CURRICULUM VITAE

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Columbia University College of Dental Medicine New York, NY May 2010
Doctor of Dental Surgery

University of Maryland, College Park College Park, MD June 2004
Bachelors of Science in Computer Science

III. RESEARCH and TEACHING EXPERIENCE

Lecture Ortho-Perio Seminar series May 2012
University of Maryland Dental School
Presented on the topic of Complications of Orthodontic Treatment

Lecture Ortho-Pedo Seminar series June 2012
University of Maryland Dental School
Presented on the topic of Headgear

Orthodontic Course 2011- Present
University of Maryland Dental School
Lectured on Diagnosis and Treatment planning to 3rd year Dental students

Growth and Development Course 2011- Present
University of Maryland Dental School
Lectured on Growth and Development to 2nd year Dental students, UMB

Teaching Assistant in Orthodontics Lab 2010- present
University of Maryland Dental School
Reviewed Clinical and Laboratory procedures with 2nd year Dental students

Student Researcher Summer 2006-2007
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National Institute of Dental and Craniofacial Research
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Studied the mechanisms of TGF-beta regulation of T-cell immunity and tolerance in animal models to understand the pathogenesis of autoimmunity and inflammation, cancer and infectious diseases

IV. PUBLICATIONS/PRESENTATIONS

Impact of Dental Symptoms on Daily Living among Harlem Adults
Nhu-Uyen Cung, Eric Schrimshaw MS, Carol Kunzel PhD
Poster Presentation at IADR Research Symposium in San Diego, CA March 2011

Findings of Carotid Calcifications Using Cone Beam Computed Tomography
Nhu-Uyen Cung, Steven R. Singer, DDS, Christos Angelopoulos, DDS
Published in Columbia Dental Review 2008-2009

A Role of Inhibitory Helix-Loop-Helix Protein ID3 in the Regulation of Salivary Glands Inflammation
Nhu-Uyen Cung, Jun Li MD PhD, Takashi Maruyama PhD, Wanjun Chen MD
Poster Presentation at NIDCR in Bethesda, MD August 2007

VI. HONORS AND AWARDS

Herbert J. Bartelstone Award for Excellence in Pharmacology May 2010

Quintessence Award Research Recipient May 2010

NIDCR Summer Research Award Recipient Summer 2008

Jack Klatell Scholarship for Outstanding Achievement Spring 2008

ADA Dental Student Award for Achievement 2007-2008

Deans Award of Recognition for Academic Achievement 2006-2007

Senatorial Scholarship 2010-present

VII. LICENSURE

Maryland Dental License August 2010
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ABSTRACT

Radiographic Evaluation of Craniofacial Skeletal Structures in Patients with Neurofibromatosis Type 1

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Introduction: Neurofibromatosis type 1 (NF1, also known as von Recklinghausen's disease) is a genetic disorder with an autosomal dominant pattern of inheritance affecting the skin, skeletal, and neural tissues. A defect in the NF1 gene results in a hyperactive Ras pathway, which can in turn activate a variety of signaling pathways in a broad range of cells and tissue types. The purpose of the study was to examine cephalometric radiographs to assess craniofacial morphology of NF1 patients. **Methods:** A total of 74 Caucasian adult patients with NF1, and their age and gender matched controls, were selected for the study. Cephalometric radiographs were obtained for all subjects and traced in the Dolphin Software. Sixteen (16) cephalometric (linear and angular) measurements reflecting the dimensions of the cranial base, maxilla, mandible, and vertical facial heights were collected and analyzed. **Results:** The results showed that patients with NF1 had shorter mandible, shorter maxilla, shorter cranial base, and shorter anterior face compared with healthy controls. The length of the mandible, anterior and posterior facial heights, ramal height and the anterior cranial base correlated with the height of NF1 patients. **Conclusion:** In conclusion, the NF1 gene influences the growth of craniofacial bones, thus contributing to the characteristic facial morphology in NF1.

Radiographic Evaluation of Craniofacial Skeletal Structures in Patients with Neurofibromatosis Type 1

Nhu-Uyen Cung, DDS

Thesis submitted to the Faculty of the Graduate School of the

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Introduction

Neurofibromatosis type 1 (NF1, also known as von Recklinghausen's disease) is a genetic disorder with an autosomal dominant pattern of inheritance affecting the skin, skeletal, and neural tissues. It affects 1 in 3000 births with no gender or race predilection[1].

