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- American Academy of Oral and Maxillofacial Radiology Achievement Award (May 2010)
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- Dean's Merit Scholarship (2006- 2010)
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- Presidential Achievers Award (Fall 2004)
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Research and Teaching Experience

Masters thesis: Radiographic evaluation of Craniofacial Skeletal Structures in pediatric patients with Neurofibromatosis Type 1. (July 2011-Present).

Lecture Ortho-Perio Seminar series

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University of Maryland Dental School

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Growth and Development Course

University of Maryland Dental School

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Research with Professor Robert Engel; Organic Chemistry
Synthesized new chiral ionic liquids, for applications from environmentally friendly organic solvents to electrolytes for batteries. (Fall 2004 - Spring 2006)

Publications

Polycations. 17. Synthesis and properties of polycationic derivatives of carbohydrates.

Thomas M, Montenegro D, Castaño A, **Friedman L**, Leb J, Huang ML, Rothman L, Lee H, Capodiferro C, Ambinder D, Cere E, Galante J, Rizzo J, Melkonian K, Engel R. Carbohydr Res. 2009 Sep 8;344(13):1620-7

Polycationic carbohydrate salts as small molecule gelators. Marie Thomas, Alejandra Castaño, **Laura Friedman**, Jay Leb, Heidi Lee, Leah Rothman and Robert Engel.

Presented at the 38th MARM of the American Chemical Society, Hershey, PA, June 2006.

Licensure

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American Association of Orthodontics (2011-present)

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Abstract

Title of Thesis: Radiographic Evaluation of the Craniofacial Skeletal Structures in Pediatric patients with Neurofibromatosis Type I

Researcher: Laura Friedman, Master of Science, 2014

Thesis Directed By: Monica Schneider, D.D.S.

Introduction: Neurofibromatosis Type I (NF1), also known as von Recklinghausen disease, is an autosomal dominant disorder that affects one in every 3000 births. There is no gender or race predilection seen in NF1 patients. Common clinical features include neurofibromas, café-au-lait spots, axillary and inguinal freckling, optic glioma, Lisch nodules and some form of bone lesions. NF1 causes a mutation in the gene that produces neurofibromin protein, which thus increases the activation of the Ras protein. This leads to rapid, radical growth of cells in the skin, skeletal and neural tissues. The craniofacial morphology of NF1 adult patients has been studied, however there have been few studies done on pediatric NF1 patients. The purpose of this study was to analyze and compare craniofacial regions, including the morphology of the cranial base and the sphenoid bone, using cephalometric radiographs of NF1 pediatric patients and age and gender matched healthy controls. **Methods:** A total of 28 pediatric NF1 patients and their age and gender matched healthy controls were used in this study. Cephalometric radiographs of the NF1 group were obtained from the NIH, and the cephalometric radiographs of their matched healthy controls were collected from The University of Maryland Dental School, orthodontic department. Sixteen cephalometric linear and

angular measurements that reflected the cranial base, vertical heights, maxilla and mandible were measured to the nearest tenth of a millimeter or degree utilizing Dolphin Software. The groups were analyzed based on the total sample, pre-pubertal and post-pubertal status, and gender. **Results:** The results showed that there were very few statistically significant differences found between the NF1 pediatric group and their matched healthy controls. The NF1 pediatric patients in the total group, pre-pubertal and post-pubertal groups were all found to have larger cranial base flexure angles compared to their matched healthy controls. It was also found that male NF1 patients had larger measurements compared to their female NF1 patients, which was also seen in the healthy control group. **Conclusion:** In conclusion, there were very few statistically significant differences found between the NF1 pediatric group and their matched controls. These differences are unlikely to have an effect on the orthodontic and orthopedic treatments performed on NF1 pediatric patients by their clinicians. Therefore, pediatric NF1 patients should be offered the same type of orthodontic and orthopedic treatment options as their matched healthy controls.

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

by
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Introduction

Neurofibromatosis are a group of genetically-inherited disorder that primarily affects the cell growth of Schwann cells. This disease primarily manifests itself in the skin, neural and skeletal tissues (Heerva et al 2011)¹. There are two forms of neurofibromatosis. They include neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, and neurofibromatosis type 2 (NF2). Recently it has been found that there is a sharp distinction between the two types of neurofibromatosis and it has been found that they each have mutations of different genes that cause their disease (Cunha et al 2004)². NF1 is due to a mutation on chromosome 17q11.2, and *NF2* is due to a mutation on chromosome 22q12.2 Both NF1 and NF2 are autosomal dominant disorders. About one half of NF cases appear to be spontaneous with no family history. NF1 comprises 85%-90% of the neurofibromatosis cases seen (Neville et al 1991)³.

NF1 is one of the most frequent human genetic diseases with a prevalence of one in every 3000 live births. There is no gender or race predilection seen in NF patients. Common clinical features of NF1 include neurofibromas, café-au-lait spots, axillary and inguinal freckling, optic glioma, Lisch nodules (pigmented hamartomas of the iris) and some form of bone lesions. (Geist et al 1992)⁴. Heerva et al (2011)¹ explained that “osseous dysplasia’s often found in NF1 include macrocephaly, sphenoid wing dysplasia, short stature, reduced bone mineral density, scoliosis, lytic bone lesions, and congenital bowing and psuedarthrosis of the tibia.”

An individual must have at least two of the seven features listed in Table 1 to meet the National Institutes of Health Diagnostic criteria for NF1 (Jett et al 2010)⁵.

However, this method works best for adult patients, because disease manifestations may not be apparent in young children (DeBella et al 2000)⁶. DeBella et al⁶ explained that diagnosis can be reliably made using these criteria by eight years of age in most children and by 20 years of age in all children. This article stated that with time most children will develop other clinical manifestations of NF1.

Table 1. NIH diagnostic Criteria for NF1 (DeBella et al 2000)⁶

Cardinal Clinical Features (Any two of more are required for Diagnosis)
six or more café-au-lait macules over 5mm in greatest diameter in pre-pubertal individuals and over 15mm in greatest diameter in post-pubertal individuals
Two or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more Lisch nodules (iris harmartomas)
A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis
A first degree relative (parent, sibling or offspring) with NF1 by the above criteria

Neurofibromatosis type 1 is caused by a mutation in the tumor suppressor gene *NF1*, located on chromosome 17q11.2. The protein product of this gene, neurofibromin 1, is a GTPase activating protein (Ras-GAP) which acts as a negative regulator of the Ras kinase pathway, therefore inactivating Ras (Schindeler et al 2006)⁷. Ras is a critical

protein involved in the regulation of cell growth; it mediates signal transmission from growth factor receptors to downstream pathways. 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 (Bollag et al 1992)⁸.

There is limited data concerning oral manifestations in children with NF1. It was found that these patients have different developmental manifestations of the craniofacial regions as well as a different morphology of the cranial base and sphenoid bone compared to unaffected controls. Geist et al (1992)⁴ found that oral manifestations are observed in about 72% of NF1 patients. The oral manifestations found in NF1 patients include dental abnormalities such as impacted, displaced, supernumerary or missing teeth, bone abnormalities such as intrabony neurofibromas, hypoplasia and deformity of the jaw, enlarged mandibular foramen, flat or missing gonial angle, coronoid notch deformity, pseudoelongation of the condylar processes and soft tissue abnormalities such as oral neurofibromas. (Bardellini et al 2011)⁹.

Fadda et al (2007)¹⁰ found that oral manifestations are present among 72%-92% of these patients. “The most common clinical finding is the enlargement of the fungiform papillae (53%), followed by the presence of intraoral neurofibromas (26%). The most common location of the peripheral neurofibromas are at the level of the tongue (often causing macroglossia), the lips, gingiva, palate, mucobuccal fold and the floor of the mouth” (Fadda et al 2007)¹⁰. Radiographic findings of these lesions include “enlargement and lowering of the mandibular foramen (34%), enlargement (29%) and branching (24%) of the mandibular canal, thinning and concavity of the ramus, increase in bone density,

decrease of mandibular angle, structural alterations of the inferior border of the mandible, and hypoplasia of the coronoid processes and condyles (Fadda et al 2007)¹⁰.

In humans, neurofibromin mRNA and protein have been detected in osteoclasts and osteocytes (Kuorilehto et al 2004)¹¹. Visnapuu et al (2012)¹² explained that the *NFI* gene is “expressed at a high level in the growth plate during endochondral ossification and in osteoclasts, osteoblasts, and osteocytes.” Dulai et al (2007)¹³ found that an increase in Ras activity enhances osteoclast-mediated resorption and reduces osteogenesis. Thus in patients with NF1, dysregulated Ras may affect bone homeostasis and bone healing.

Since osteoclasts and osteoblasts are the foundation of orthodontic tooth movement and orthopedic effects, a better understanding of their role in the craniofacial morphology of children with NF1 is needed. If these children are deficient in neurofibromin, which is involved in osteoclast and osteoblast function, patients with NF1 may have delayed or non-responsive orthodontic results. If they have smaller craniofacial structures than healthy controls, orthopedic and functional appliances used during orthodontic treatment may not be effective. These patients may not benefit from early treatment or they may only benefit from one phase of orthodontic treatment to align their teeth, but not necessarily to fix their sagittal discrepancy. Future periodontal disease due to the disruption of osteoclast and osteoblast function is another possibility.

During normal growth and development, the cranial base is formed by endochondral ossification. Initially the bones of the base of the skull are formed in cartilage, and later the cartilage is transformed to bone. There are also bands of cartilage,

called synchondroses, in the centers of ossification between bones. There is the sphenoccipital synchondrosis between the sphenoid and occipital bones, the inter-sphenoid synchondrosis between the two sphenoid bones, and the sphenothmoidal synchondrosis between the sphenoid and ethmoid bones. These areas have bands of maturing cartilage and will eventually be replaced by bone (Proffit WR. 2000)¹⁴.

The mandible is formed by both endochondrial and intramembranous ossification. The condyles have a cartilaginous precursor, and the remainder of the mandible is formed directly from bone. The cranial vault as well as the naso-maxillary complex is also formed by intramembranous ossification, with no cartilaginous replacement.

Heerva et al (2011)¹ explained that the “craniofacial bones (the ethmoid, frontal, parts of the temporal, the occipital bones, and the sphenoid wings) are developed through endochondrial ossification. . . the cranial base is composed, in the midline, of occipital, sphenoid, ethmoid and frontal bones, and exerts considerable influence on facial growth.” Jeffery et al (2002)¹⁵ also explained that the development of the skull base is complex “involving mesodermal condensation, chondrification and bone formation from multiple centers of endochondral ossification.”

Proffit (2000)¹⁴ explained that teeth move during orthodontics when there is pressure and tension selectively applied to each side of the tooth. Bone is removed from the pressure side, and bone is added and remodeled on the tension side of the tooth. The tooth moves through the bone carrying its attachment apparatus with it. In order for a tooth to move, osteoclasts remove the bone on the pressure side and then the osteoblasts form new bone on the tension side. If there is a disruption in this mechanism due to a

defect in the neurofibromin protein or due to an increase in the Ras-pathway, too much osteoclast activity and not enough osteoblast activity can lead to bone loss and periodontal disease.

Purpose of Study

Previous studies, including Heerva et al (2011)¹ and Dr. Cung's master thesis (2013)¹⁶, found NF1 adult patients to have statistically significant shorter mandibles, maxilla's and cranial bases compared to healthy controls. There have not been any studies that found significant differences in NF1 pediatric populations. The Heerva et al 2011 study concluded that "the mandible, the maxilla and the cranial base were statistically significantly shorter in adult patients with NF1 compared with controls, but not in the younger patients, apparently because of the small number of patients in the latter group." In Dr. Cung's master thesis (2013)¹⁶, she concluded that orthodontic treatment and orthopedic appliances may be contraindicated in NF1 patients due to their inherent smaller craniofacial structures. However, it is important to study the NF1 pediatric patients during puberty, when orthopedic and functional appliances would be most effective in their orthodontic treatment.

The purpose of this study was to cephalometrically analyze and compare the craniofacial regions, including the morphology of the cranial base and the sphenoid bone, in pediatric patients with NF1 and a sex and age- matched sample of healthy control subjects. The specific areas of investigation include the morphologic differences in oro-cranial structures, including the maxilla, mandible and facial heights, and osseous abnormalities involving the sphenoid bone.

