevention, treatment options and anticipatory guidance for dental providers.

Methods: This retrospective chart review investigates the unique and specific dental and orthodontic differences of patients with 22q11.2 DS as compared with peers of the same age and sex without 22q11 DS. All patients were patients of Nationwide Children's Hospital. Data collection included a retrospective chart review of medical history and dental and orthodontic clinical findings. Variables selected regarding medical history include age, sex, failure to thrive, history of low birthweight, congenital cardiac differences, neonatal and childhood endocrine disturbances, hypocalcemia, and velopharyngeal insufficiency. Clinical dental and orthodontic

variables include cleft status, anterior-posterior skeletal class, transverse skeletal relationship, dental occlusion, vertical dental relationships, presence of crossbite, arch length, presence of oral-nasal fistula, frenal attachment, dental history, gingivitis, oral hygiene, and caries.

All analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics of patient characteristics were tabulated for patients diagnosed with 22q11 DS. Associations between dental characteristics and heart/prematurity conditions were examined using Chi-square tests, Fisher's exact tests, and Welch's two sample t-tests. Four multiple logistic regression models were developed to examine whether the four significant associations remain statistically significant after adjusting for age and gender. Descriptive statistics of patient characteristics were tabulated by presence of 22q11 DS diagnosis. Logistic regression was used to examine whether certain patient characteristics are associated with having 22q11 DS. $P < 0.05$ was considered as statistically significant.

Results: Results indicate that patients with 22q11 DS were more likely to have cleft palate ($p < 0.0001$), increased overbite ($p < 0.0001$) and open bite ($p = 0.002$) (Table 2). Increased overbite and open bite were both significantly associated with the study group ($p < 0.0001$, $p = 0.002$), Results also indicated that patients with 22q11 DS are less likely to have active caries ($p < 0.001$) (Table 2). Failure to thrive was also associated with the study population ($p = 0.0002$) (Table 2). Cardiac conditions were linked to increased overjet ($p = 0.04$) and open bite ($p = 0.03$) (Table 4). Endocrine conditions were associated with lower face asymmetry (Table 4). Hypocalcemia was associated with decreased mandibular arch length and minor mandibular crowding (Table 4).

Conclusion: Patients with 22q11 DS have unique dental and orthodontic differences. Patients with 22q11 DS have a high risk of having medical conditions that are known to affect tooth development including failure to thrive, prematurity, cleft palate, and congenital heart defects. The craniofacial clinical presentation of 22q11 DS patients can vary widely, and dental and orthodontic treatment considerations should be individualized for each patient. Future research is needed to further define the oral health status of patients with 22q11 DS.

Dedication

This document is dedicated to my husband and parents, who have supported me through my entire education.

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Hammersmith K, Winter S, DiPaolo M, Claman D. Recruiting from a Distance Part 1: Virtual Externships. *J Dent Educ.* 2020;1-2.

Fields of Study

Major Field: Dentistry

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Chapter 1: Introduction

22q11.2 deletion syndrome (22q11 DS) is the most common human genetic microdeletion syndrome and one of the most common human multiple anomaly syndromes. Previous research shows that the prevalence of 22q11 DS is 1:3,000 - 1:4,000 live births.[1,20] Despite its prevalence, the literature defining the oral health status of patients with 22q11DS is somewhat limited.[1] It has been previously established that the 22q11 DS phenotype may have craniofacial and dental differences.[1]

Historically, patients with 22q11 DS may have been classified into one or more of any number of previously established named conditions based on phenotypic presentation, including DiGeorge Syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Shprintzen syndrome, CATCH-22, and more.[1,2] This difference in classification, in some part, can be attributed to the variable clinical presentation of the syndrome. More recently, the 22q11.2 deletion was found in all of the previously listed conditions.[1] Current diagnosis of 22q11 DS is now achieved through genetic testing, such as fluorescence in situ hybridization (FISH) or microarray testing. Currently, the routine newborn screenings panel does not include 22q11 DS.[5,20]

Genotypic variation in the 22q11 DS population arises from the deletion of a within the long arm of chromosome 22, near the middle of the chromosome at a location known as q11.2.[1,6,20] This deletion usually occurs de novo and is roughly 3 MB pairs in size; this can have an effect on approximately 30 genes.[20,21] This section of chromosome 22 houses the TBX1 gene, which has been linked previously to cleft palate in animal studies.[6]

The clinical phenotype of 22q11 DS is highly variable.[2] Previous research shows that over 180 medical and dental features both have been described, but no single feature occurs in all cases.[2] The range of clinical features include congenital heart disease, palatal abnormalities, characteristic facial features, immune deficiencies, hypocalcemia, feeding and swallowing problems, renal anomalies, hearing loss, velopharyngeal insufficiency or dysfunction, and laryngotracheoesophageal anomalies. The syndrome can also include growth hormone deficiencies, asymmetric crying facies, autoimmune disorders due to thymus hypoplasia, hypoparathyroidism with hypocalcemia, seizures, CNS anomalies, skeletal abnormalities such as scoliosis, polydactyly. In addition, craniosynostosis, ophthalmologic abnormalities, enamel hypoplasia, ADHD, autism, learning disabilities, developmental delays, intellectual disabilities, psychiatric conditions have been identified, among other features.[1,2,3,17] It should also be noted that it is common for any of the clinical findings of 22q11 DS are highly variable in their level of severity.[3]