NF1 is characterized by a wide variability and unpredictability of clinical manifestations in multiple organ systems. Common signs and symptoms of NF1 include multiple café-au-lait spots, maxillary and inguinal freckling, multiple discrete dermal neurofibromas, learning disabilities, Lisch nodules, and increased risk of a variety of benign and malignant tumors. Skeletal abnormalities occur in nearly half of NF1 patients. These skeletal manifestations that have been reported included focal bony lesions, mild shortness of stature, tibial dyplasia, scoliosis, and sphenoid wing dysplasia[2].

Individuals with NF1 are heterozygous (haploinsufficient) for a loss-of-function mutation in *NF1*, the gene that encodes the tumor suppressor neurofibromin, which negatively regulates the activity of an intracellular signaling molecule Ras by acting as a GTPase activating protein (Ras-GAP). At a cellular level, this results in a hyperactive Ras pathway, which can in turn activate a variety of signaling pathways in a broad range of cells and tissue types[3].

Various Ras-GAP proteins, like neurofibromin, accelerate the hydrolysis of Ras-GTP to Ras-guanosine diphosphate (GDP), converting it from an active form to the inactive

form, and thereby negatively regulating the Ras signal[4]. Ras is a small G- protein involved in transmitting signals from growth factor receptors to a cascade downstream that alters gene expression in various cells. Studies indicate that besides its tumor suppressor role, neurofibromin regulates cellular proliferation, differentiation, development, and homeostasis in many tissues. Neurofibromin functions in neuron differentiation[5], cardiac development[6], repair of the vascular endothelium[7], lymphocyte genesis and function[8], wound healing mediated by fibroblasts[9], and osteoblast differentiation and mineralization[10].

Kuorilehto et al[11] demonstrated an intense expression of neurofibromin in murine cartilage and the periosteum. Thus, a deficiency in *NF1* expression may lead to various clinical manifestations due to inappropriate development of bones[11]. Yu et al[12] determined that neurofibromin and its control of Ras signaling are necessary for osteoprogenitor homeostasis. Kolanczyk et al[13] found that osteoblasts from NF1-deficient mice show decreased abilities to differentiate and mineralize, whereas chondrocytes demonstrate a lower proliferation rate and defective differentiation. In a more recent study, Chen et al[14] used RT-PCR, immunofluorescence, and Western blot experiments to demonstrate the expression of neurofibromin in human osteoblasts and chondrocytes. These study results support a role of neurofibromin in normal bone development and remodeling in humans.

Animal models with hyperactive Ras pathways have been found to develop shorter faces and dwarf-like phenotypes[15]. Previous work has shown evidence of a shortened cranial

base in individuals with NF1[16], of which the sphenoid bone is an important skeletal element. The shortened cranial base may give rise to differences in facial projection and cranial shape[17]. Moreover, morphological differences in the sphenoid bone may explain its predilection to dysplasia, a common problem in NF1.

NF1 is associated with a variety of skeletal abnormalities. Our interest is focused on the effects of NF1 mutations in the development of craniofacial structures. Dental abnormalities, including increased caries, premature tooth eruption, and periapical cemental dysplasia have been reported in the literature[18]. More recent studies reported the presence of an enlarged mandibular foramen, a wide and branching inferior alveolar canal, a shorter mandible, maxilla and cranial base [16,18]. In general, there is limited literature regarding dental abnormalities and craniofacial skeletal characteristics in individuals with NF1.

Purpose of Study

The aim of this study is a cephalometric analysis of craniofacial regions, in particular the morphology of the cranial base and sphenoid bone, in adults with NF1 with an age and sex-matched sample of healthy control subjects. Specific areas of investigation include: 1) morphologic differences in oro-cranial structures (maxilla, mandible, facial heights), 2) osseous abnormalities involving the sphenoid bone (which is prone to dysplasia in NF1), and 3) the correlations between 16 cephalometric measurements and three phenotypic features of NF1 (height, head circumference, interpupillary distance).

Hypothesis 1 – Differences between NF1 and Control

H_0: There is no significant difference between NF1 patients and their matched healthy controls in the 16 cephalometric measurements listed below.