Hypotheses- Differences between Pediatric NF1 and Control Patients

H₀: There is no significant difference between NF1 pediatric patients and their matched healthy controls in the sixteen 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. Ba-SN

H₁: There is a significant difference between pediatric NF1 patients and their matched healthy controls in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

H₂: There is a significant difference between pre-pubertal pediatric NF1 patients and their matched healthy controls in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

H₃: There is a significant difference between post-pubertal pediatric NF1 patients and their matched healthy controls in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

H₄: There is a significant difference between male pediatric NF1 patients and their matched healthy controls in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

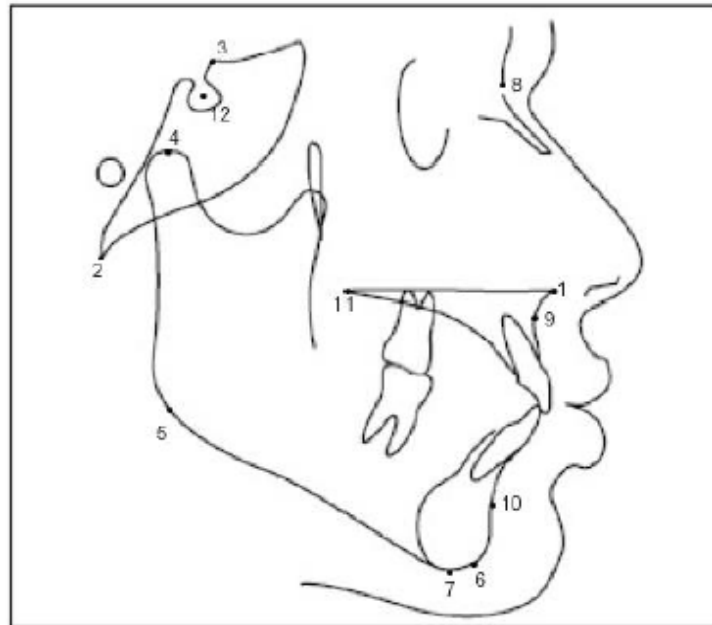
H₅: There is a significant difference between female pediatric NF1 patients and their matched healthy controls in the developmental manifestations of the craniofacial regions

and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

H6: There is a significant difference between male pediatric NF1 patients and female NF1 patients in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

H7: There is a significant difference between female healthy control patients and male healthy controls in the developmental manifestations of the craniofacial regions and morphology of the cranial base and sphenoid bone as seen in the 16 cephalometric measurements.

Figure I. Cephalometric Landmarks



1. ANS (Anterior Nasal Spine), tip of the anterior nasal spine;
2. Ba (Basion), most postero-inferior 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 antero-inferior 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 2. 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 the 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 the cranial base
	ANB	Angle measured between maxilla and mandible with respect to N, denotes the sagittal relationship between the 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 the ramus of the mandible

	Sn-GoGn	Measures as an 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 SN and B point, denotes the sagittal relationship of the mandible to the cranial base
Cranial Base		
	S-N	Measured from Nasion to Sella in mm, denotes the length of anterior cranial base
	S-Ba	Measured from Sella-to Basion in mm, denotes length of posterior cranial base
	Ba-SN	Cranial base angle formed by Nasion-Sella-Basion, denotes cranial base flexure

Table 2. Continued

Material and Methods

Sample Selection

A total of 31 records of pediatric patients with NF1 that had lateral cephalometric radiographs were available and obtained, but three radiographs were not diagnostic and had only clinical photographs and no lateral cephalometric radiographs. The radiographs that were not diagnostic did not have the proper contrast, and many important landmarks were not visible. Therefore, a total of 28 NF1 pediatric patients: 18 male and ten female, were included in the study (See table 3). These patients were diagnosed with NF1 and evaluated at The National Institute of Health in Bethesda, Maryland. They were evaluated as part of a Natural History Study and Longitudinal Assessment of Children, Adolescents, and Adults with Neurofibromatosis Type 1 NCI protocol 08-C-0079

(Brigitte Widemann, PI). The University of Maryland Institutional Review Board (IRB) gave approval for Winnie Cung’s research project¹⁶ on NF1 adult patients and it was renewed on January 22, 2013 for the purpose of this study.

Age- (in years), ethnicity- and gender-matched controls (n=28 per group) were selected from a group of healthy pediatric patients with no history of genetic disorders. These patients had undergone orthodontic evaluation in the Department of Orthodontics at University of Maryland School of Dentistry, Baltimore, Maryland. Since all NF1 subjects were Caucasian, all the matched control subjects were Caucasian (Table 3).

The mean age of the NF1 group was 14.10 +/-4.72. The mean age of the control group was 13.98 +/-4.11. The male to female ratio was 36:22. There were 18 male subjects (64.3%) in each group and ten female subjects (35.7%) in each group. All subjects were Caucasian (Table 3).

Table 3. Demographics of subjects in the study

Demographics	NF1	Control
Gender		
Males	18 (64.3%)	18 (64.3%)
Females	10 (35.7%)	10 (35.7%)
Age	14.10 +/-4.72	13.98 +/- 4.11
Head Circumference	*N/A	*N/A
Height	*N/A	*N/A

*N/A: Information not available

Methods

Cephalometric radiographs and patient characteristics for the NF1 patients were obtained from the National Institute of Health. Cephalometric radiographs and patient characteristics for the healthy control group were collected from the University Of Maryland School Of Dentistry, Orthodontic Department. The NF1 group and the control group were combined and then randomized. An independent research assistant (a third year dental student) randomized the cephalometric radiographs and assigned numbers to each subject. The subject's group, age, race, ethnicity and identity were blinded to the investigator (LF). The cephalometric radiographs were then traced by LF for landmarks and measurements. Linear and angular measurements were measured, to the nearest tenth of a millimeter or degree, utilizing Dolphin software (Dolphin imaging version 11.5, Dolphin Imaging and Management Solutions, Chatsworth, CA).

Statistical analysis

All statistical analyses were performed using IBM SPSS Base 20.0 statistical package (IBM Corporation, Armonk, NY). All 28 pediatric NF1 patients and 28 pediatric healthy controls were included in the statistical analysis. The data were tested for significant differences using repeated measure Analysis of Variance (ANOVA). A p-value of ≤ 0.05 was considered significant. The groups were analyzed based on total sample, pre-pubertal and post-pubertal status, and gender.

Results

A total of 28 NF1 and 28 healthy control subjects were included in this study. The mean age of the NF1 group was 14.10 +/-4.72. The mean age of the control group was 13.98 +/-4.11. There were 18 male subjects from each group and ten female subjects from each group. All subjects were Caucasian. The data was broken up into a total sample, pre-pubertal and post-pubertal status, and gender.

Total Sample NF1 vs Control

Of the 16 comparisons, only one was statistically significant for the total sample of 28 NF1 patients vs. 28 healthy control patients. This measurement was Ba-SN: the cranial base angle formed by Nasion-Sella-Basion ($F=5.99$, $p=0.018$). This angle describes the cranial base flexure. Given the total number of analyses, 16, and one significant analysis, this result could have happened by chance. The mean and standard deviation were larger for the NF1 group ($\bar{X}=133.9$, $SD=8.61$) than for the healthy control group ($\bar{X}=129.4$, $SD=4.40$). The other measurements did not show any significant difference when comparing the two groups (Table 4 and Figure 2).

Pre-pubertal NF1 vs Control

Of the 16 analyses, none were statistically significant in the comparison between the pre-pubertal group of NF1 patients and the healthy control patients. There were 19 NF1 and 19 healthy control pre-pubertal patients. The remainder of the sample were post-

pubertal patients. In the pre-pubertal group, three analyses approached significance, Ba-SN ($F=2.69$, $p=0.11$), mandibular length ($F=3.23$, $p=0.081$), and Co-Go ($F=2.82$, $p=0.102$) (Table 5 and Figure 3). Given the total number of analyses, 16, and three analyses approaching significance, these results could have happened by chance. Ba-SN is the cranial base angle formed by Nasion-Sella-Basion. This angle describes the cranial base flexure. The mean and standard deviation were larger for the NF1 group ($\bar{X}=133.0$, $SD=8.72$) than for the healthy control group ($\bar{X}=129.2$, $SD=4.93$). Mandibular length is measured from condylion to gnathion in mm. The mean was smaller, but the standard deviation was larger for the NF1 group ($\bar{X}=104.42$, $SD=11.18$) compared to the healthy control group ($\bar{X}=110.0$, $SD=7.60$). Co-Go is measured from condylion to gonial angle and denotes the height of the ramus of the mandible. The mean was smaller, but the standard deviation was larger for the NF1 group ($\bar{X}=49.15$, $SD=6.17$) compared to the healthy control group ($\bar{X}=52.1$, $SD=4.48$).

Post-pubertal NF1 vs Control

The remaining subjects, the post-pubertal group, included nine NF1 patients and nine control patients. No statistical comparisons in this set were statistically significant (Table 6 and Figure 4). One measurement approached significance, Ba-SN: the cranial base angle formed by Nasion-Sella-Basion ($F=3.820$, $p=0.068$). This angle describes the cranial base flexure. Given the total number of analyses, 16, and one analysis approaching significance, this result could have happened by chance. The mean and

standard deviation were larger for the NF1 group (\bar{X} =135.7, SD=8.56) than for the healthy control group (\bar{X} =129.8, SD=3.24).

Gender Male NF1 vs Male Control

The groups were also analyzed based on male gender. There were 18 male NF1 patients and 18 male control patients. In the male group, only one analysis was statistically significant, and one analysis approached significance (Table 7 and Figure 5). The measurement that was statistically significant was Ba-SN: the cranial base angle formed by Nasion-Sella-Basion (F=4.126, p=0.050). This angle describes the cranial base flexure. The mean and standard deviation were larger for the male NF1 group (\bar{X} =132.6, SD=8.83) than for the healthy male control group (\bar{X} =128.1, SD=3.6). The comparison that approached significance was LFH/TFH (F=2.516, p=0.122). LFH/TFH is the ratio of Lower Anterior Facial Height to Total Facial Height and denotes the proportion of the lower anterior face. The mean and standard deviation were larger for the male NF1 group (\bar{X} =56.1, SD=2.26) than for the healthy male control group (\bar{X} =55.0, SD=1.62). Given the total number of analyses, 16, one significant analysis and one analysis approached significance, this result could have happened by chance. The data set was also used multiple times in in this study. Multiple uses of the data may also indicate the possibility of chance.

Gender Female NF1 vs Female Control

The female group was divided into ten NF1 patients and ten control patients. Three of the sixteen comparisons were statistically significant, and one analysis approached significance (Table 8 and Figure 6). Given the total number of analyses, 16, three significant analyses and one analysis approached significance, this result could have happened by chance. Due to the data being used multiple times, the p value needs to be smaller for there to be a significant difference. Therefore due to the multiple uses of the data, these results could have happened by chance. The comparisons that were statistically significant were PFH/AFH (F=8.836, p=0.08), S-Ba (F=9.307, p=0.007), and Sn-GoGn base (F=8.05, p=0.011). PFH/AFH is the ratio of Posterior Facial Height to Anterior Facial height. This describes the differential length of the anterior and posterior face. The mean was smaller, but the standard deviation was larger for the PFH/AFH for the female NF1 group (\bar{X} =62.48, SD=4.40) than for the healthy female control group (\bar{X} =67.06, SD=2.08). S-Ba, which is measured from Sella- to Basion in mm, describes the length of the posterior cranial base. The mean was smaller, but the standard deviation was larger for the S-Ba measurement for the female NF1 group (\bar{X} =39.2, SD=3.16) than for the healthy female control group (\bar{X} =42.8, SD=2.04). Sn-GoGn is measured as the angle formed by S-N and the lower border of the mandible. This describes the vertical relationship of the mandible to the cranial. The mean and standard deviation for the Sn-GoGn measurement were larger for the female NF1 group (\bar{X} =33.5, SD=3.44) than for the healthy female control group (\bar{X} =29.4, SD=3.03). The analysis that approached significance was SNB (F=3.586, p=0.074), which is the angle measured between S-N and B point. This describes the sagittal relationship of the mandible to the cranial base. The

mean was smaller, but the standard deviation was larger for the female NF1 group ($\bar{X}=76.61$, $SD=3.65$) than for the healthy female control group ($\bar{X}=79.3$, $SD=2.76$).

Gender Male vs Female, NF1

The data was also analyzed based on male and female in the experimental and control groups. In the male vs. female NF1 group, there were 18 male NF1 patients and ten female NF1 patients examined. There were three analyses that were statistically significant, and two analyses that were approaching significance (Table 9 and Figure 7). The measurements that were statistically significant were PFH/AFH ($F=6.308$, $p=0.019$), S-Ba ($F=11.038$, $p=0.003$), and PFH ($F=6.97$, $p=0.014$). PFH/AFH is the ratio of Posterior Facial Height to Anterior Facial height. This measurement describes the differential length of the anterior and posterior face. The mean and standard deviation measurement were larger for the male NF1 group ($\bar{X}=67.66$, $SD=5.61$) than for the female NF1 group ($\bar{X}=62.48$, $SD=4.40$). S-Ba, which is measured from Sella- to Basion in mm, describes the length of the posterior cranial base. The mean and standard deviation were larger for the male NF1 group ($\bar{X}=45.46$, $SD=5.47$) than for female NF1 ($\bar{X}=39.17$, $SD=3.16$). PFH is the posterior facial height, measured from Sella-Gonion. This measurement describes the length of the posterior face. The mean and standard deviation were larger for the male NF1 group ($\bar{X}=76.57$, $SD=9.16$) than for the female NF1 group ($\bar{X}=67.39$, $SD=8.14$). Two analyses in this group approached significance; they were Co-Go ($F=3.11$, $p=0.089$) and PNS-ANS ($F=3.497$, $p=0.073$). Co-Go is measured from condylion to gonial angle. This describes the height of the ramus of the

mandible. The mean and standard deviation were larger for the male NF1 group (\bar{X} =53.72, SD=8.36) than for the female NF1 group (\bar{X} =48.58, SD=5.04). PNS-ANS, the maxillary length, is the distance measured from the anterior nasal spine to posterior nasal spine. The mean is larger, but the standard deviation is smaller for the male NF1 group (\bar{X} =46.71, SD=5.29) than for the female NF1 group (\bar{X} =42.76, SD=5.49). Given the total number of analyses, 16, three significant analyses and two analyses approached significance, these results could have happened by chance. The data was also used in multiple analyses, which can also contribute to the results occurring by chance.