Velopharyngeal dysfunction (VPD) is frequently observed in patients with 22q11 DS. VPD is a result of anatomic and/or functional differences in the soft palate and pharynx.[20] It occurs when the soft palate does not close tightly against the posterior pharyngeal wall, leading to air escaping from the oral cavity into the nasal cavity during speech.[18] This air escape imparts a hypernasal quality to the affected person's speech. Hypernasality can have significant effects on the intelligibility of speech, which is often complicated by compensatory articulation patterns.[19,20] VPD may be a result of underlying structural conditions such as submucous cleft palate which is found in 10-15% of patients with 22q11 DS, palatopharyngeal disproportions, or asymmetry, and the dysfunction may persist even after surgical correction.[11,18] Speech and language disorders including VPD are found in around 90% of the 22q11 DS population.[1,2,3,20]

Congenital heart defects are a common finding in patients with 22q11 DS, occurring in about 92% of the affected population, and are generally conotruncal heart defects. Conotruncal defects may include Tetralogy of Fallot, interrupted aortic arch, ventricular septal defects, vascular ring, and truncus arteriosus.[3,20]

Psychiatric conditions are present in around 79% of the affected population.[21] These psychiatric conditions include psychosis, mood disorders, anxiety disorders, and attention deficit-hyperactivity disorder.[21] Patients with 22q11 DS may have cognitive impairment of variable severity, ranging from borderline developmental differences to moderate intellectual disability.[22] Patients with 22q11 DS may also be highly emotionally reactive, have problems with regulation of emotion and behavior, be socially withdrawn, have poor peer relations, and social and general anxieties.[22] Another common psychiatric condition associated with 22q11 DS is schizophrenia, which usually occurs in adulthood.[24] Approximately one percent of patients with schizophrenia have 22q11 DS, making 22q11 DS the only confirmed recurrent genetic component that has ever been identified in schizophrenia.[24]

Dental and orthodontic characteristics of patients with DiGeorge Syndrome and other named conditions within the 22q11DS umbrella have been investigated previously. These studies have shown a higher prevalence of malocclusion and dental anomalies than the unaffected population.[1,2,3] These anomalies include enamel hypoplasia, lower face retrusion, tooth agenesis, class II malocclusion, and dental caries.[1,2,17] It is only recently that this area of research has been extended to the broader 22q11 DS population, inclusive of its sub-categories.[4] Current studies on the oral health status of patients with 22q11 DS are few and are comprised of small sample sizes outlined below. Additionally, the relationship, if any, of a given dental characteristic to a specific component condition of 22q11 DS has not been established.

It has also been demonstrated that patients with 22q11 DS have craniofacial differences. As previously described, patients with 22q11 DS experience palatal abnormalities such as velopharyngeal incompetence or dysfunction in up to 90% of the population and submucous cleft palate has been shown in 10-15% of the population.[1,2,3,11,18,20] Skeletal abnormalities such as lower face retrusion with a significantly smaller SNB angle have been found.[2] Malocclusions including angle class II occlusion with increased overjet have been established.[2]

The dental features of 22q11 DS are more variably and less understood. Tooth agenesis, also known as hypodontia, has been found in 5.5% of the population.[1,2,3] Enamel hypomineralization, enamel hypoplasia, and anatomic dental anomalies have been observed.[1,2,3,4] Enamel hypoplasia was observed at a rate of 30% and enamel hypomineralization was observed at a rate of 41%, which is significantly higher than the unaffected population, in which hypomineralization and hypoplasia been found to range between 5-15%[1] Lastly, severe rates of dental caries have also been observed in the 22q11 DS population, with higher rates of caries found than in the general population.[1,2,3,4]

A study 2017 from Lewyllie investigated the craniofacial and dental features of patients with 22q11 deletion syndrome in a sample size of 20 subjects.[2] In this study, investigators analyzed the craniofacial features of patients with 22q11 DS based on 3-dimensional facial scans, 2-dimensional clinical photographs, panoramic and cephalometric radiographs, and dental casts.[2] The conclusions of this study showed of significant retrusion of the lower part of the face and a higher prevalence of tooth agenesis.[2] This study lacked a control group, and the findings were compared against broad standards found in the literature.[2] These comparisons were not matched for age and sex.[2]

In 2002 Klingberg researched and published a study on oral manifestations of patients with 22q11 DS, finding that in the 53 patients included in the study, that dental anomalies, enamel hypomineralization, hypodontia, and dental caries were registered in high numbers in patients with 22q11 DS.[1] The main purpose of this study was to describe the oral manifestations of 22q11 DS and to relate the findings to medical conditions.[1] This study concluded that 22q11 DS affects the oral cavity and dental characteristics in a number of ways, as described above.[1] These findings are of particular importance in patients with 22q11 DS, as the congenital heart malformations and immunological problems found in the 22q11 DS population with the increased risk of infective endocarditis and other infections.[1] This study also lacked a control group and compared their findings to the broad standards found in the literature as well.[1] Further dental research and advocacy is clearly merited as these past studies, though small in sample size and lacking appropriate controls, indicate unique craniofacial, dental and orthodontic characteristics.[1,2]

As stated previously, failure to thrive, prematurity, and congenital heart defects are also commonly found in patients with 22q11 DS.[3] Prior dental research has shown that each of these conditions independently may be related to certain dental abnormalities. Specifically, failure to thrive is associated with enamel hypoplasia and severe early childhood caries.[12] Prematurity has been shown to be associated with increased caries susceptibility and enamel defects.[14] Congenital heart defects have been shown to be associated with enamel hypoplasia and caries.[13] This further shows that patients with 22q11 DS who have these associated conditions as part of their phenotype may be more likely to have a high caries risk.

The burden of pediatric and adult dental caries in the United States cannot be overstated.[15] Each year 24 million school hours are lost due to unplanned, emergency dental

care.[15] In 2017, there were 2.1 million emergency room visits for dental emergencies, and in the 17 year span between 1996-2013, $26.5 billion was spent on dental care for children and adolescents.[15] That being said, the financial and emotional burden of extensive orthodontic treatment, and the disease burden and cosmetic burden of enamel hypoplasia are high.[12,13,14,15] Patients with 22q11 DS may be at a higher risk for all of these dental conditions.