A. Vertical facial projection

1. AFH
2. PFH
3. PFH/AFH
4. UAFH
5. LAFH
6. LAFH/AFH

B. Maxilla

7. ANS-PNS
8. SNA
9. ANB

C. Mandible

10. Co-Gn
11. Co-Go
12. SNB
13. Sn-GoGn

D. Cranial Base

14. S-N
15. S-Ba
16. SNBa

H_1: There is a significant difference between NF1 patients and their matched healthy controls in the 16 cephalometric measurements

Hypothesis 2 – Correlation between cephalometric measurements and phenotypes in NF1 patients

H_0: There are no significant correlations between the sixteen cephalometric measurements and the three phenotypic measurements.

H_1: There are significant correlation between the sixteen cephalometric measurements and the three phenotypic measurements.

Material And Methods

Sample Selection

A total of 74 patients, 45 females (20-80 years of age), and 29 males (21-66 years of age) were included in the study. These patients were diagnosed with NF1 and evaluated at the National Institutes of Health in Bethesda, MD as part of a protocol to quantitatively phenotype and identify genetic modifiers of severity in NF1 (Variation in Gene Expression in Neurofibromatosis Type 1, 05-HG-0152, Douglas Stewart, PI).

Age (in years), ethnicity and gender matched controls were selected from a group of healthy patients with no history of genetic disorders, who earlier had undergone

orthodontic evaluation in the Department of Orthodontics, University of Maryland School of Dentistry, Baltimore, MD (UMB).

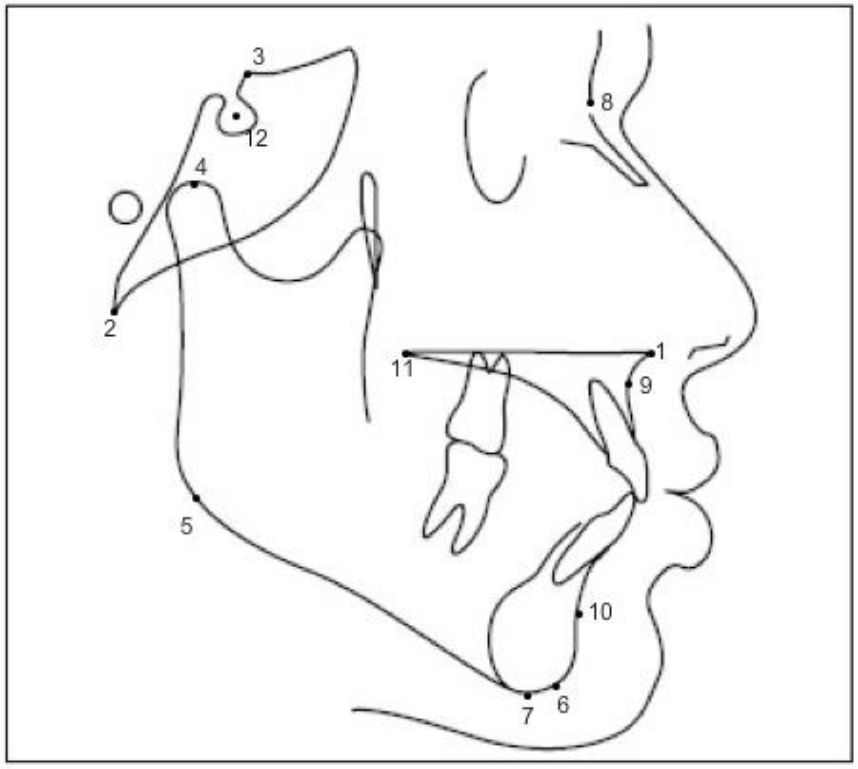
The mean age of both the NF1 and control subjects was 40.1 years (SD 15.2, range 20–80 years). The male-to-female ratio was comparable at 29/45. All subjects were Caucasian.

Methods

For all subjects, cephalometric radiographs were obtained from the National Institutes of Health and UMB for comparative analysis. All of the subjects' identities were blinded to the investigator (WC). An independent research assistant numbered cephalometric radiographs in a random order. Cephalometric radiographs were then traced for landmarks and measurements by the investigator. Linear and angular measurements were measured to the nearest tenth of a millimeter or degree, respectively, utilizing Dolphin software.