Gender Male vs Female, Control

The data analyzed for the male vs. female in the control group showed six out of sixteen statistically significant results and three analyses that approached significance (Table 10 and Figure 8). There were 18 male control patients and ten female control patients. The analyses that were statistically significant were Co-Gn (F=5.133, p=0.032), Ba-SN (F=5.612, p=0.026), S-N (F=9.051, p=0.006), S-Ba (F=4.398, p=0.046), LAFH (F= 8.034, p=0.009), and UAFH (F=5.409, p=0.028). The three analyses approaching significance were maxillary unit length, Co-Go and PFH. Co-Gn is measured from condylion to gnathion in mm. This describes the total mandibular length. The mean and standard deviation were larger for the male control group (\bar{X} =114.32, SD=7.67) than for the female control group (\bar{X} =107.74, SD=6.75). Ba-SN is the cranial base angle formed by Nasion-Sella-Basion. This measurement describes the cranial base flexure. The mean and standard deviation were smaller for the male control group (\bar{X} =128.06, SD=3.60)

than for the female control group (\bar{X} =131.86, SD=4.83). S-N is measured from Nasion to Sella in mm. This describes the length of the anterior cranial base. The mean and standard deviation were larger for the male control group (\bar{X} =69.62, SD=4.23) than for the female control group (\bar{X} =64.89, SD=3.47). S-Ba is measured from Sella-Basion in mm. This describes the length of the posterior cranial base. The mean and standard deviation were larger for the male control group (\bar{X} =44.94, SD=2.84) than for the female control group (\bar{X} =42.80, SD=2.04). LAFH is measured the lower anterior facial height from ANS-Menton. The mean was larger but the standard deviation was smaller for the male control group (\bar{X} =63.92, SD=4.11) than for the female control group (\bar{X} =58.77, SD=5.41). UAFH is the upper anterior facial height measured from Nasion-ANS. The mean was larger but the standard deviation was smaller for the male control group (\bar{X} =50.98, SD=3.50) than for the female control group (\bar{X} =47.63, SD=3.94). The three analyses that approached significance were maxillary unit length (F= 2.99, p=0.096), Co-Go (F= 2.836, p=0.104) and PFH (F=4.20, p=0.051). The maxillary unit length is measured from the anterior nasal spine to the posterior nasal spine. The mean was larger but the standard deviation as smaller for the male control group (\bar{X} =85.91, SD=6.0) than for the female control group (\bar{X} =81.78, SD=6.17). Co-Go is the condyion to gonial angle measured in mm. This describes the height of the ramus of the mandible. The mean and standard deviation were larger for the male control group (\bar{X} =55.55, SD=6.25) than for the female control group (\bar{X} =51.84, SD=4.05). PFH is the posterior facial height measured from Sella-Gonion. This measurement describes the length of the posterior face. The mean and standard deviation were larger for the male control group (\bar{X} =76.26, SD=8.36) than for the female control group (\bar{X} =70.26, SD=5.19)

Table 4. Total NF1 vs Control measurements

		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	NF1	28	55.793	2.3319	.4407	2.787	.101**
	Control	28	54.821	2.0108	.3800		
PFH_AFH	NF1	28	65.807	5.7153	1.0801	.949	.334
	Control	28	67.107	4.1467	.7837		
PNS_ANS	NF1	28	45.300	5.5991	1.0581	.530	.530
	Control	28	46.179	4.7576	.8991		
Max_unit_Length	NF1	28	82.611	7.7810	1.4705	.933	.338
	Control	28	84.436	6.2789	1.1866		
SNA	NF1	28	81.468	4.5488	.8596	.667	.418
	Control	28	80.089	7.6850	1.4523		
Mandibular_Length	NF1	28	109.664	12.5386	2.3696	.678	.414
	Control	28	111.971	7.9097	1.4948		
Co_Go	NF1	28	51.882	7.6662	1.4488	1.669	.202
	Control	28	54.225	5.7726	1.0909		
SNB	NF1	28	78.061	4.5011	.8506	.383	.538
	Control	28	78.746	3.7534	.7093		
ANB	NF1	28	3.414	3.1359	.5926	1.853	.179
	Control	28	2.389	2.4578	.4645		
Ba_S_N	NF1	28	133.889	8.6108	1.6273	5.993	.018*
	Control	28	129.414	4.4059	.8326		
S_N	NF1	28	66.711	6.1416	1.1606	.712	.402
	Control	28	67.929	4.5386	.8577		
Posterior_cranial_base	NF1	28	43.214	5.6232	1.0627	.664	.419
	Control	28	44.179	2.7509	.5199		
Sn_GoGn	NF1	28	31.321	6.1354	1.1595	1.173	.284
	Control	28	29.671	5.2308	.9885		

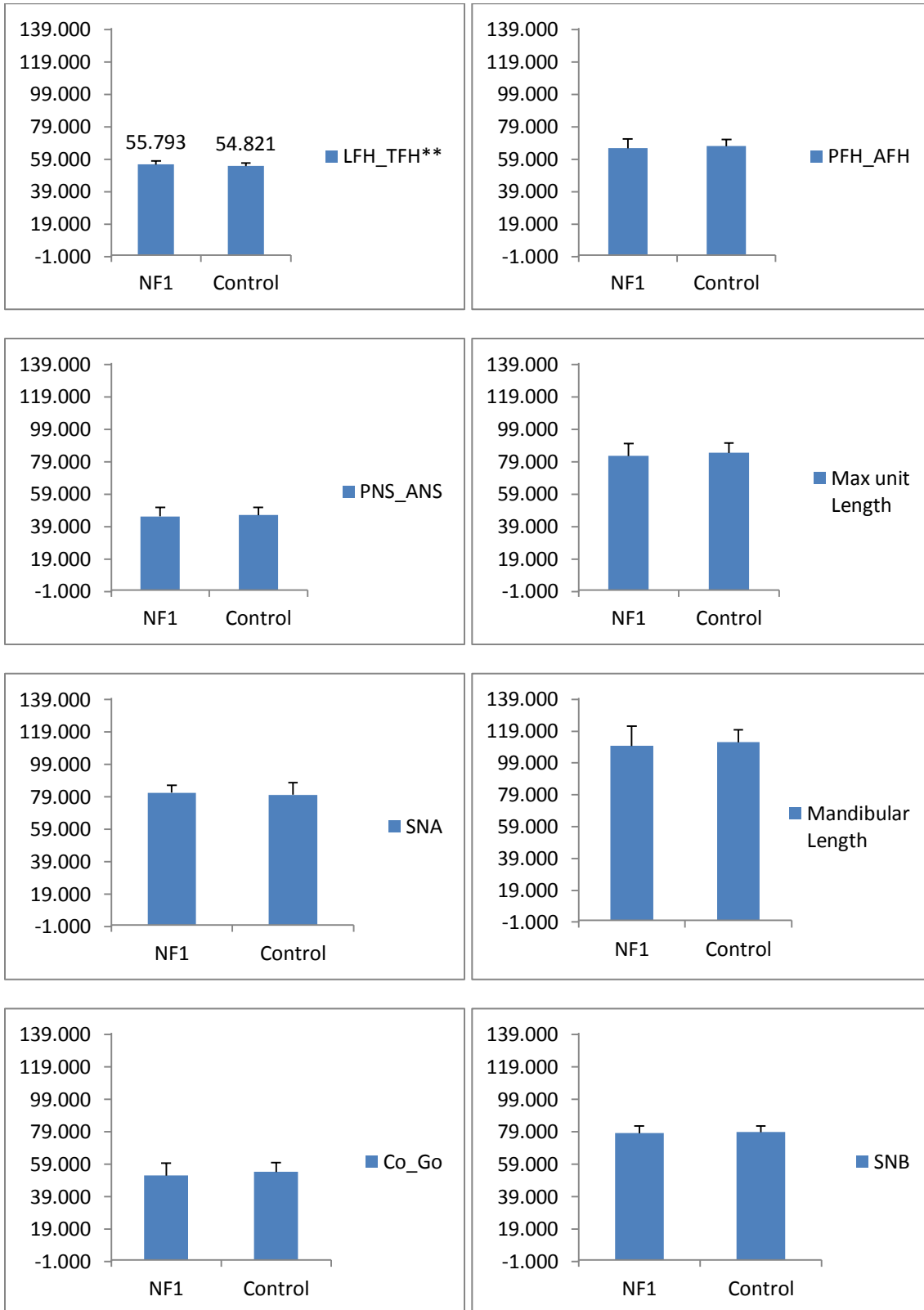
LAFH	NF1	28	64.586	8.8699	1.6763	1.670	.202
	Control	28	62.079	5.1688	.9768		
UAFH	NF1	28	48.871	4.3677	.8254	.676	.415
	Control	28	49.786	3.9430	.7452		
PFH	NF1	28	73.293	9.7445	1.8415	.121	.730
	Control	28	74.114	7.8451	1.4826		