These dental characteristics, in conjunction with the myriad other clinical features of the 22q11 DS phenotype, may require specialized and often interdisciplinary management. Specifically, congenital heart malformations and immunological problems may both influence routine dental and orthodontic management, with the increased risk of infective endocarditis or dental infections affecting treatment options and antibiotic considerations.[1] Dental and orthodontic care may be complicated by behavioral and learning differences. Understanding the ramifications of 22q11 DS, both orally and systemically, will help provide the best dental and oral care for patients with 22q11 DS.

The primary purpose of this study is to define the oral health status and orthodontic characteristics of patients with 22q11 DS. Secondary objectives include identifying any oral health disparities that may be present in patients with 22q11 DS in order to provide more appropriate prevention, treatment options and anticipatory guidance as a dental provider. A tertiary goal is to use the identified dental characteristics to help dentists in assisting with identifying, diagnosing, and treating patients with 22q11 DS, as well as laying the groundwork for future research.

There are two main aims of this study. The first is to determine if patients with 22q11 DS have unique dental characteristics. The second is to determine if any dental characteristics are associated with specific systemic conditions commonly associated with the syndrome. This

research will further define the oral health status of patients with 22q11 DS in a meaningful way that will influence treatment recommendations for these patients in the future.

The 22q Center at Nationwide Children's Hospital (NCH) is a global center for patients with 22q11 DS. This clinic has an average of 202 patient visits each year for patients with 22q11 DS. Given this, NCH is in a position to conduct a study that obtains a significantly larger sample size based on the annualized number of patients with 22q11 deletion syndrome treated at the 22q Center each year.

Chapter 2. Methods

Study Design

This study is a retrospective chart review of medical history and dental and orthodontic findings of Nationwide Children's Hospital patients taken during routine dental exams. Data gathered from age and sex-matched controls were matched to corresponding patients with the 22q11 DS diagnosis.

Data Abstraction

A data query was performed for our study population and our control population. The study group included 201 individuals aged 0 - <18 years of age with a previous genetic diagnosis of 22q11 deletion syndrome by genetic testing including FISH or microarray seen at the Nationwide Children's Craniofacial Clinic for a routine exam in the last 5 years. The control group included 201 subjects of the same age and sex aged 0 - <18 years of age, with no previous diagnosis of 22q11 deletion syndrome, who were seen in the Nationwide Children's Dental Clinic for a routine dental exam and prophylaxis in the last year. Controls were randomly selected from patients who had dental hygiene visits at NCH dental clinic from 1/1/2020 to 12/31/2020 and were matched with cases based on age at visit and gender using R package 'MatchIt'.

Variables of interest requested in data query included age, gender, cleft status, anterior-posterior profile, transverse profile, occlusion, open bite, crossbite, arch length, oral nasal fistula, abnormal frenal attachment, dental history, gingivitis, oral hygiene, prematurity, failure to thrive,

low birthweight, heart condition, endocrine condition, hypocalcemia, velopharyngeal insufficiency/hypernasality, and VPI repair surgery.

Statistical Analysis

All analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics of patient characteristics were tabulated for patients diagnosed with 22q11 DS (Table 5). Association between dental characteristics and heart/prematurity conditions were examined using Chi-squared tests, Fisher's exact tests, and Welch's two sample t-tests (Table 3). Four multiple logistic regression models were developed to examine whether the four significant associations (shown in Table 3) remain statistically significant after adjusting for age and gender (Table 4). Descriptive statistics of patient characteristics were tabulated by presence of 22q11 DS diagnosis (Table 1). Logistic regression was used to examine whether certain patient characteristics are associated with having 22q11 DS (Table 2). $P < 0.05$ was considered as statistically significant.

Chapter 3. Results

The statistical analysis included 201 cases and 201 controls. Descriptive statistics with a comparison of all variables of cases versus controls are summarized below in Table 1. The mean patient age was 9 years (SD = 61, 80) and 59% of patients were male. Note that molar occlusion, abnormal frenal attachment, and gingivitis were not tested in the logistic regression, as they had high levels of missingness and the levels of missingness varied greatly between the groups.

Table 1. Patient characteristics in comparison of cases versus controls		
Patient characteristics	**Controls (N=201)**	**Cases (N=201)**
Age at visit in months, mean (SD)	104 (61)	112 (80)
Gender, n (%)		
Male	119 (59%)	111 (55%)
Female	82 (41%)	90 (45%)
Cleft lip, n (%)		
None	200 (99.5%)	200 (99.5%)
Left, complete	1 (0.5%)	1 (0.5%)
Cleft Palate, n (%)		
None	198 (98.5%)	162 (81%)
Yes	3 (1.5%)	39 (19%)
Molar left, n (%)		
I	61 (30%)	78 (40%)
II	23 (12%)	26 (13%)
III	14 (7%)	5 (2%)
IV	0 (0%)	30 (15%)
V	0 (0%)	19 (9%)
VI	0 (0%)	3 (1%)
Missing	**103 (51%)**	**40 (20%)**
Molar right, n (%)		
I	57 (28%)	79 (39%)
II	24 (12%)	25 (13%)