The cephalometric landmarks used in the study are illustrated and explained in Figure I. Cephalometric measurements of specific bones extracted from the landmarks are abbreviated and explained in Table I.

Figure I. Cephalometric Landmarks



1. ANS (Anterior Nasal Spine), tip of the anterior nasal spine;
2. Ba (Basion), most posteroinferior point of the basilar part of the occipital bone;
3. Cl (Clinoidale), most superior point on the contour of the anterior clinoid;
4. Co (Condylion), most superior point of the mandibular condyle;
5. Go (Gonion), the most inferior, posterior, and lateral point on the angle of the mandible
6. Gn (Gnathion), most anteroinferior midline point on the mandible
7. M (Menton), most inferior point of the mandibular symphysis
8. N (Nasion), most anterior point on the frontonasal suture
9. A (Point A), deepest concavity of the anterior bony outline of the maxilla
10. B (Point B), deepest concavity of the anterior bony outline of the mandible
11. PNS (Posterior Nasal Spine), tip of the posterior spine of the palatine bone in the hard palate;
12. S (Sella), midpoint of sella turcica.

Table I. Definition of Skeletal Measurements

Vertical Facial Proportions

AFH: Anterior Facial Height, measured from Nasion-Menton, denotes length of anterior face

PFH: Posterior Facial Height, measured from Sella-Gonion, denotes length of posterior face

PFH/AFH: ratio of Posterior Facial Height to Anterior Facial Height; denotes differential length of anterior and posterior face

UAFH: Upper Anterior Facial Height, measured from Nasion-ANS

LAFH: Lower Anterior Facial Height, measured from ANS-Menton

LAFH/TAFH: ratio of Lower Anterior Facial Height to Total Facial Height; denotes proportion of lower anterior face.

Maxilla

PNS-ANS: maxillary length, distance measured from the anterior nasal spine to posterior nasal spine.

SNA: angle measured between Sella-Nasion and A point, denotes sagittal relationship of the maxilla to cranial base

ANB: angle measured between maxilla and mandible with respect to N, denotes the sagittal relationship between maxilla and the mandible

Mandible

Co-Gn: measured from condylion to gnathion in mm, denotes total mandibular length

Co-Go: condylion to gonial angle measured in mm, denotes the height of ramus of mandible

Sn-GoGn: measured as angle formed by S-N and lower border of the mandible (GoGn), denotes vertical relationship of the mandible to the cranial base.

SNB: angle measured between S-N and B point, denotes sagittal relationship of the mandible to cranial base

Cranial Base

S-N: measured from Nasion to Sella in mm, denotes length of anterior cranial base

S-Ba: measured from Sella-to Basion in mm, denotes length of posterior cranial base

SNBa: cranial base angle formed by Nasion-Sella-Basion, denotes cranial base flexure

Statistical analysis

All statistical analyses were performed using IBM SPSS Base 20.0 statistical package (IBM Corporation, 1998, Version 20). A total of 74 NF1 patients and 74 healthy controls were included in the statistical analysis. Participants were age, ethnicity, and gender matched. The data was tested for significant differences using paired *t*-tests. The correlations between the cephalometric measurements and the three phenotypic measurements of a subgroup of 68 NF1 patients were analyzed (6 subjects were excluded due to missing data). Significant correlations were then used in a standard multiple regression analysis on height. A p-value of ≤ 0.05 was considered significant.

Results

The subjects in the NF1 group had an average of 164.8 cm in height (SD 8.8), 57.5 cm in head circumference (SD 2.4) and 5.6 cm interpupillary distance (SD .4). Patient characteristics are summarized in Table II.

Table II. Characteristics of NF1 Group and Control Group

	NF1	**Control**
Number of Patients	74	74
Male	29	29
Female	45	45
Age (years)	40.1 ± 15.2	40.1 ± 15.2
Race		
Caucasian	Caucasian	Caucasian
Phenotypes (cm)		
Height	164.8 ± 8.8	*
Head Circumference	57.5 ± 2.4	*
Interpupillary Distance	5.6 ± 0 .4	*

* unavailable in control group

In general, the results showed that the NF1 group displayed significantly shorter anterior and posterior facial height, a shorter maxilla, a shorter mandible, a shorter ramus, and a shorter cranial base when compared with the controls. There were no significant differences in the lower facial dimensions, maxillary and mandibular position with respect to the cranial base, and cranial base flexion. Comparisons of specific cephalometric measurements are described below.