Table 4. Continued

* Statistically significant, $p \leq 0.05$

**Approaching significance, $p = 0.101$

Figure 2. Total NF1 vs Control measurements



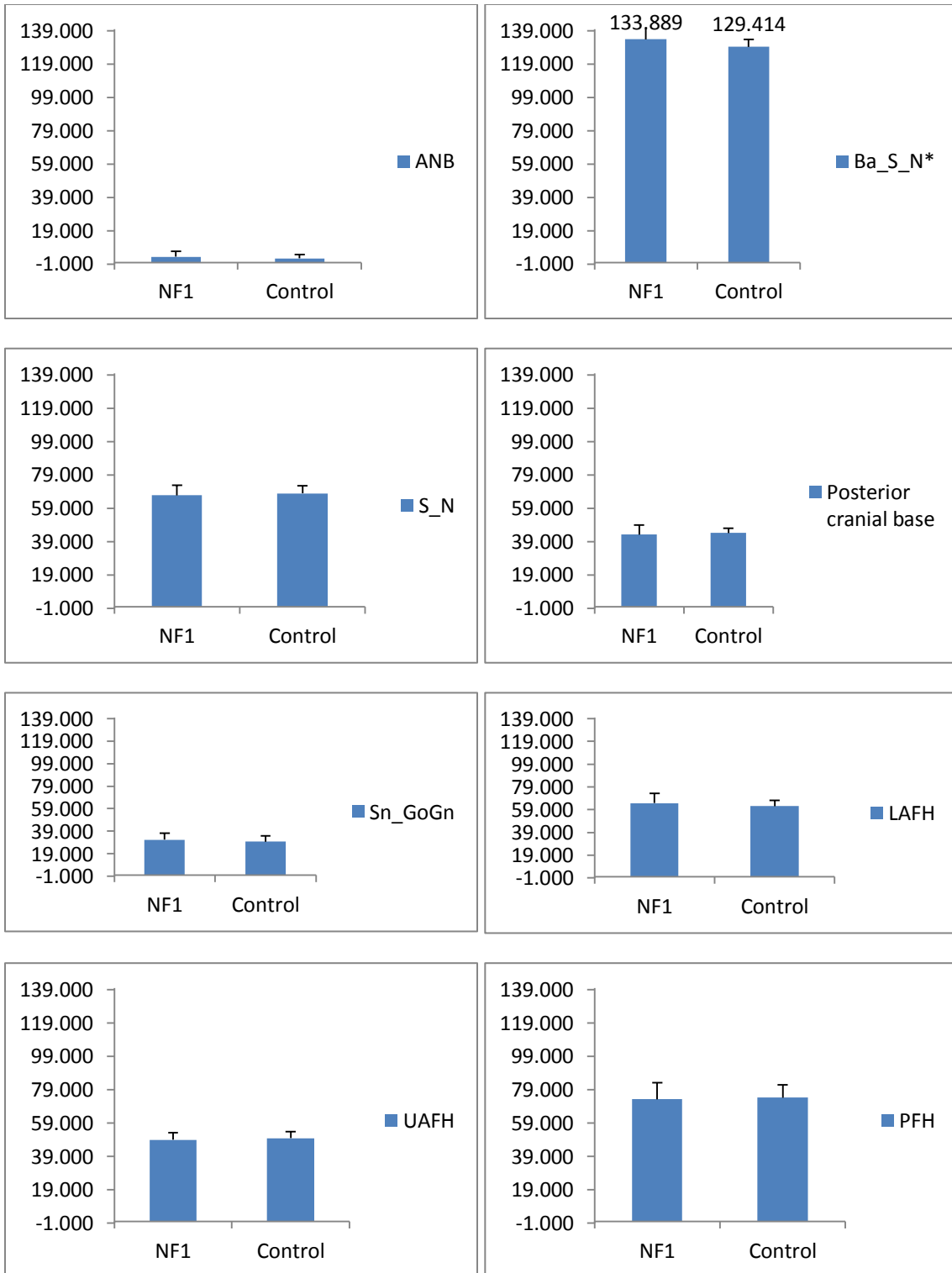


Figure 2. Contiued

* Statistically significant, $p \leq 0.05$

**Approaching significance, $p = 0.101$

Table 5. Pre-pubertal NF1 vs. Control Measurements

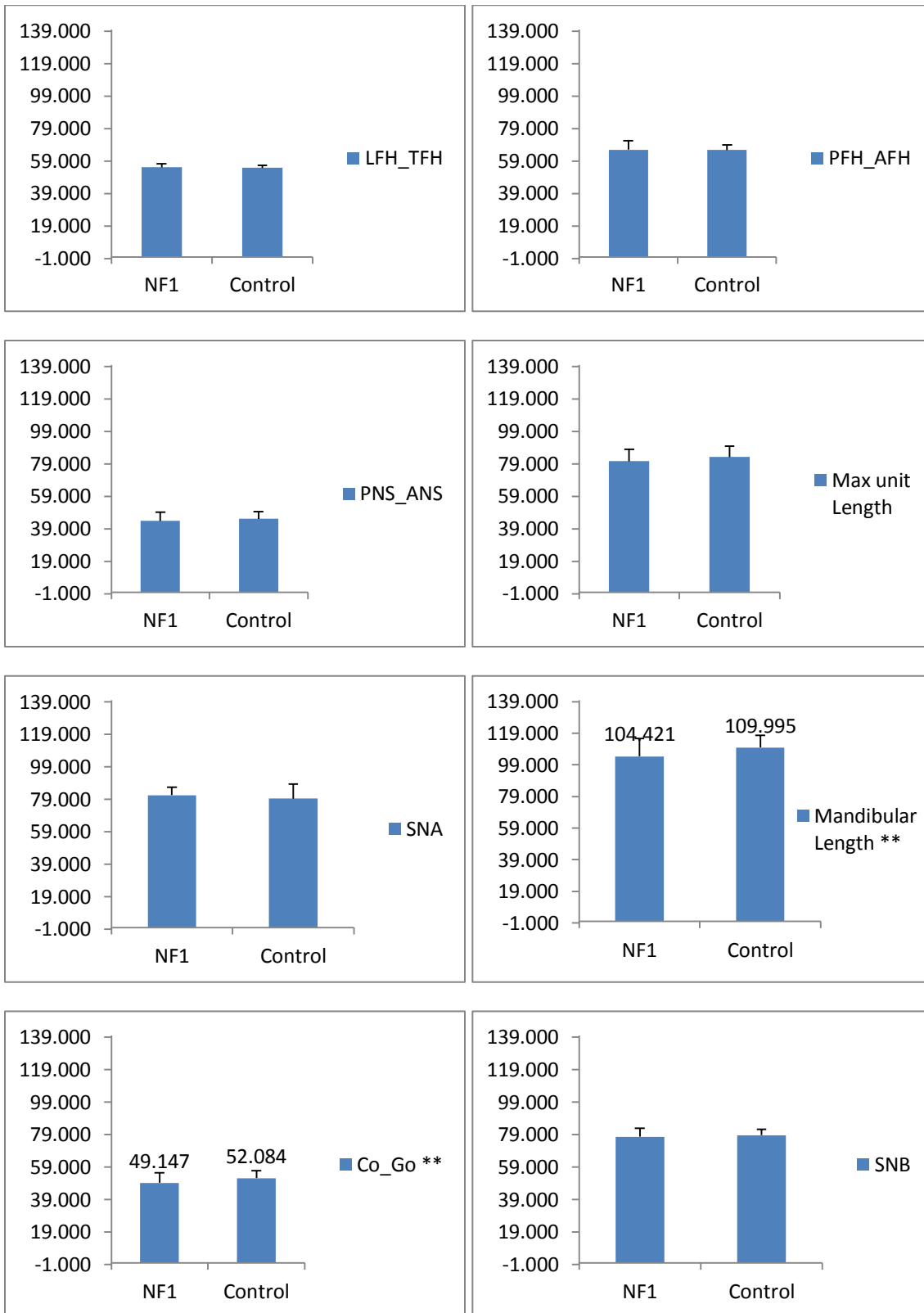
		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	NF1	19	55.205	1.9893	.4564	.389	.537
	Control	19	54.842	1.5774	.3619		
PFH_AFH	NF1	19	65.995	5.5249	1.2675	.016	.900
	Control	19	65.811	3.1385	.7200		
PNS_ANS	NF1	19	43.779	5.3432	1.2258	.721	.401
	Control	19	45.137	4.4744	1.0265		
Max_unit_Length	NF1	19	80.589	7.4929	1.7190	1.350	.253
	Control	19	83.247	6.5792	1.5094		
SNA	NF1	19	81.389	5.0944	1.1687	.700	.408
	Control	19	79.400	9.0300	2.0716		
Mandibular_Length	NF1	19	104.421	11.1832	2.5656	3.228	.081**
	Control	19	109.995	7.6005	1.7437		
Co_Go	NF1	19	49.147	6.1710	1.4157	2.818	.102**
	Control	19	52.084	4.4797	1.0277		
SNB	NF1	19	77.574	5.1457	1.1805	.395	.533
	Control	19	78.489	3.7180	.8530		
ANB	NF1	19	3.837	3.3005	.7572	2.271	.141
	Control	19	2.453	2.2660	.5199		
Ba_S_N	NF1	19	133.005	8.7203	2.0006	2.688	.110**
	Control	19	129.237	4.9337	1.1319		
S_N	NF1	19	65.153	5.4389	1.2478	1.351	.253
	Control	19	66.963	4.0663	.9329		
Posterior_cranial_base	NF1	19	43.016	5.0797	1.1654	.609	.440
	Control	19	44.068	2.9596	.6790		
Sn_GoGn	NF1	19	31.221	5.9220	1.3586	.023	.879
	Control	19	30.958	4.6223	1.0604		

LAFH	NF1	19	61.737	6.2813	1.4410	.074	.787
	Control	19	61.211	5.5954	1.2837		
UAFH	NF1	19	47.600	4.0401	.9269	1.241	.273
	Control	19	49.000	3.7002	.8489		
PFH	NF1	19	70.768	9.3635	2.1481	.063	.804
	Control	19	71.426	6.5927	1.5125		

Table 5. Continued

** Approaching significance, $p = 0.081, 0.102, 0.110$

Figure 3. Pre-pubertal NF1 vs. Control Measurements



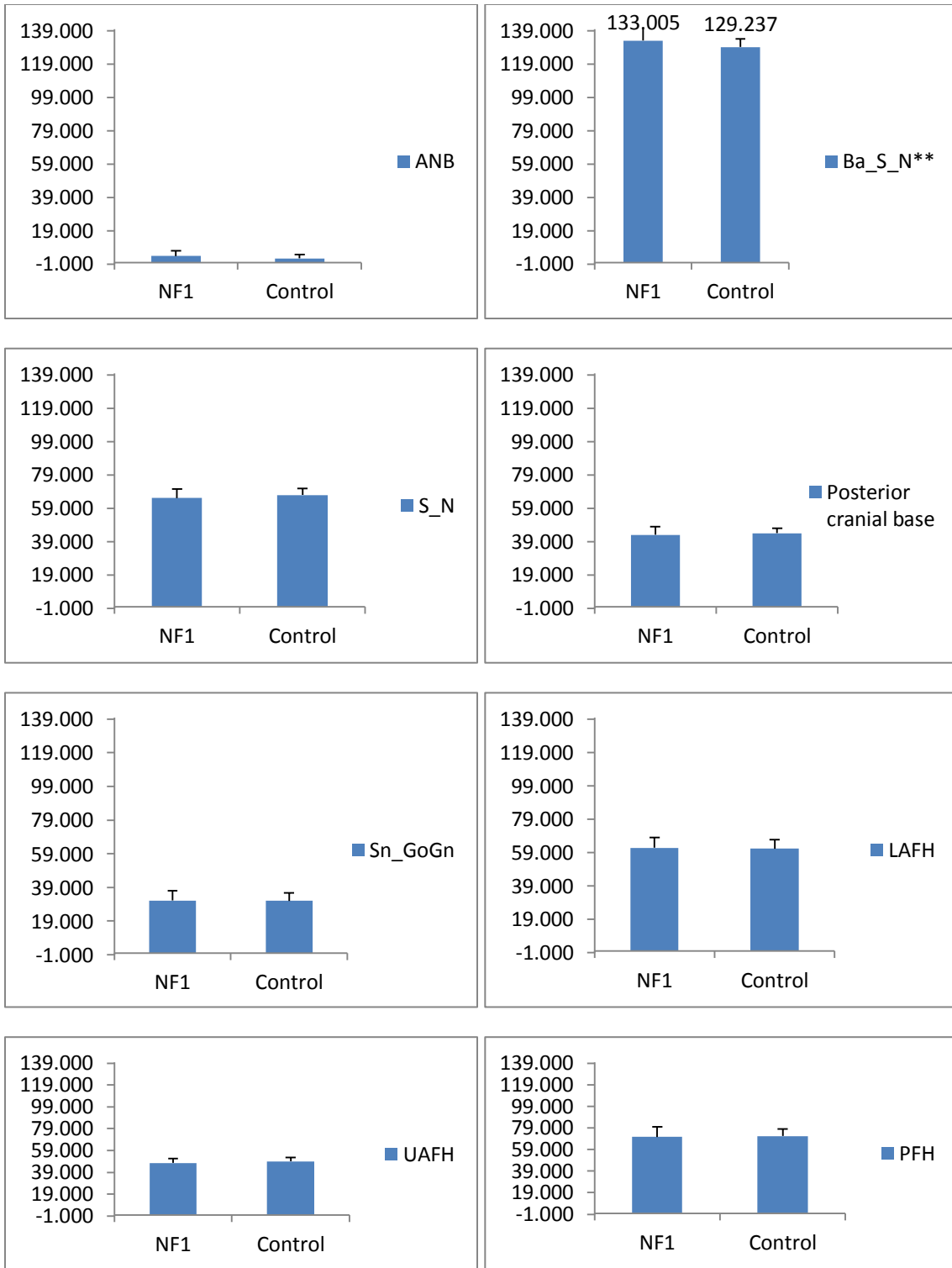


Figure 3. Continued

** Approaching significance, $p= 0.081, 0.102, 0.110$

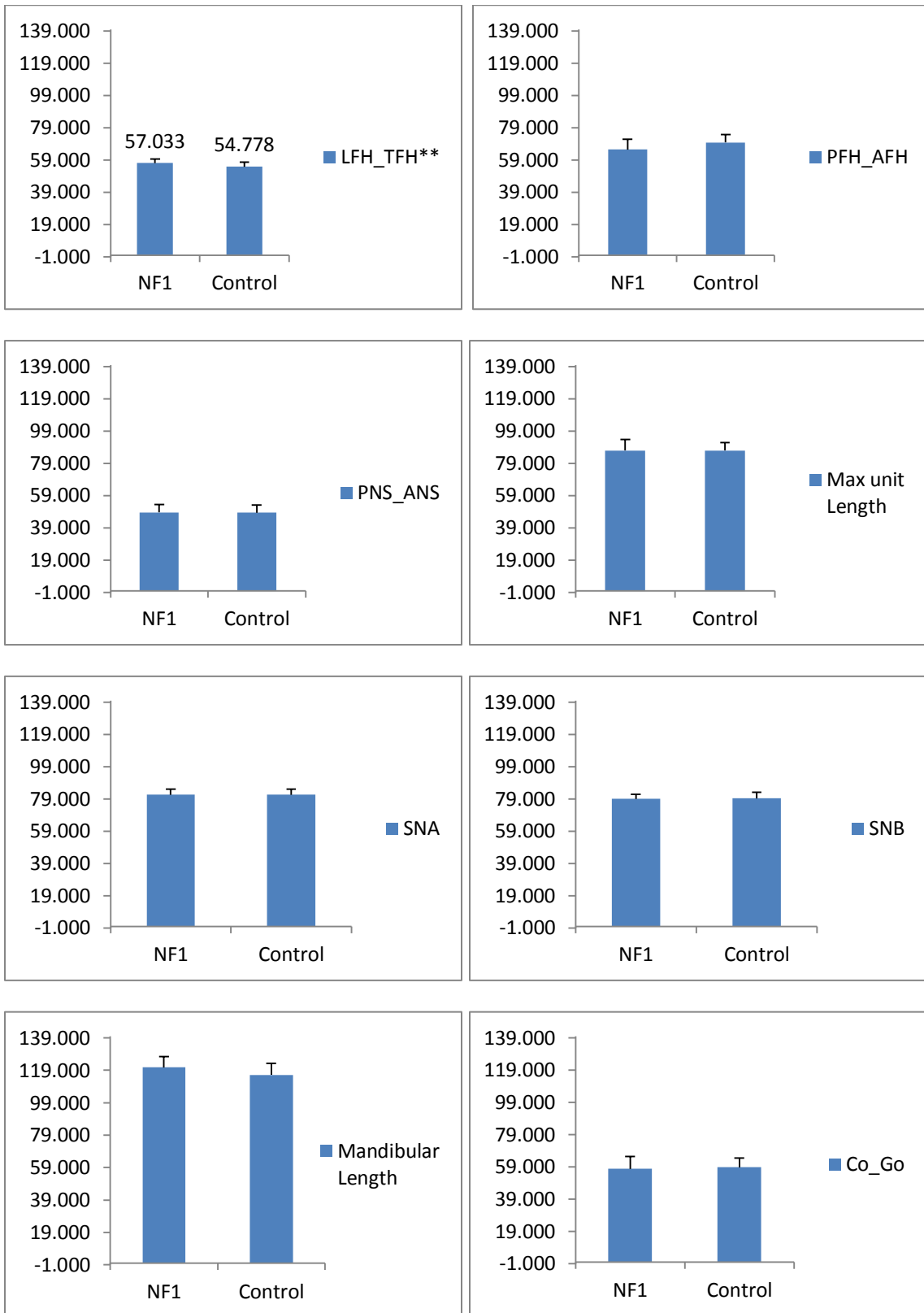
Table 6. Post-pubertal NF1 vs. Control Measurements