III	19 (10%)	5 (2%)
IV	0 (0%)	29 (15%)
V	0 (0%)	18 (9%)
VI	0 (0%)	3 (1%)
Missing	**101 (50%)**	**42 (21%)**
Overbite in percentage, mean (SD)	38 (29)	59 (28)
Overjet in mm, mean (SD)	2.6 (2.0)	2.8 (2.2)
Open bite, n (%)		
Yes	7 (3%)	21 (10%)
No	122 (61%)	87 (43%)
Missing	72 (36%)	93 (46%)
Crossbite, n (%)		
Yes	21 (10%)	31 (15%)
No	117 (59%)	170 (85%)
Missing	63 (31%)	0 (0%)
Abnormal frenal attachment, n (%)		
Yes	5 (2%)	7 (3%)
No	25 (12%)	194 (97%)
Missing	**171 (85%)**	**0 (0%)**
Gingivitis, n (%)		
Yes	94 (47%)	121 (60%)
No	25 (12%)	63 (31%)
Missing	**82 (41%)**	**17 (8%)**
Presence of caries, n (%)		
Yes	113 (56%)	28 (14%)
No	88 (44%)	131 (65%)
Missing	0 (0%)	42 (21%)
Prematurity, n (%)		
Yes	9 (4%)	14 (7%)
No	192 (96%)	187 (93%)
Failure to Thrive, n (%)		
Yes	4 (2%)	26 (13%)
No	197 (98%)	175 (87%)
Low Birth weight, n (%)		
Yes	3 (1%)	1 (0%)
No	198 (99%)	200 (100%)

Note: Molar left, molar right, abnormal frenal attachment, gingivitis were not tested in logistic regression models because they have high levels of missingness and the missingness levels were largely uneven between cases and controls. (see highlights in orange).

Logistic regression was used to investigate if there were any dental or orthodontic characteristics associated with having 22q11 DS, when adjusted for age and gender. It was found that cleft palate ($p < 0.0001$), increased overbite ($p < 0.0001$), and open bite ($p = 0.002$) were all significantly associated with having 22q11 DS, as summarized below in Table 2. Cleft palate was 15.98 times more likely to be associated with having 22q11 DS. For every one percent increase in overbite, the odds of having 22q11 DS increase by 3%. Patients with 22q11 DS were 4.25 times more likely to have an open bite. Presence of caries ($p < 0.0001$) was less likely to be associated with patients with 22q11 DS. Patients with 22q11 DS were 7.66 times more likely to have a failure to thrive diagnosis.

Table 2. Logistic regression to examine whether certain patient characteristics are associated with having 22q11 deletion syndrome.

Patient characteristics	**Adjusted OR***	**95% CI**	**P-value**
Cleft Palate			
None	Reference		
Yes	15.98	(5.65, 66.98)	**<0.0001**
Overbite in percentage	1.03	(1.02, 1.04)	**<0.0001**
Overjet in mm	1.05	(0.94, 1.19)	0.41
Open bite			
No	Reference		
Yes	4.25	(1.80, 11.22)	**0.002**
Crossbite			
No	Reference		
Yes	1.04	(0.57, 1.92)	0.9
Presence of caries			
No	Reference		
Yes	0.17	(0.10, 0.27)	**<0.0001**

Prematurity			
No	Reference		
Yes	1.72	(0.73, 4.25)	0.22
Failure to Thrive			
No	Reference		
Yes	7.66	(2.90, 26.4)	**0.0002**
* All logistic regression models were adjusted for age at visit and gender.			

The following table describes the test performed to investigate associations between dental characteristics and medical comorbidities including prematurity, failure to thrive, cardiac conditions, and endocrine conditions (Table 3). Lines marked in red had a significant association and are further outlined in Table 4.

Table 3. Testing associations between dental characteristics and heart/prematurity conditions

Dental characteristics	**Heart/ prematurity conditions**	**Test performed**	**P-value**	**Association?**
Cleft Palate	Prematurity	Fisher's exact test	0.31	No
A-P	Prematurity	Fisher's exact test	0.67	No
Transverse	Prematurity	Fisher's exact test	0.5	No
Molar left	Prematurity	Fisher's exact test	0.27	No
Molar right	Prematurity	Fisher's exact test	0.26	No
Overbite in percentage	Prematurity	Welch's Two sample t test	0.35	No
Overjet in mm	Prematurity	Welch's Two sample t test	0.19	No
Open bite	Prematurity	Fisher's exact test	1	No
Crossbite	Prematurity	Fisher's exact test	0.46	No
Maxilla Arch Length	Prematurity	Fisher's exact test	0.3	No
Mandibula arch length	Prematurity	Fisher's exact test	0.24	No
Oral nasal fistula	Prematurity	Fisher's exact test	1	No

Abnormal frenal attachment	Prematurity	Fisher's exact test	0.4	No
Gingivitis	Prematurity	Fisher's exact test	0.75	No
Oral Hygiene	Prematurity	Fisher's exact test	0.19	No
Presence of caries	Prematurity	Fisher's exact test	1	No
Cleft Palate	Failure to Thrive	Chi-squared test	0.12	No
A-P	Failure to Thrive	Fisher's exact test	0.71	No
Transverse	Failure to Thrive	Fisher's exact test	0.63	No
Molar left	Failure to Thrive	Fisher's exact test	0.28	No
Molar right	Failure to Thrive	Fisher's exact test	0.24	No
Overbite in percentage	Failure to Thrive	Welch's Two sample t test	0.05	No
Overjet in mm	Failure to Thrive	Welch's Two sample t test	0.05	No
Open bite	Failure to Thrive	Fisher's exact test	0.07	No
Crossbite	Failure to Thrive	Fisher's exact test	1	No
Maxilla Arch Length	Failure to Thrive	Fisher's exact test	0.28	No
Mandibula arch length	Failure to Thrive	Fisher's exact test	0.37	No
Oral nasal fistula	Failure to Thrive	Fisher's exact test	1	No
Abnormal frenal attachment	Failure to Thrive	Fisher's exact test	1	No
Gingivitis	Failure to Thrive	Chi-squared test	0.12	No
Oral Hygiene	Failure to Thrive	Fisher's exact test	0.66	No
Presence of caries	Failure to Thrive	Fisher's exact test	0.77	No
Cleft Palate	Heart Condition	Chi-squared test	0.2	No