Vertical Dimensions of the Face

The vertical measurements of the face showed that NF1 adults had a shorter anterior facial height (AFH) as well as posterior facial height (PFH). The anterior facial height was 9.6mm shorter in NF1 patients when compared to controls (t=4.7, p=.0005), while the posterior facial height was 2.4mm shorter (t=1.9, p=.03). Similarly, the ratio between the posterior facial height and anterior facial height (PFH/AFH) was found to be higher in the NF1 group when compared to the control group (t=-2.8, p=.004) as expected. Both upper (UAFH) and lower anterior facial heights (LAFH) in the NF1 group were also found to be significantly reduced when compared to the control (UAFH: p= t=3.3, .001; LAFH: t=4.8, p=.0005). The ratio of the lower anterior facial height to the total anterior height (LAFH/AFH) was not found to be significantly different between NF1 patients and healthy controls (t=1.1, p=.14). The measurements in the vertical dimensions are summarized in Table III.

Table III. Differences in **Vertical** Measurements between NF1 and control subjects

Cephalometric Measurement	Control	NF1	Mean Difference	t	p-value
AFH	124.7 ± 17	115.1 ± 8	-9.6	4.7	.0005*
PFH	79.2 ± 9	76.8 ± 8	-2.4	1.9	.03*
PFH/AFH	63.0 ± 10	66.7 ± 5	3.7	-2.8	.004*
UAFH	53.9 ± 4	51.6 ± 4	-2.3	3.3	.001*
LAFH	67.8 ± 7	63.6 ± 6	-4.2	4.8	.0005*
LAFH/AFH	55.7 ± 2	55.3 ± 3	-.4	1.1	.14

** significant*

Maxilla

The data showed that patients with NF1 had a shorter maxilla when compared with controls. The mean difference in maxillary length (ANS-PNS) between the NF1 and the controls was 3.1mm (t=-.0001, p=.0005). However, the SNA measurement in the NF1 group was not significantly different from the control group (mean difference= .2, t=-.33, p=.352). The ANB measurement in the NF1 group was found to be 1.4 degrees less in NF1 patients when compared to the control group (t=3.6, p=.005). Comparisons of maxillary measurements between the experimental and control groups are summarized in Table IV.

Table IV. Differences in **Maxillary** Measurements between NF1 and control subjects

Cephalometric Measurement	Control	NF1	Mean Difference	t	p-value
ANS-PNS	50.4 ± 5	47.3 ± 4	-3.1	4.2	.0005*
SNA	80.9 ± 4	81.2 ± 4	.2	-.33	.352
ANB	3.8 ± 3	2.2 ± 3	-1.4	3.6	.005*

**significant*

Mandible

The mean difference in mandibular length (Co-Gn) of NF1 patients was 4.3mm shorter when compared to the control group (t=3.5, p = 0.005). The ramal height (Co-Go) was was 3.1 mm shorter in patients with NF1 when compared to controls (t=2.8, p= 0.003). The mean difference in the mandibular angle (Sn-GoGn) in the NF1 group was 2.1 degrees smaller when compared to the controls (t=2.0, p=.006). The position of the mandible with respect to the cranial base (SNB) was found to be 1.8 degrees higher when compared to the control group (t=-2.6, p=.006). Comparisons of mandibular measurements between the experimental and control groups are summarized in Table V.

Table V. Differences in **Mandibular** Measurements between NF1 and control subjects

Cephalometric Measurement	Control	NF1	Mean Difference	t	p-value
Co-Gn	120.1 ± 9	115.8 ± 7	-4.3	3.5	.0005*
Co-Go	58.5 ± 7	55.4 ± 7	-3.1	2.8	.003*
Sn-GoGn	31.5 ± 7	29.4 ± 6	-2.1	2.0	.026*
SNB	77.1 ± 4	78.9 ± 4	1.8	-2.6	.006*

** significant*

Cranial Base

Patients with NF1 had both a shorter anterior cranial base (S-N) and posterior cranial base (S-Ba) when compared to the controls. Specifically, the mean differences were 3.4mm (t=4.4, p=.0005) for the anterior and 2.1mm (t=2.0, p=.027) for the posterior respectively. The mean difference in cranial base flexure (SNBa) between the NF1 group and the control group was found to be approaching significance (t=-1.7, p=.051). Comparisons of cranial base measurements between the experimental and control groups are summarized in Table VI.