		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	NF1	9	57.033	2.6263	.8754	3.064	.099**
	Control	9	54.778	2.8363	.9454		
PFH_AFH	NF1	9	65.411	6.4268	2.1423	2.732	.118
	Control	9	69.844	4.8425	1.6142		
PNS_ANS	NF1	9	48.511	4.9471	1.6490	.003	.955
	Control	9	48.378	4.8301	1.6100		
Max_unit_Length	NF1	9	86.878	6.9155	2.3052	.001	.982
	Control	9	86.944	5.0230	1.6743		
SNA	NF1	9	81.633	3.3756	1.1252	.003	.957
	Control	9	81.544	3.5139	1.1713		
Mandibular_Length	NF1	9	120.733	6.7880	2.2627	1.926	.184
	Control	9	116.144	7.2322	2.4107		
Co_Go	NF1	9	57.656	7.5768	2.5256	.117	.736
	Control	9	58.744	5.7834	1.9278		
SNB	NF1	9	79.089	2.6545	.8848	.016	.902
	Control	9	79.289	3.9945	1.3315		
ANB	NF1	9	2.522	2.7128	.9043	.040	.845
	Control	9	2.256	2.9674	.9891		
Ba_S_N	NF1	9	135.756	8.5656	2.8552	3.820	.068**
	Control	9	129.789	3.2429	1.0810		
S_N	NF1	9	70.000	6.5426	2.1809	.000	.990
	Control	9	69.967	5.0431	1.6810		
Posterior_cranial_base	NF1	9	43.633	6.9549	2.3183	.101	.755
	Control	9	44.411	2.3966	.7989		
Sn_GoGn	NF1	9	31.533	6.9327	2.3109	2.354	.144
	Control	9	26.956	5.6606	1.8869		
LAFH	NF1	9	70.600	10.8068	3.6023	3.075	.099**
	Control	9	63.911	3.7625	1.2542		
UAFH	NF1	9	51.556	3.9642	1.3214	.003	.954
	Control	9	51.444	4.1359	1.3786		
PFH	NF1	9	78.622	8.7245	2.9082	.092	.765
	Control	9	79.789	7.5192	2.5064		

Table 6. Continued

** Approaching significance, $p = 0.068, 0.099$

Figure 4. Post-pubertal NF1 vs. Control Measurements



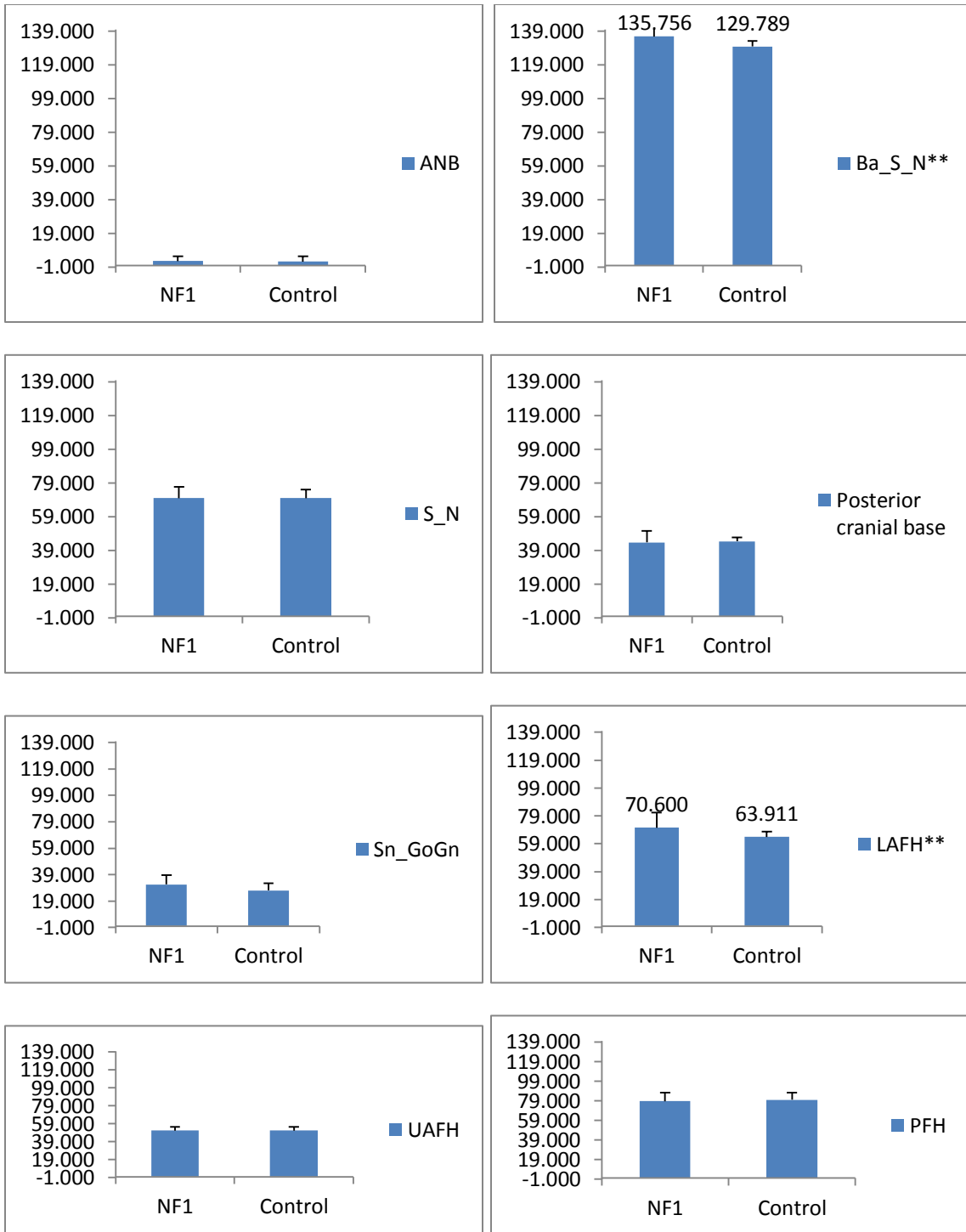


Figure 4. Continued

** Approaching significance, $p = 0.068, 0.099$

Table 7. Gender Male NF1 vs. Male Control Measurements

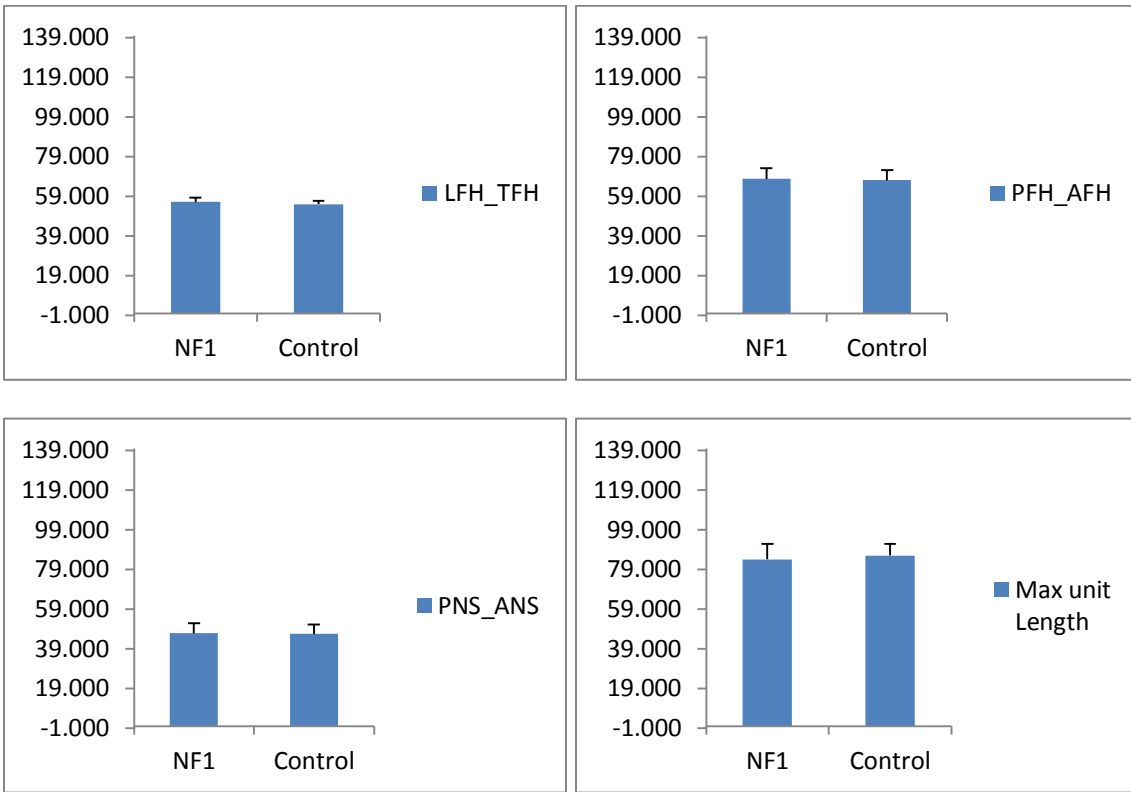
		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	NF1	18	56.061	2.2557	.5317	2.516	.122
	Control	18	55.022	1.6225	.3824		
PFH_AFH	NF1	18	67.656	5.6111	1.3226	.087	.770
	Control	18	67.133	5.0006	1.1786		
PNS_ANS	NF1	18	46.711	5.2863	1.2460	.014	.907
	Control	18	46.517	4.5944	1.0829		
Max_unit_Length	NF1	18	84.072	7.7952	1.8373	.629	.433
	Control	18	85.911	6.0026	1.4148		
SNA	NF1	18	82.189	4.1904	.9877	.815	.373
	Control	18	80.939	4.1180	.9706		
Mandibular_Length	NF1	18	111.533	12.8697	3.0334	.624	.435
	Control	18	114.322	7.6711	1.8081		
Co_Go	NF1	18	53.717	8.3628	1.9711	.555	.461
	Control	18	55.550	6.2483	1.4727		
SNB	NF1	18	78.867	4.8158	1.1351	.091	.765
	Control	18	78.411	4.2446	1.0005		
ANB	NF1	18	3.333	2.9468	.6946	.851	.363
	Control	18	2.506	2.4087	.5677		
Ba_S_N	NF1	18	132.622	8.8313	2.0815	4.126	.050*
	Control	18	128.056	3.6028	.8492		
S_N	NF1	18	67.672	6.6439	1.5660	1.097	.302
	Control	18	69.617	4.2291	.9968		
Posterior_cranial_base	NF1	18	45.461	5.4741	1.2903	.126	.724
	Control	18	44.944	2.8413	.6697		
Sn_GoGn	NF1	18	30.111	7.0136	1.6531	.016	.899

	Control	18	29.828	6.2071	1.4630		
LAFH	NF1	18	65.878	9.1319	2.1524	.690	.412
	Control	18	63.917	4.1113	.9690		
UAFH	NF1	18	49.611	4.7586	1.1216	.972	.331
	Control	18	50.983	3.4983	.8246		
PFH	NF1	18	76.572	9.1584	2.1587	.012	.914
	Control	18	76.256	8.3594	1.9703		