A-P	Heart Condition	Fisher's exact test	0.42	No
Transverse	Heart Condition	Fisher's exact test	0.29	No
Molar left	Heart Condition	Fisher's exact test	0.45	No
Molar right	Heart Condition	Fisher's exact test	0.33	No
Overbite in percentage	Heart Condition	Welch's Two sample t test	0.73	No
Overjet in mm	Heart Condition	Welch's Two sample t test	**0.03**	Yes
Open bite	Heart Condition	Chi-squared test	**0.04**	Yes
Crossbite	Heart Condition	Chi-squared test	0.38	No
Maxilla Arch Length	Heart Condition	Fisher's exact test	0.74	No
Mandibula arch length	Heart Condition	Fisher's exact test	0.16	No
Oral nasal fistula	Heart Condition	Fisher's exact test	0.49	No
Abnormal frenal attachment	Heart Condition	Fisher's exact test	0.68	No
Gingivitis	Heart Condition	Chi-squared test	0.33	No
Oral Hygiene	Heart Condition	Chi-squared test	0.47	No
Presence of caries	Heart Condition	Chi-squared test	0.8	No
Cleft Palate	Endocrine Condition	Chi-squared test	0.84	No
A-P	Endocrine Condition	Fisher's exact test	0.59	No
Transverse	Endocrine Condition	Fisher's exact test	**0.02**	Yes
Molar left	Endocrine Condition	Fisher's exact test	0.47	No
Molar right	Endocrine Condition	Fisher's exact test	0.22	No
Overbite in percentage	Endocrine Condition	Welch's Two sample t test	0.47	No
Overjet in mm	Endocrine Condition	Welch's Two sample t test	0.19	No

Open bite	Endocrine Condition	Fisher's exact test	0.23	No
Crossbite	Endocrine Condition	Fisher's exact test	0.36	No
Maxilla Arch Length	Endocrine Condition	Fisher's exact test	1	No
Mandibula arch length	Endocrine Condition	Fisher's exact test	0.7	No
Oral nasal fistula	Endocrine Condition	Fisher's exact test	1	No
Abnormal frenal attachment	Endocrine Condition	Fisher's exact test	0.68	No
Gingivitis	Endocrine Condition	Chi-squared test	0.09	No
Oral Hygiene	Endocrine Condition	Chi-squared test	0.78	No
Presence of caries	Endocrine Condition	Chi-squared test	0.79	No
Cleft Palate	Hypocalcemia	Chi-squared test	0.71	No
A-P	Hypocalcemia	Fisher's exact test	0.76	No
Transverse	Hypocalcemia	Fisher's exact test	0.59	No
Molar left	Hypocalcemia	Fisher's exact test	0.96	No
Molar right	Hypocalcemia	Fisher's exact test	0.96	No
Overbite in percentage	Hypocalcemia	Welch's Two sample t test	0.89	No
Overjet in mm	Hypocalcemia	Welch's Two sample t test	0.07	No
Open bite	Hypocalcemia	Fisher's exact test	0.55	No
Crossbite	Hypocalcemia	Fisher's exact test	0.3	No
Maxilla Arch Length	Hypocalcemia	Fisher's exact test	0.74	No
Mandibula arch length	Hypocalcemia	Fisher's exact test	**0.004**	Yes
Oral nasal fistula	Hypocalcemia	Fisher's exact test	1	No
Abnormal frenal attachment	Hypocalcemia	Fisher's exact test	0.35	No
Gingivitis	Hypocalcemia	Chi-squared test	0.91	No
Oral Hygiene	Hypocalcemia	Chi-squared test	0.05	No
Presence of caries	Hypocalcemia	Chi-squared test	0.63	No

Cleft Palate	VPI Hypernasality	Fisher's exact test	0.67	No
A-P	VPI Hypernasality	Fisher's exact test	0.7	No
Transverse	VPI Hypernasality	Fisher's exact test	0.72	No
Molar left	VPI Hypernasality	Fisher's exact test	0.71	No
Molar right	VPI Hypernasality	Fisher's exact test	0.47	No
Overbite in percentage	VPI Hypernasality	Welch's Two sample t test	0.37	No
Overjet in mm	VPI Hypernasality	Welch's Two sample t test	0.53	No
Open bite	VPI Hypernasality	Chi-squared test	0.11	No
Crossbite	VPI Hypernasality	Chi-squared test	0.3	No
Maxilla Arch Length	VPI Hypernasality	Fisher's exact test	0.3	No
Mandibula arch length	VPI Hypernasality	Fisher's exact test	0.14	No
Oral nasal fistula	VPI Hypernasality	Fisher's exact test	1	No
Abnormal frenal attachment	VPI Hypernasality	Fisher's exact test	0.7	No
Gingivitis	VPI Hypernasality	Chi-squared test	0.08	No
Oral Hygiene	VPI Hypernasality	Chi-squared test	0.69	No
Presence of caries	VPI Hypernasality	Chi-squared test	0.06	No
Cleft Palate	VPI Surgery	Chi-squared test	0.92	No
A-P	VPI Surgery	Fisher's exact test	0.81	No
Transverse	VPI Surgery	Fisher's exact test	1	No
Molar left	VPI Surgery	Fisher's exact test	0.1	No
Molar right	VPI Surgery	Fisher's exact test	0.05	No
Overbite in percentage	VPI Surgery	Welch's Two sample t test	0.27	No
Overjet in mm	VPI Surgery	Welch's Two sample t test	0.92	No
Open bite	VPI Surgery	Fisher's exact test	0.36	No