Table VI. Differences in **Cranial Base** Measurements between NF1 and control subjects

Cephalometric Measurement	Control	NF1	Mean Difference	t	p-value
S-N	72.3 ± 6	68.7 ± 4	-3.4	4.4	.0005*
S-Ba	46.3 ± 8	44.2 ± 7	-2.1	2.0	.027*
SNBa	125.6 ± 17	129.2 ± 11	3.5	-1.7	.051

**significant*

Correlation of cephalometric measurements with height in NF1 patients

The average height of adult patients with NF1 was 164.8 ± 8.8 centimeters. Using Pearson's r, a significant positive correlation between height versus anterior facial height (r=.33, p=.005), posterior facial height (r=.32, p=.008), length of mandible (r=.40, p=.001), ramal height (r=.30, p=.015), and anterior cranial base (r=.34, p=.004) was found in patients with NF1 (Table VII). Correlations of the remaining 11 cephalometric

measurements with height were non-significant.

Correlation of cephalometric measurements with head circumference in NF1 patients

The average head circumference in adult patients with NF1 was 57.5 ± 2.4 centimeters. Using Pearson's r, a positive correlation between head circumference versus length of anterior cranial base was found in patients with NF1 (r=.313, p=.009). All other correlations were non-significant.

Correlation of cephalometric measurements with interpupillary distance in NF1 patients

The average interpupillary distance in adult patients with NF1 was 5.6 ± .4 centimeters. Using Pearson's r, no significant correlations were found between the interpupillary distance and the sixteen cephalometric measurements in NF1 patients.

Table VII - Correlations Between Cephalometric Measurements and NF1 Phenotypes

	Height			Head Circumference			Interpupillary Distance		
Cephalometric Measurement	r	r^2	p-value	r	r^2	p-value	r	r^2	p-value
AFH	.33	.11	.005*	.142	.02	.248	-.011	.01	.929
PFH	.32	.10	.008*	.157	.03	.201	-.048	.01	.699
PFH/AFH	.07	.01	.585	-.067	.01	.585	-.040	.01	.747
UAFH	.190	.04	.120	.187	.04	.126	-.040	.01	.746
LAFH	.319	.10	.008	.069	.01	.576	-.005	.01	.969
LAFH/AFH	.151	.02	.220	-.077	.01	.531	.021	.01	.864
ANS-PNS	.102	.01	.408	.036	.01	.772	-.060	.01	.625
SNA	.186	.03	.129	-.016	.01	.896	-.190	.04	.120
ANB	.001	.01	.994	.005	.01	.969	-.084	.01	.495
Co-Gn	.40	.16	.001*	.163	.03	.187	-.092	.01	.457
Co-Go	.30	.09	.015*	.110	.01	.371	-.064	.01	.603
Sn-GoGn	-.076	.01	.537	.096	.01	.436	-.035	.01	.774
SNB	.173	.03	.158	-.018	.01	.884	-.123	.02	.317
S-N	.34	.12	.004*	.313	.10	.009*	.216	.05	.077
S-Ba	.179	.03	.144	.107	.01	.385	-.061	.01	.620
SNBa	-.079	.01	.523	.174	.03	.169	-.121	.01	.341

Standard Multiple Regression Analysis with <u>Height</u> in NF1 patients

The standard multiple regression analysis of these significant correlations showed an increased positive correlation with total body height (r=.439, p=.019), and showed significant correlations among the five cephalometric measurements (Table VIII).

Table VIII. Intercorrelation Analysis of Significant Cephalometric Measurements

		Pearson's r					
		Height	AFH	PFH	Co-Gn	Go-Gn	S-N
p-value	Height	-----	.334	.320	.397	.293	.341
	AFH	.003*	-----	.684	.682	.555	.369
	PFH	.004*	.0001*	-----	.712	.858	.515
	Co-Gn	.0001*	.0001*	.0001*	-----	.766	.490
	Co-Go	.008*	.0001*	.0001*	.0001*	-----	.339
	S-N	.002*	.001*	.0001*	.0001*	.002*	-----

** significant*

Discussion

Our findings provide a more complete understanding of the underlying craniofacial morphologic features in NF1. In general, our results indicated that NF1 patients exhibit a shorter cranial base, smaller maxilla, shorter mandible, and diminished facial height. These findings in patients with NF1 suggest a role for neurofibromin in skeletal development.