Table 7. Continued

*Statistically significant, $p \leq 0.05$

Figure 5. Gender Male NF1 vs. Male Control Measurements



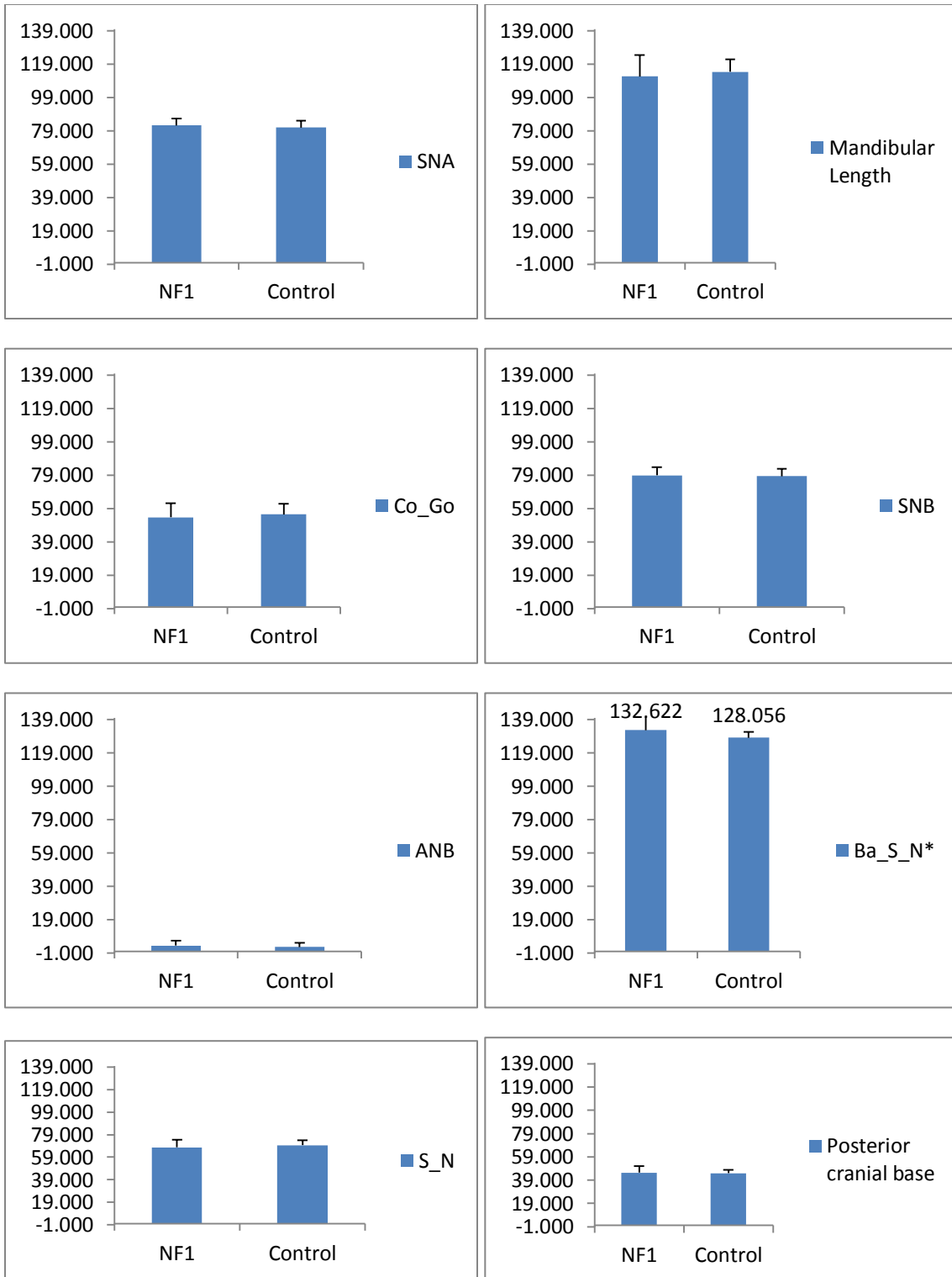


Figure 5. Continued

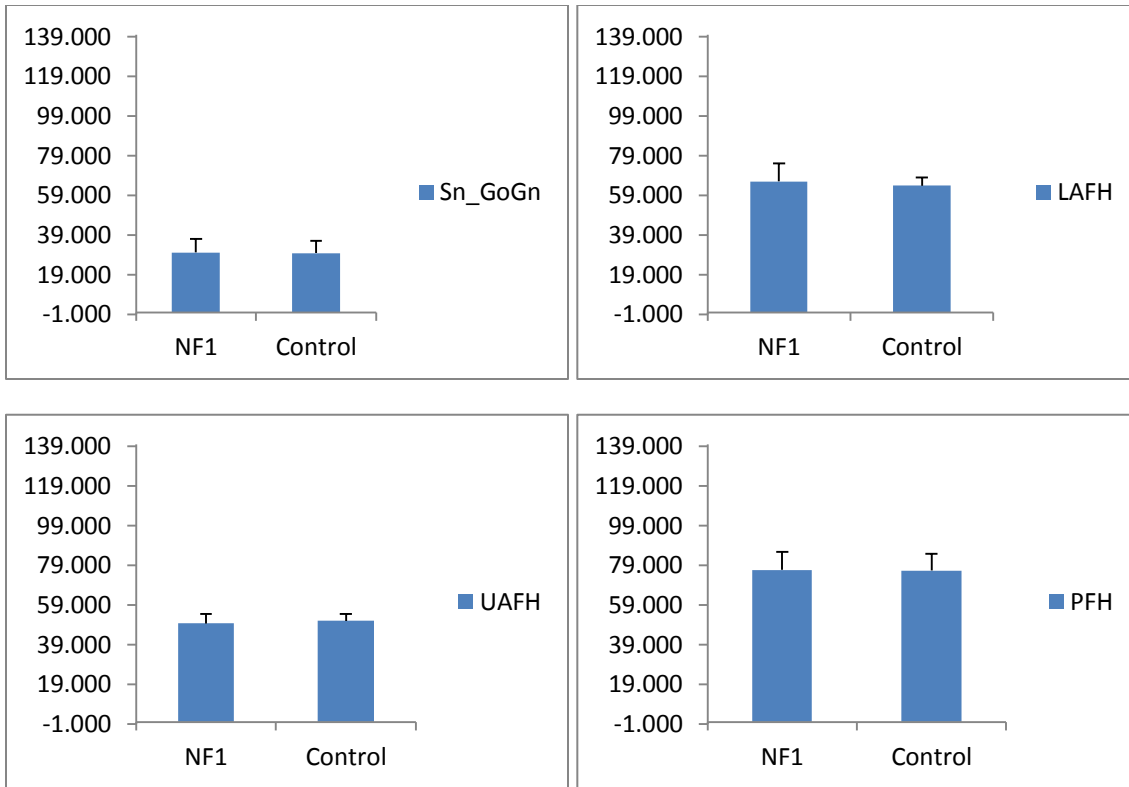


Figure 5. Continued

*Statistically significant, $p \leq 0.05$

Table 8. Gender Female NF1 vs. Female Control Measurements

		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	NF1	10	55.310	2.5097	.7936	.546	.469
	Control	10	54.460	2.6328	.8326		
PFH_AFH	NF1	10	62.480	4.4035	1.3925	8.836	.008*
	Control	10	67.060	2.0855	.6595		
PNS_ANS	NF1	10	42.760	5.4876	1.7353	1.373	.257
	Control	10	45.570	5.2339	1.6551		
Max_unit_Length	NF1	10	79.980	7.4088	2.3429	.349	.562
	Control	10	81.780	6.1664	1.9500		
SNA	NF1	10	80.170	5.0986	1.6123	.155	.698
	Control	10	78.560	11.8787	3.7564		
Mandibular_Length	NF1	10	106.300	11.7996	3.7314	.112	.742
	Control	10	107.740	6.7520	2.1352		
Co_Go	NF1	10	48.580	5.0365	1.5927	2.545	.128
	Control	10	51.840	4.0486	1.2803		
SNB	NF1	10	76.610	3.6516	1.1547	3.586	.074**
	Control	10	79.350	2.7573	.8719		
ANB	NF1	10	3.560	3.6142	1.1429	.945	.344
	Control	10	2.180	2.6624	.8419		
Ba_S_N	NF1	10	136.170	8.1321	2.5716	2.075	.167
	Control	10	131.860	4.8353	1.5291		
S_N	NF1	10	64.980	4.9600	1.5685	.002	.963
	Control	10	64.890	3.4723	1.0980		
Posterior_cranial_base	NF1	10	39.170	3.1605	.9994	9.307	.007*
	Control	10	42.800	2.0418	.6457		

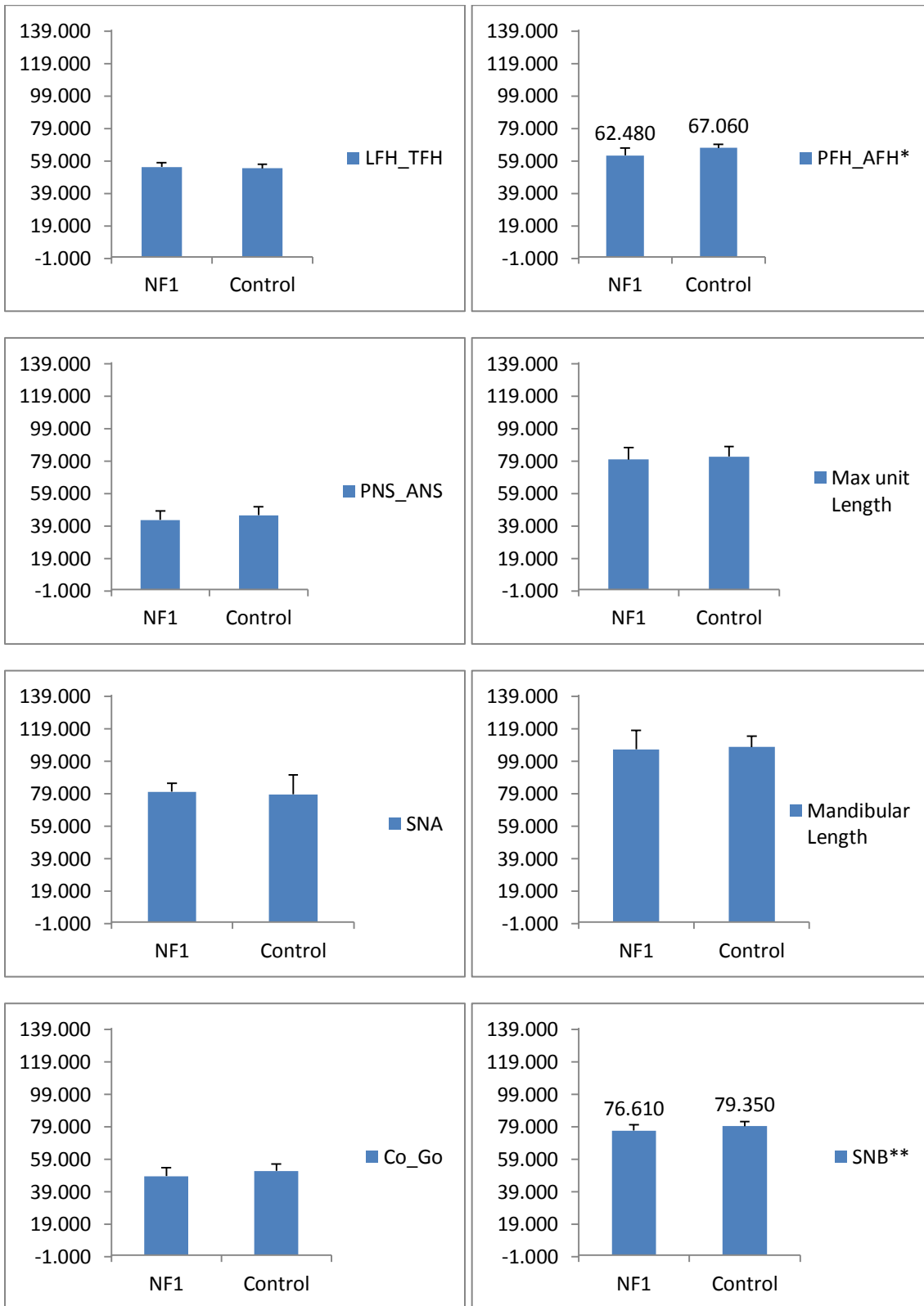
Sn_GoGn	NF1	10	33.500	3.4367	1.0868	8.050	.011*
	Control	10	29.390	3.0285	.9577		
LAFH	NF1	10	62.260	8.3163	2.6298	1.237	.281
	Control	10	58.770	5.4132	1.7118		
UAFH	NF1	10	47.540	3.3755	1.0674	.003	.957
	Control	10	47.630	3.9362	1.2447		
PFH	NF1	10	67.390	8.1369	2.5731	.884	.360
	Control	10	70.260	5.1930	1.6422		