Crossbite	VPI Surgery	Chi-squared test	0.76	No
Maxilla Arch Length	VPI Surgery	Fisher's exact test	0.2	No
Mandibula arch length	VPI Surgery	Fisher's exact test	0.07	No
Oral nasal fistula	VPI Surgery	Fisher's exact test	1	No
Abnormal frenal attachment	VPI Surgery	Fisher's exact test	1	No
Gingivitis	VPI Surgery	Chi-squared test	0.23	No
Oral Hygiene	VPI Surgery	Chi-squared test	0.71	No
Presence of caries	VPI Surgery	Fisher's exact test	0.17	No

Logistic regression was used to investigate if any of the medical conditions were associated with dental characteristics, when adjusted for age and gender as summarized below in Table 4. It was found that both increased overjet ($p = 0.04$) and open bite ($p = 0.03$) were significantly associated with the presence of cardiac conditions. Lower face asymmetry ($p = 0.03$) was associated with endocrine conditions. Hypocalcemia ($p = 0.005$) was associated with reduced mandibular arch length/mild crowding.

Table 4. Logistic regression to examine whether the associations shown in Table 2 remain statistically significant after adjusting for age and gender.

Outcome	**Patient characteristics**	**Adjusted OR***	**95% CI**	**P-value**
Cardiac Condition	Overjet in mm	0.8	(0.64, 0.97)	**0.04**
Cardiac Condition	Open bite			
	No	Reference		
	Yes	3.08	(1.10, 8.81)	**0.03**
Endocrine Condition	Transverse			
	symmetric	Reference		
	lower face asymmetry	0.27	(0.08, 0.85)	**0.03**
Hypocalcemia	Mandibula arch length			

	normal	Reference		
	spacing	2.32	(1, 1.004)	0.05
	mild crowding	8.88	(2.34, 58.31)	**0.005**
	severe crowding	0.99	(0.24, 5.03)	0.99
* All logistic regression models were adjusted for age at visit and gender.				

Table 5 below shows all of the characteristics within the 22q11 DS population. A number or variables listed below were not available to compare with the control population including regular dental check-up history, anterior-posterior profile, transverse profile, maxillary and mandibular arch length, oral nasal fistula, oral hygiene, cardiac conditions, endocrine conditions, hypocalcemia, and velopharyngeal insufficiency and associated surgical repair.

Table 5. Patient characteristics (cases only)	
Patient characteristics	**Cases (N=201)**
Age at visit in months, mean (SD)	112 (80)
Gender, n (%)	
Male	111 (55%)
Female	90 (45%)
Regular Dental Check-up history, n (%)	
Yes	138 (69%)
No	37 (18%)
Missing	26 (13%)
Cleft lip, n (%)	
None	200 (99.5%)
Left, complete	1 (0.5%)
Cleft Alveolus, n (%)	
None	200 (99.5%)
Bilateral complete	1 (0.5%)
Cleft Palate, n (%)	
None	162 (81%)
Soft and hard	7 (3%)
Soft	9 (5%)
Bifid uvula	3 (1%)
Submucous cleft	20 (10%)

A-P, n (%)	
class I	116 (58%)
class II	70 (35%)
class III	9 (4%)
Missing	6 (3%)
Transverse, n (%)	
symmetric	156 (78%)
midface asymmetry	6 (3%)
lower face asymmetry	13 (6%)
Missing	26 (13%)
Molar left, n (%)	
I	78 (40%)
II	26 (13%)
III	5 (2%)
IV	30 (15%)
V	19 (9%)
VI	3 (1%)
Missing	40 (20%)
Molar right, n (%)	
I	79 (39%)
II	25 (13%)
III	5 (2%)
IV	29 (15%)
V	18 (9%)
VI	3 (1%)
Missing	42 (21%)
Overbite in percentage, mean (SD)	59 (28)
Overjet in mm, mean (SD)	2.8 (2.2)
Open bite, n (%)	
Yes	21 (10%)
No	87 (43%)
Missing	93 (46%)
Crossbite, n (%)	
Yes	31 (15%)
No	170 (85%)
Crossbite Location, n (%)	
anterior	12 (6%)
anterior, right posterior	1 (0.5%)
anterior, left posterior	4 (2%)
anterior, right posterior, left posterior	1 (0.5%)
right posterior	3 (1%)

left posterior	8 (4%)
right posterior, left posterior	2 (1%)
No crossbite	170 (85%)
Maxilla Arch Length, n (%)	
normal	63 (31%)
spacing	86 (43%)
mild crowding	35 (17%)
severe crowding	10 (5%)
Missing	7 (4%)
Mandibula arch length, n (%)	
normal	63 (31%)
spacing	71 (35%)
mild crowding	46 (23%)
severe crowding	10 (5%)
Missing	11 (6%)
Oral nasal fistula, n (%)	
Yes	2 (1%)
No	199 (99%)
Abnormal frenal attachment, n (%)	
Yes	7 (3%)
No	194 (97%)
Location frenal attachment, n (%)	
Maxillary anterior	2 (1%)
Mandibular anterior	2 (1%)
Missing	197 (98%)
Gingivitis, n (%)	
Yes	121 (60%)
No	63 (31%)
Missing	17 (8%)
Oral Hygiene, n (%)	
good	38 (19%)
fair	123 (61%)
poor	36 (18%)
Missing	4 (2%)
Presence of caries, n (%)	
Yes	28 (14%)
No	131 (65%)
Missing	42 (21%)
Prematurity, n (%)	
Yes	14 (7%)
No	187 (93%)

Failure to Thrive, n (%)	
Yes	26 (13%)
No	175 (87%)
Low Birth weight, n (%)	
Yes	1 (0%)
No	200 (100%)
Heart Condition, n (%)	
Yes	143 (71%)
No	58 (29%)
Endocrine Condition, n (%)	
Yes	49 (24%)
No	152 (76%)
Hypocalcemia, n (%)	
Yes	35 (17%)
No	166 (83%)
VPI Hypernasality, n (%)	
Yes	81 (40%)
No	120 (60%)
VPI Surgery, n (%)	
Yes	35 (17%)
No	166 (83%)