The cranial base is a midline structure composed of basioccipital, sphenoid, ethmoid, and frontal bones in the midline, and temporal bones laterally. The early embryologic precursor of the cranial base is a cartilaginous plate, later replaced by bone through endochondral ossification[19]. Individual bones are then connected by cartilaginous structures, called synchondroses, which are morphologically similar to long bone growth

plates[20,21]. Our data showed that both the anterior cranial base and posterior cranial base are shortened in patients with NF1. This finding is in support of a previous study that suggested that NF1 has a role in endochondral bone formation, citing impairment in long bone formation, which is formed the same way through a cartilaginous plate[10].

Although our data showed that both the anterior and posterior base in NF1 patients are shorter when compared to the control group, the mean difference in anterior cranial base length was more marked than the posterior cranial base. This difference could be explained by the difference in growth between the anterior base and the posterior cranial base[20]. The anterior and posterior parts of the cranial base, demarcated by the sella turcica, develop at different rates. Studies have shown that linear growth of the anterior cranial base is approximately twice that of the posterior base [19, 22]. This difference is due to the early ossification and maturation of the posterior cranial base in contrast to the anterior cranial base. The cribriform plate of ethmoid, which is part of the anterior cranial base, completes its growth at the end of the second year postnatally[20]. Thereafter, growth of the anterior cranial base takes place in the sphenoethmoidal synchondrosis and the cartilage between mesethmoid and frontal bones as long as the cartilage persists. The active and prolonged growth of the anterior cranial base is consistent with that of the upper-middle face and essential for craniofacial growth[19]. Though both anterior and posterior cranial base ossify by endochondral ossification, the cartilaginous growth, found to be abnormal in NF1[10], has a greater influence on the anterior cranial base. We speculate that this may be likely responsible for the greater difference in the anterior cranial base compared to the posterior cranial base in the NF1 group.

The cranial base also exerts great influence on facial growth and plays an important role in coordinating craniofacial growth. During its growth, it carries the upper-middle face forward, inferiorly and laterally. A deficiency in anterior cranial base growth is often accompanied by midfacial deficiency[19]. Our data showed that maxillary length is significantly shorter in NF1 patients. Thus, NF1 patients may appear to have a mid-face deficiency due to a combination of a smaller maxilla and reduced projection due to the shortened anterior cranial base. The severely shortened cranial base length in the NF1 group caused the SNA value to be similar to that in the control group due a retruded nasion point, even with smaller maxillas. It has also been reported that facial retraction in modern humans compared to other primates might be the result of a difference in cranial base flexion[17], which was found to be approaching significance based on our data.

Similiarly, we found a significantly shorter mandible and mandibular ramus in the NF1 group, which are in agreement with a previous study by Heerva[16]. Due to the severely shortened cranial base length in the NF1 group, SNB was found to be signigicantly different but still similar (mean difference of only 1.8 degrees) to that in the control group due to a retruded nasion point, even with a smaller mandible. Mandibular overclosure, as reflected by a decreased mandibular plane angle (Sn-GoGn), further increases the relative mandibular prognathism. Therefore, the small, retruded maxilla and relatively prognathic mandible led to a smaller ANB.

Overall, NF1 patients appear to have short faces due to the decrease in vertical

dimensions of the jaws. Our data showed a significant decrease in the anterior facial height and posterior facial heights. The decrease in anterior facial height is more marked, confirmed by a significant increase in the posterior facial height to anterior facial height (PFH/AFH) ratios. The anterior facial height is decreased proportionally because similar reductions in the upper and lower anterior facial heights led to similar lower anterior facial heights to total anterior facial height ratios (LAFH/AFH).

Our Pearson tests revealed positive correlations between five cephalometric measurements (Go-Gn, S-N, AFH, PFH, Co-Go) and total body height in NF1 patients, with correlations ranging from .31 to .40. It is interesting to note that these five cephalometric measurements are linear, whereas no angle measurements were significant.