Table 8. Continued

*Statistically significant, $p \leq 0.05$

**Approaching significance, $p=0.074$

Figure 6. Gender Female NF1 vs. Female Control Measurements



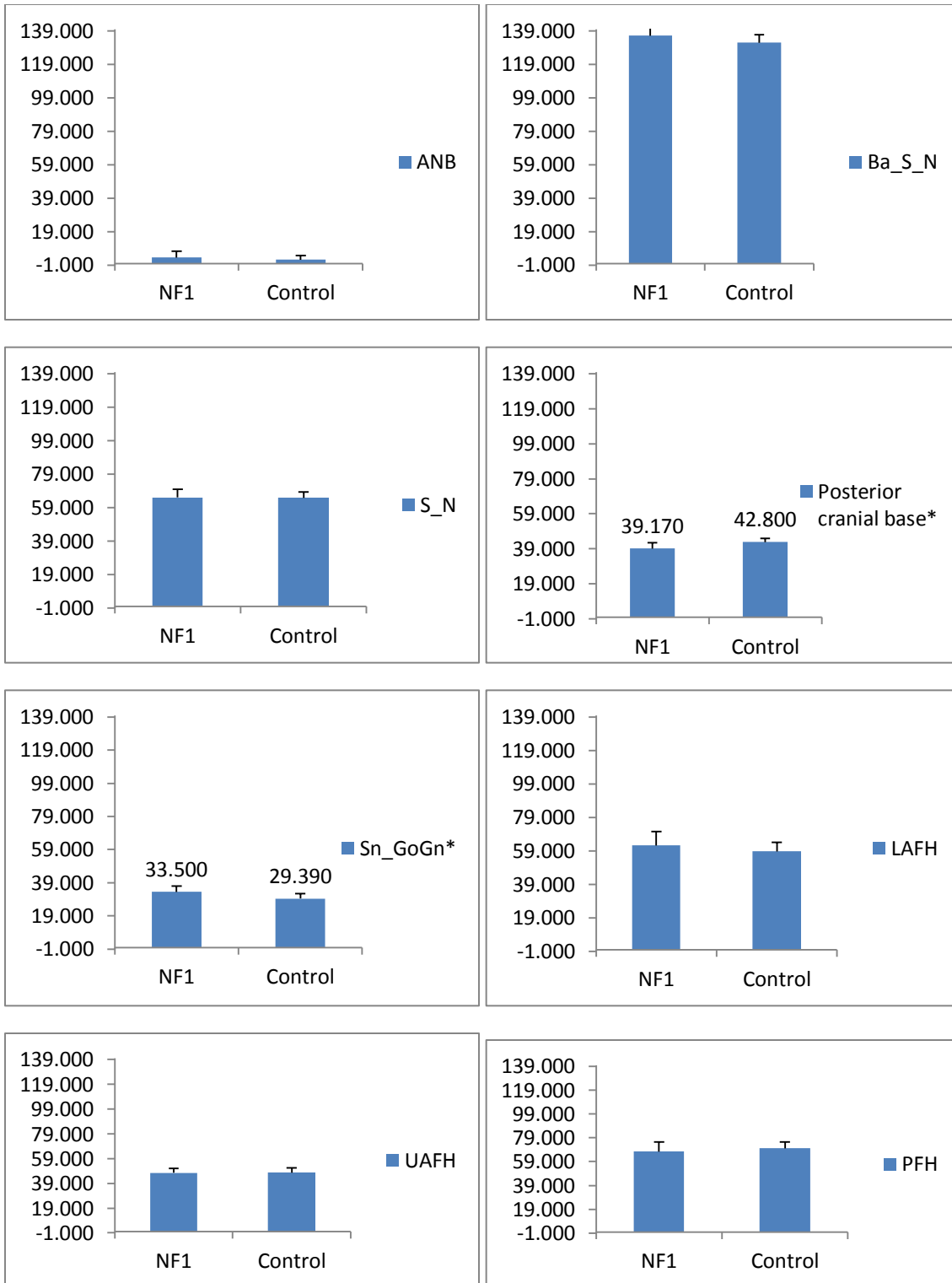


Figure 6. Continued

*Statistically significant, $p \leq 0.05$

**Approaching significance, $p = 0.074$

Table 9. Gender Male vs. Female NF1 group measurements

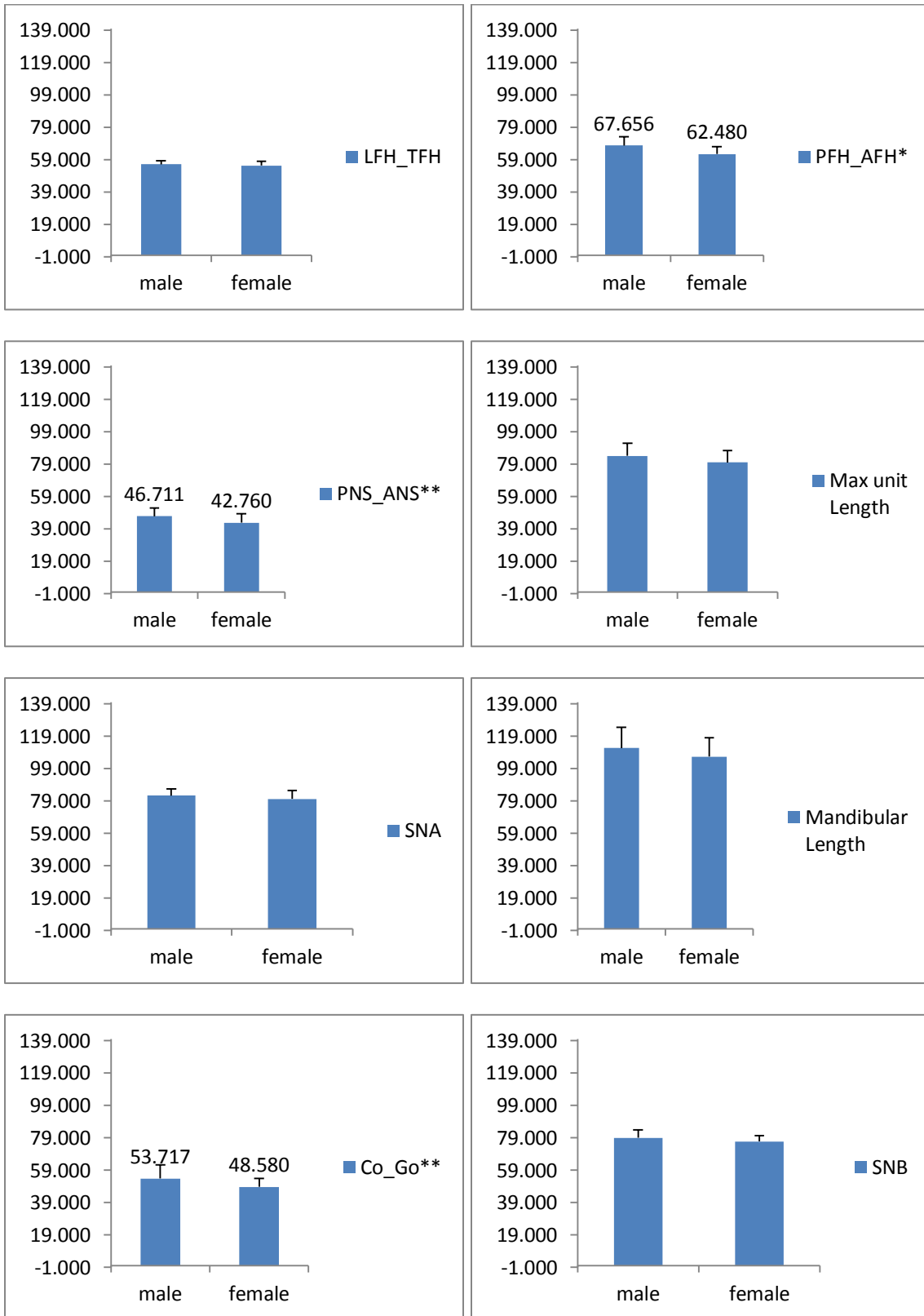
		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	male	18	56.061	2.2557	.5317	.659	.424
	female	10	55.310	2.5097	.7936		
PFH_AFH	male	18	67.656	5.6111	1.3226	6.308	.019*
	female	10	62.480	4.4035	1.3925		
PNS_ANS	male	18	46.711	5.2863	1.2460	3.497	.073**
	female	10	42.760	5.4876	1.7353		
Max_unit_Length	male	18	84.072	7.7952	1.8373	1.833	.187
	female	10	79.980	7.4088	2.3429		
SNA	male	18	82.189	4.1904	.9877	1.279	.268
	female	10	80.170	5.0986	1.6123		
Mandibular_Length	male	18	111.533	12.8697	3.0334	1.125	.299
	female	10	106.300	11.7996	3.7314		
Co_Go	male	18	53.717	8.3628	1.9711	3.112	.089**
	female	10	48.580	5.0365	1.5927		
SNB	male	18	78.867	4.8158	1.1351	1.655	.210
	female	10	76.610	3.6516	1.1547		
ANB	male	18	3.333	2.9468	.6946	.032	.859
	female	10	3.560	3.6142	1.1429		
Ba_S_N	male	18	132.622	8.8313	2.0815	1.095	.305
	female	10	136.170	8.1321	2.5716		
S_N	male	18	67.672	6.6439	1.5660	1.247	.274
	female	10	64.980	4.9600	1.5685		
Posterior_cranial_base	male	18	45.461	5.4741	1.2903	11.038	.003*
	female	10	39.170	3.1605	.9994		
Sn_GoGn	male	18	30.111	7.0136	1.6531	2.037	.165

	female	10	33.500	3.4367	1.0868		
LAFH	male	18	65.878	9.1319	2.1524	1.072	.310
	female	10	62.260	8.3163	2.6298		
UAFH	male	18	49.611	4.7586	1.1216	1.471	.236
	female	10	47.540	3.3755	1.0674		
PFH	male	18	76.572	9.1584	2.1587	6.970	.014*
	female	10	67.390	8.1369	2.5731		

Table 9. Continued

*Statistically Significant, $p \leq 0.05$ **Approaching significance, $p = 0.073, 0.089$

Figure 7. Gender Male vs. Female NF1 group measurements



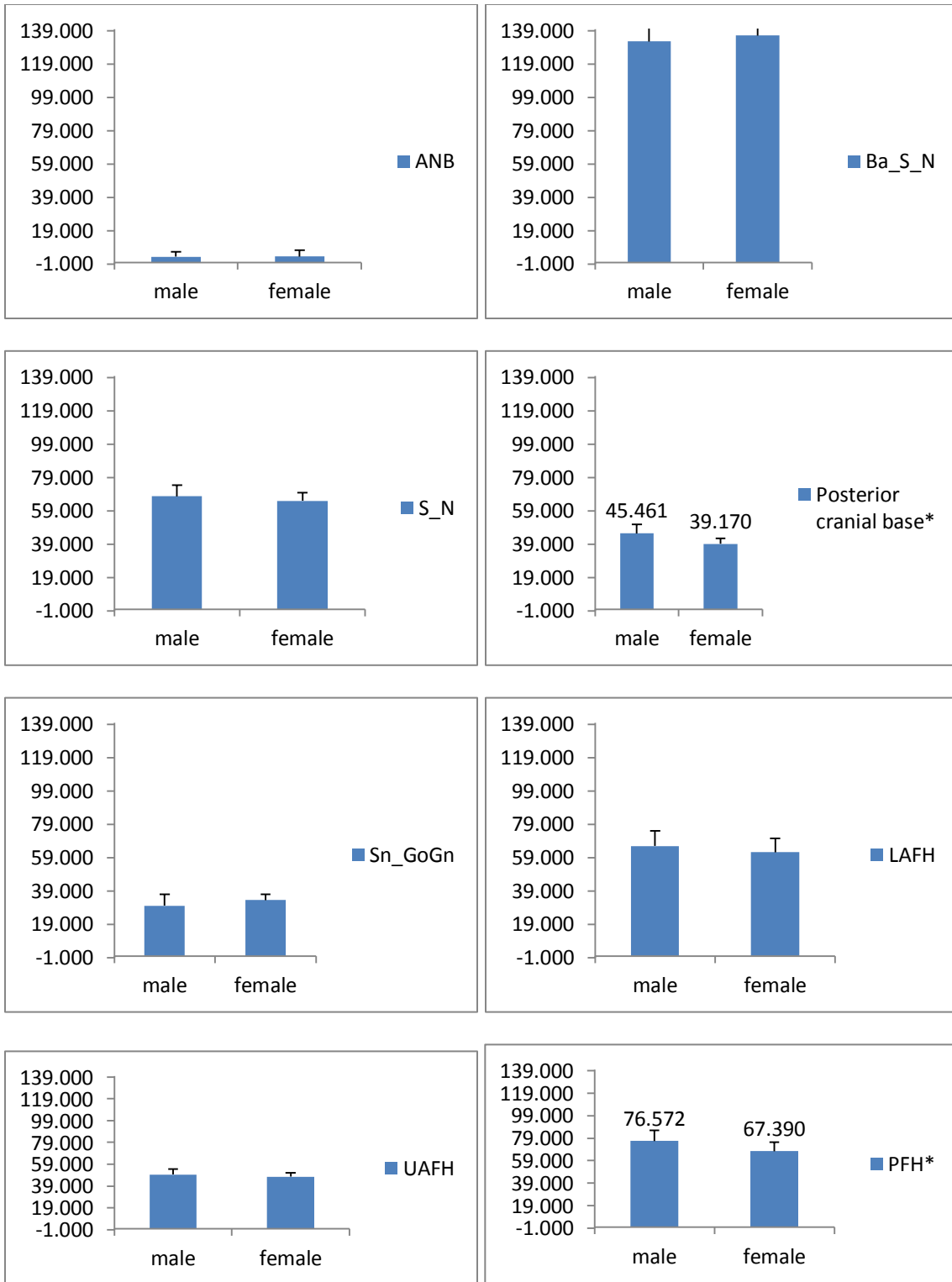


Figure 7. Continued

*Statistically Significant, $p \leq 0.05$

**Approaching significance, $p = 0.073, 0.089$

Table 10. Gender Male vs. Female Control group measurements

		N	Mean	Std. Deviation	Std. Error	F	Sig.
LFH_TFH	male	18	55.022	1.6225	.3824	.493	.489
	female	10	54.460	2.6328	.8326		
PFH_AFH	male	18	67.133	5.0006	1.1786	.002	.965
	female	10	67.060	2.0855	.6595		
PNS_ANS	male	18	46.517	4.5944	1.0829	.247	.623
	female	10	45.570	5.2339	1.6551		
Max_unit_Length	male	18	85.911	6.0026	1.4148	2.988	.096**
	female	10	81.780	6.1664	1.9500		
SNA	male	18	80.939	4.1180	.9706	.607	.443
	female	10	78.560	11.8787	3.7564		
Mandibular_Length	male	18	114.322	7.6711	1.8081	5.133	.032*
	female	10	107.740	6.7520	2.1352		
Co_Go	male	18	55.550	6.2483	1.4727	2.836	.104
	female	10	51.840	4.0486	1.2803		
SNB	male	18	78.411	4.2446	1.0005	.393	.536
	female	10	79.350	2.7573	.8719		
ANB	male	18	2.506	2.4087	.5677	.109	.744
	female	10	2.180	2.6624	.8419		
Ba_S_N	male	18	128.056	3.6028	.8492	5.612	.026*
	female	10	131.860	4.8353	1.5291		
S_N	male	18	69.617	4.2291	.9968	9.051	.006*
	female	10	64.890	3.4723	1.0980		
Posterior_cranial_base	male	18	44.944	2.8413	.6697	4.398	.046*
	female	10	42.800	2.0418	.6457		
Sn_GoGn	male	18	29.828	6.2071	1.4630	.043	.837