Chapter 4. Discussion

Results indicate that patients with 22q11 DS were more likely to have cleft palate ($p < 0.0001$), increased overbite ($p < 0.0001$) and open bite ($p = 0.002$) (Table 2). All types of cleft palate were included in this categorization including cleft of the soft palate, soft and hard cleft palate, bifid uvula, and submucous cleft. Though these variables were collected individually for the study group, the data available for the control group did not have this level of detail, therefore, the data were combined. Cleft palate was found in 19% of the study population, consistent with current literature, in which some type of anatomic difference to the palate was observed in 9-11% of cases.[6] Presence of anatomic palatal differences in the 22q11 DS population has been researched, and a possible association between two adjacent single nucleotide polymorphisms upstream of TBX1 and the cleft palate phenotype has been documented in animal models utilizing mice.[6] The TBX1 gene lies within the 22q11 region, and it has been shown that inactivation of one TBX1 allele does not cause cleft palate, but inactivation of both alleles does.[6] Though definitive genetics on the presence of cleft palate in patients with 22q11 DS is still unknown, the association is well-established and currently being investigated.[6]

Increased overbite and open bite were both significant findings within the study group ($p < 0.0001$, $p = 0.002$). (Table 2). Overbite and open bite are both measures of the vertical relationship of the anterior teeth, and significant results for both variables is interesting, as these two types of occlusal findings represent ends of the vertical spectrum. Increased overbite and an open bite may both be secondary manifestations of a class II skeletal profile, which is indicative of smaller lower jaw in relation to the upper jaw. The class II profile may be a resultant of the

mandibular retrusion that has been established as a contributing factor in previous studies on patients with 22q11 DS.[2] Vertical relationship of the incisors can also be influenced by environmental factors and habits such as digit sucking or prolonged pacifier use; the presence of a non-nutritive sucking habit was not studied here. Also, the variability of depth of bite may highlight the fact that the phenotype of 22q11 DS is also highly variable.

Results also indicated that patients with 22q11 DS are less likely to have active caries ($p < 0.001$) (Table 2). There are considerations regarding this finding. First, there was high level of missingness from the study population for this variable, making this data point weak from a statistical standpoint. Second, the control patients would have likely received a radiographic evaluation at the time of clinical exam, as this type of evaluation is a routine part of the dental recall exam. In this, for the control population, there is better diagnostic ability to detect caries, which is an observational bias towards caries in the control group. The study population received only a visual exam and so for many patients, interproximal and other small caries may not have been detected. Third, the affected population data only documented active carious lesions detected during that unique appointment, not total caries experience, which would include both treated and untreated decay. Fourth, the control data collection period including a period of time in which the NCH Dental Clinic was temporarily closed for routine care for approximately 6 weeks, due to the COVID-19 pandemic. Due to this, upon re-opening, the patients with untreated decay, and therefor highest risk for caries were preferentially scheduled. Additionally, because of delays in preventative care, new carious lesions may have formed that would ordinarily have been previously addressed. Thus, the study year selected may have a disproportionately high number of caries in the control population. The findings here that show patients with 22q11 DS are less likely to have caries (Table 2) is inconsistent with the previous

literature, that shows affected patients may have increased risk for caries and impaired oral health. This warrants further investigation.[1]

Failure to thrive was also associated with the study population ($p = 0.0002$) (Table 2). This association remains significant after adjusting for age and gender. This supports previous literature which highlights failure to thrive as a coexisting condition in many 22q11 DS patients.[5] Failure to thrive occurs when a patient's weight gain is consistently and significantly below set percentiles of that of other children of similar age and sex and is often also associated with feeding problems.[5] It has been found that at least 30% of patients with 22q11 DS have feeding difficulties, which can also arise from preexisting palatal anomalies.[5,11]

Velopharyngeal insufficiency or dysfunction (VPD) was found in 40% of the study population (Table 5). This finding supports similar research findings that have found the prevalence of VPD in the study population at 30% or higher.[10,11,20]

Cardiac conditions were linked to increased overjet ($p = 0.04$) and open bite ($p = 0.03$) (Table 4). This association remains significant after adjusting for age and gender. In data collection, a variety of cardiac conditions qualified as a positive finding, including those more minor defects that do not merit surgery or have physical restrictions. The most common congenital heart defects associated with 22q11 DS include tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosis.[3] These anatomic differences are often termed conotruncal heart defects, which are those heart defects characterized by a structural abnormality of the cardiac outflow tract.[7] Research shows that conotruncal heart defects may be related to neural crest cell proliferation early in fetal development.[7] The association found between cardiac conditions and these malocclusions is interesting, and it is possible that the neural crest cells affected in conotruncal heart defects may also influence other dental

characteristics and dental development. Atypical neural crest migration patterns have been implicated in other craniofacial conditions, including Treacher-Collins syndrome, fetal alcohol syndrome, hemifacial macrosomia and craniofrontonasal syndrome or dysplasia.[23]

Endocrine conditions were associated with lower face asymmetry (Table 4). This association remains significant after adjusting for age and gender. It is widely known and accepted that patients with 22q11 DS often have unique facial characteristics including malar hypoplasia, small and down-slanting palpebral fissures, low nasal bridge, prominent nose with squared-off or bulbous nasal tip, the oral aperture may be small and open at rest, and auricles may be malformed.[1] It has also been established that asymmetric crying facies occur more frequently in the 22q11 DS population than in the general population.[8] Asymmetric crying facies is a result of inadequate downward motion of the lip, found to be associated with the depressor anguli oris and the depressor labii inferioris muscles, which are both innervated by the mandibular branches of the facial nerve.[8] The defect occurs as a result of compression of the facial nerve, or faulty development of the nerve or muscles.[8] In our study, the lower face asymmetry found in the 22q11 DS population was not associated with a functional shift that may be related to crossbites; in essence, crossbites were not detected more frequently in the study group than in the control group (Table 2). With this understanding, it is suggestive is that the asymmetry of the lower face seen in the study population may not be related to crossbite/functional shift and may have different anatomic and neuromuscular origins. When lower face asymmetry and midface asymmetry were combined, 9% of the study population had asymmetry. This indicates that facial asymmetry in general should be more frequently acknowledged as a clinical finding within the phenotype of 22q11 DS.[8] Additionally, the

relationship of facial asymmetry without a lateral functional shift/crossbite in the 22q11 DS population could be further studied in light of the presence of infantile asymmetric crying facies.