Based on the results of correlation analyses between the cephalometric measurements and head circumference and interpupillary distance, little conclusion can be made. Since the percentage of the significant correlations (1/32, 3.1%) was so low, the lone correlation could have happened by chance. Therefore, the correlation results for these two phenotypes are not meaningful.

The standard multiple regression using the significant cephalometric measurements increased the Pearson's r to .439 when compared to the individual correlations which ranged from .31 to .40. This increase is minimal because of the significant correlations found between the five cephalometric measurements, demonstrating that they are intercorrelated. Although there are many predictors of height in patients with NF1, our

results indicated that 19.2 percent of one's height is directly accounted for by the five significant cephalometric measurements.

Clinical treatment of NF1 patients may present challenges to orthodontists in due to an inherent impairment of bone development, mainly the mandible and maxilla. In treating Class II patients, orthodontists often use orthopedic appliances to promote differential growth of the jaws using headgears and functional appliances. A headgear is used to restrict the anterior-inferior growth vector of the maxilla thus allowing the mandible to catch up, while functional appliances such as the Herbst have been found to increase mandibular length by 1mm[23,24]. Orthodontists should be more conservative about the treatment outcomes when using these orthopedic modifications in NF1 patients since treatment effects may be minimal compared to healthy patients, deeming the treatment not worthwhile.

Moreover, the principle of tooth movement lies in the theory of bone remodeling, which involves bone apposition and bone resorption. Both processes are driven by osteoblasts and osteoclasts. Studies have shown that cultured osteoprogenitors and osteoblasts from NF1 haploinsufficient humans have reduced expression of bone markers and produce less mineralized matrix[25]. With respect to bone resorption, studies have shown that NF1-affected osteoclasts have increased osteoclastic activity, boosting bone resorption[26-28]. Together, reduced bone apposition and increased bone resorption during orthodontic treatment may lead to progressive periodontal bone loss for the patient. Therefore, orthodontists should devise shorter treatment plans and utilize lighter mechanical forces

to move the teeth to minimize possible periodontal bone loss.

Research Limitations

One limitation to our study lies in the selection of the control group. The control subjects used for this study were selected from the dental school for two main reasons. The main reason is that of radiation exposure concern. It is impractical for healthy subjects to be exposed to unnecessary exposure for the purpose of a study as cephalometric radiographs are only taken when a patient is undergoing orthodontic evaluation. Since this is not possible, an alternative method of establishing the norm was to use longitudinal growth records from studies that have been done. Although many longitudinal growth studies revealed valuable established norms, the age range of most subjects in those studies was 6-25 years of age, which does not match the age range of our experimental group[29]. Therefore, control subjects selected in this study were healthy patients with no known genetic condition that presented to the University of Maryland School of Dentistry for orthodontic treatment. In most cases, these patients had malocclusions of varying severity, necessitating orthodontic treatment. Hence, the differences found in this study cannot be broadly applied to the general healthy population.

An attempt was made to choose a subject pool that was racially diverse however this proved to be impossible. The 74 cephalometric radiographs of NF1 patients included in this study were of patients of Caucasian descent. A total of 20 other patients (17 Caucasian, 2 African-American, 1 Asian-American) were excluded from the study due to: 1. missing radiographs, 2. poor radiographic quality, or 3. there was no matched-control available.

Future Research

A more reliable way of quantifying craniofacial skeletal structures would be through the use of CT scans of the craniofacial region. CT technology would allow accurate and reliable measurements of the bones in vertical and transverse as well as sagittal dimensions. A more comprehensive study of the craniofacial region could also include analysis of the dentition such as aberrant abnormalities in terms of tooth shape and size. In addition, since NF1 patients have smaller mandibles and maxillas, it may be of interest to study the pharyngeal airways as there is a documented association between the size of the jaws and airway efficiency.

Conclusion

The aim of this study was to compare the manifestations of the craniofacial and oro-dental regions through the use of cephalometric radiographs. Based on the results of this study, we can conclude that when compared to a population who seek orthodontic treatment, NF1 patients have:

1. a shorter cranial base.
2. a shorter maxillary length.
3. a shorter mandible and a shorter ramus.
4. shorter faces.

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