Hypocalcemia was associated with decreased mandibular arch length and minor mandibular crowding (Table 4). This association remains significant after adjusting for age and gender. The nature of neonatal and infantile hypocalcemia is highly variable, and this retrospective study was unable to analyze if the subject's hypocalcemia was chronic or transient, early or late onset, what level of supplementation the patient received, and parental compliance with supplementation. Currently, certain high-risk infants—such as preterm infants, those of diabetic mothers, those with prenatal asphyxia, and those infants of extremely low birthweight, are screened for hypocalcemia.[9] In this, infants who do not meet criteria for screening may suffer from lack of management and/or delayed supplementation. To further complicate things, patients with hypocalcemia are usually asymptomatic.[9] The finding of hypocalcemia in association with reduced mandibular arch length and mild crowding also merits future study (Table 4).

Table 5 summarizes all of the findings found only within the study population. Variables that we did not have available to compare to the control population include regular dental check-up history, anterior-posterior facial profile, transverse facial profile, maxillary and mandibular crowding, oral nasal fistula, oral hygiene, diagnosis of cardiac condition, endocrine condition, hypocalcemia, or VPD and history of VPD surgery. As mentioned above, the study group had an incidence of VPD of 40%, which supports the current literature.[11] Hypocalcemia had a prevalence of 17% within the study group. The study group had a 69% rate of regular dental check-ups. The most common cleft type was submucous cleft, at 10% of the population, which also supports the literature that has found submucosal cleft palate at a rate of 15% in patients with 22q11 DS.[11] 9% of the study group had some type of facial asymmetry, consistent with the

literature, that has found asymmetric crying facies in 14% of patients with 22q11 DS.[8] Gingivitis (60%) and fair to poor oral hygiene (79%) was found in the study population, indicating that the study group population is likely to be at medium to high caries risk. High caries rate has been found in previous literature.[2] (Table 5)

Molar occlusion, abnormal frenal attachment, and gingivitis all had high levels of missingness and were excluded from analysis between the study group and the control group. However, molar occlusion in the study group did closely mimic the molar occlusion in the control group (Table 1). The prevalence of gingivitis was high for both groups and abnormal frenal attachments were seen at a similar rate as well (Table 1).

Strengths of this study include its robust sample size, which is over three times that of past studies.[1] This is also the first study on dental and orthodontic characteristics that provided an age and sex-matched control group, rather than comparing to broad standards.[1,2] There were many other strengths including access to comprehensive medical and surgical history, which provided insight on links between various comorbidities with dental and craniofacial characteristics.

Limitations of this study include the fact that radiographic analysis was not possible within the study population, so we were unable to analyze for tooth agenesis, a finding previously demonstrated in higher numbers in the 22q11 DS population.[2] Another major limitation was we could not analyze any information regarding enamel defects, which is another finding previously demonstrated in the 22q11 DS population.[1] The final limitation was this study's retrospective nature, which impacted the study in several ways. First, we were unable to determine if patients in either group had undergone orthodontic treatment, which can significantly change clinical dental and orthodontic findings. However, as patients had a mean

age of 9 years old, it is unlikely that they have already undergone orthodontic intervention, and this should be viewed only as a minor limitation. Secondly, there was incomplete data for many variables and the data was collected by a large number of providers (over 20) with no calibration or standardization. However, these providers all trained in the same residency program and each of the variables collected were objective variables with well-defined clinical features.

Future research on the oral health status of patients with 22q11 DS is indicated. There were variables not available for study in this research that have been identified in previous studies, including enamel defects and tooth agenesis.[1,2] Additionally, the addition of prospective data collection would allow for parent interview for history of fluoride history, habits, feeding history, and trauma which are all environmental factors that can affect dental development and other dental clinical findings, independent of genetic factors. Also, a parent history may provide further detail on medical history including calcium supplementation, and surgical history which will help to further define medical and dental variables.

The acquisition of a radiographic analysis within the study population would allow for both comprehensive assessment of tooth agenesis, caries, and other anomalies such as the presence of supernumerary teeth. Further research between any association between enamel defects and caries rate, as well as in association with medical comorbidities is warranted. A prospective study is in the data collection phase now at Nationwide Children's Hospital collecting many of these variables. This study offers preliminary support for the importance of this upcoming prospective study.

There is still much to learn about the oral health status of patients with 22q11 DS, but this study both confirms the current literature and providers a new insight and perspective on the oral health status of patients with 22q11 DS.

Chapter 5. Conclusion

1. Patients with 22q11 DS have unique dental and craniofacial characteristics.
2. Patients with 22q11 DS have a high risk of having medical conditions that are associated with dental and craniofacial differences, such as failure to thrive, prematurity, palatal differences and congenital heart defects.
3. The craniofacial clinical presentation of 22q11 DS patients can vary widely, and dental and orthodontic treatment considerations should be individualized for each patient.
4. Future research is needed to further define the oral health status of patients with 22q11 DS.

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