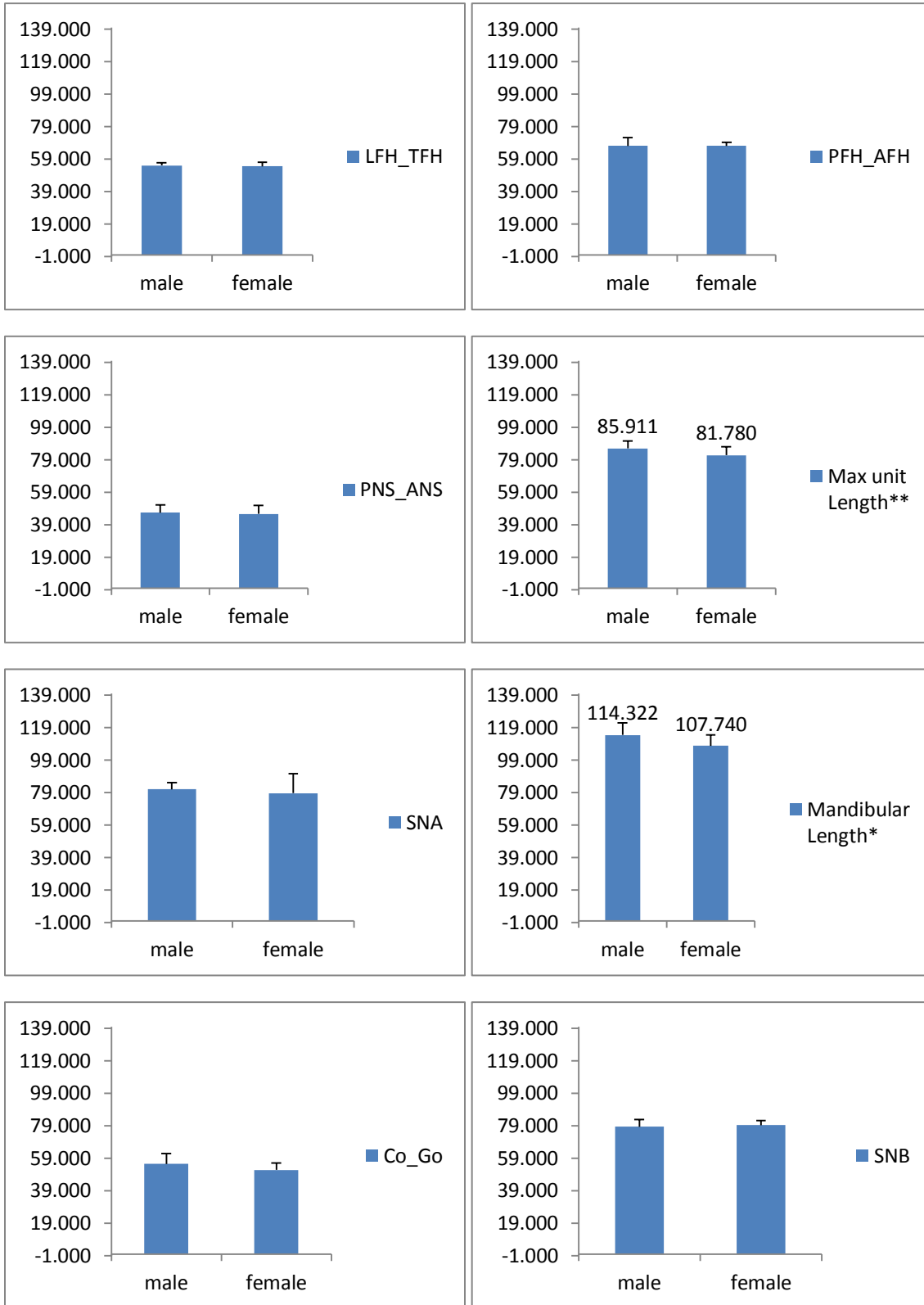
	female	10	29.390	3.0285	.9577		
LAFH	male	18	63.917	4.1113	.9690	8.034	.009*
	female	10	58.770	5.4132	1.7118		
UAFH	male	18	50.983	3.4983	.8246	5.409	.028*
	female	10	47.630	3.9362	1.2447		
PFH	male	18	76.256	8.3594	1.9703	4.200	.051**
	female	10	70.260	5.1930	1.6422		

Table 7. Continued

*Statistically Significant, $p \leq 0.05$

**Approaching significance, $p = 0.096, 0.051$

Figure 8. Gender Male vs. Female Control group measurements



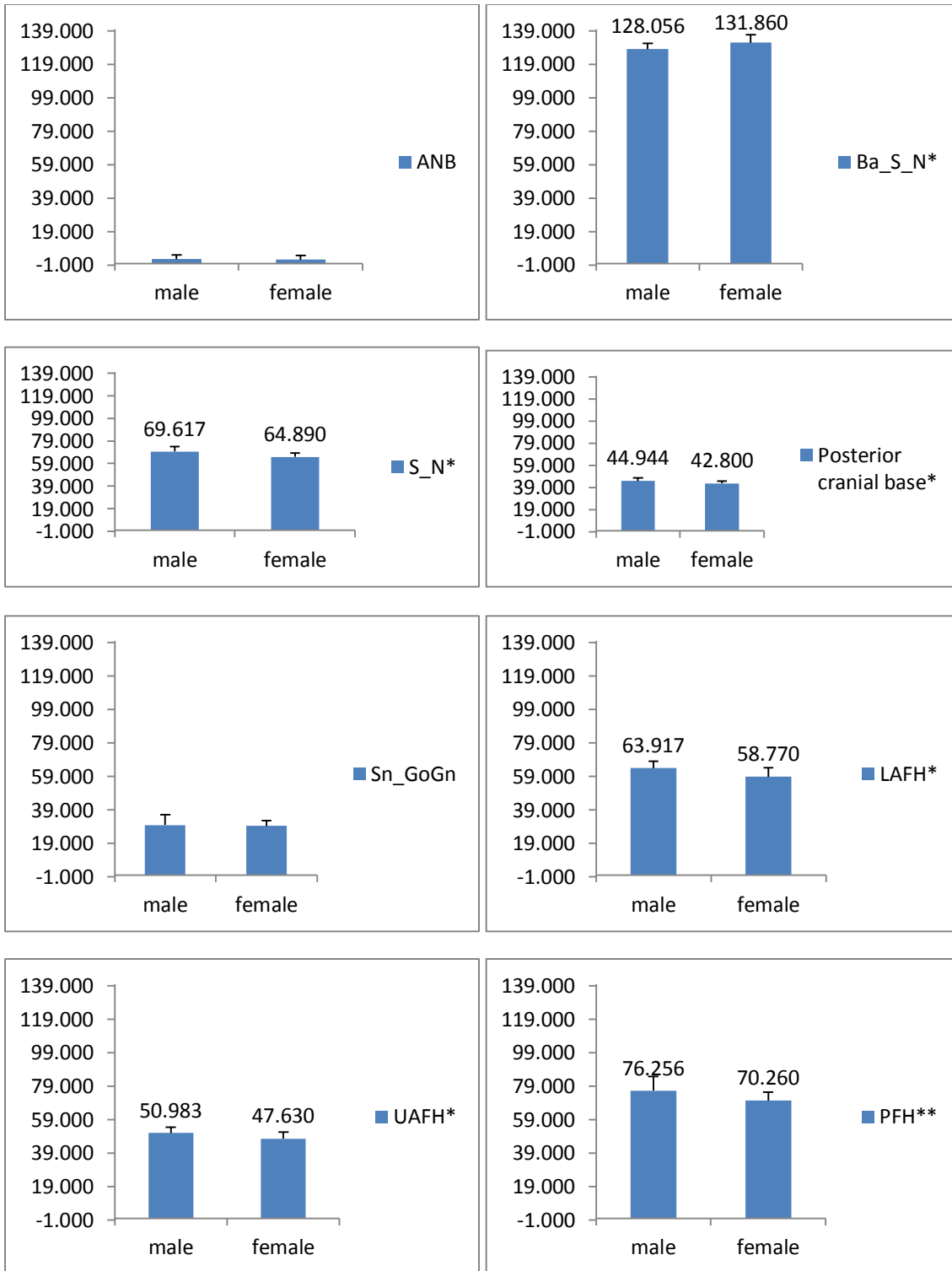


Figure 8. Continued

*Statistically Significant, $p \leq 0.05$

**Approaching significance, $p = 0.096, 0.051$

Table 11. Summary of Significant and Approaching Significant Results

Analysis	Variable	P-Value	Significant	Approaching Significance	Clinically Relevant
<i>Total NF1 Vs Control</i>					
	Ba-SN	.018	+		Yes
	LFH/TFH	.101		+	No
<i>Pre-pubertal NF1 vs Control</i>					
	CoGo	.102		+	No
	Mandibular Length	.081		+	Yes
	Ba-SN	.110		+	Yes
<i>Post-Pubertal NF1 vs Control</i>					
	LFH/TFH	.099		+	Yes
	LAFH	.099		+	Yes
	Ba-SN	.068		+	Yes
<i>Gender male NF1 vs male control</i>					
	Ba-SN	.05	+		Yes
<i>Gender Female NF1 vs female control</i>					
	PFH/AFH	.008	+		Yes
	SNB	.074		+	Yes
	Posterior cranial base	.007	+		Yes
	Sn-GoGn	.011	+		Yes

<i>Male vs female NF1</i>					
	PFH/AFH	.019	+		Yes
	PNS-ANS	.073		+	Yes
	CoGo	.089		+	Yes
	Posterior cranial base	.003	+		Yes
	PFH	.014	+		Yes
<i>Male vs female control</i>					
	Max unit length	.096		+	Yes
	Man length	.032	+		yes
	Ba-SN	.026	+		Yes
	SN	.006	+		Yes
	Posterior cranial base	.046	+		Yes
	LAFH	.009	+		Yes
	UAFH	.028	+		Yes
	PFH	.051		+	Yes

Table 11. Continued

Discussion

In the present study, 16 craniofacial measurements were analyzed on lateral cephalometric radiographs of 28 NF1 patients and 28 matched healthy control patients. The radiographs for the NF1 patients were obtained from the NIH, and the matched healthy control radiographs were collected from The University of Maryland Dental School, orthodontic clinic. The total groups of NF1 vs healthy controls were analyzed, including pre-pubertal, and post-pubertal subjects. The groups were also compared based on gender. Due to the small sample of patients with lateral cephalometric radiographs that were available from The NIH, analyses that were both approaching significance and clinically important were presented in this manuscript.

It has been found that adults with NF1 disease show a decrease in bone mineral density and a decrease in height. Tucker et al (2009)¹⁷ found that patients with NF1 “are shorter than expected and often have low bone mineral density.” The study by Heerva et al (2011)¹ and the unpublished master’s thesis by Cung et al(2013)¹⁶ found that NF1 adults had a decrease in their craniofacial structures compared to their matched healthy controls. Heerva et al (2011)¹ was unable to find statistically significant differences in the pediatric NF1 group due to the small number of pediatric NF1 patients in their study. They both concluded that the growth of the craniofacial bones may be regulated by the *NF1* gene. In the current study, few differences were found in the craniofacial structures of the pediatric NF1 patients compared to their matched healthy controls. Dulai et al (2007)¹³ found that “no osteopenia was seen in children younger than ten years.” They therefore hypothesized that osteopenia in NF1 may become more problematic with age. This may also explain why certain bone manifestations in these patients increase in

severity with age, for example scoliosis. Jett et al (2010)¹⁸ also found that “many people with NF1 have only milder manifestations of the disease, such as pigmented lesions, Lisch nodules, or learning disabilities, but the frequency of more serious complications increases with age. Various manifestations of NF1 have different characteristic times of appearance.”

An important part of orthodontic treatment during adolescence is utilization of the growth of the jaws. It is best to take advantage of patients with skeletal discrepancies during adolescence to make use of their growth potential. When patients have a skeletal discrepancy, it is standard practice for the clinician to make the most of the mandibular and maxillary growth to try to relieve this discrepancy. Therefore, orthodontists are interested in the growth of the craniofacial structures, especially the maxilla and the mandible (Ochoa et al 2004)¹⁹. Growth studies to date demonstrate relatively larger changes in male subjects when compared to female subjects. Ochoa et al (2004)¹⁹ also stated that growth of the face is closely related to growth of the body and therefore growth accelerates during adolescence. Therefore, adolescence would be the best time for orthodontists to try to manage the orthopedic growth effects of the maxilla and the mandible with different types of appliances. Since few statistically significant differences were seen in the maxilla and the mandible of NF1 patients versus the control group, orthodontists should be able to use orthopedic treatment options on patients that have discrepancies in their maxillary and mandibular jaw relationships.

Snodell et al (1993)²⁰ showed that “timing orthodontic treatment to coincide with growth may be a considerable factor in the stability of the dentition. As many clinicians use maxillary orthopedics, the timing of its use is important.” Visnapuu et al (2011)¹²

discussed that the “engagement of an orthodontic specialist for the treatment of patients with NF1 at an early phase one is of utmost importance for the comprehensive care of these patients. Expert knowledge of orthodontics and orthopedics can be used to guide the facial growth and alignments of dentition to prevent and decrease the need for extensive orthodontic and surgical intervention.”

Total NF1 vs Control

In this study, comparison of NF1 vs healthy controls, Ba-SN was the only statistically significant difference found. The angle was larger in the NF1 group compared to the control group. With growth, the nasion usually migrates forward and downward, thus decreasing the Ba-SN angle with age. Ursi et al (1993)²¹ discussed that in normal growth, the nasion increases in thickness by surface deposition and increasing pneumatization of the frontal sinus. This occurs during adolescence. It was found in the study by Ursi et al (1993)²¹ that the frontal sinuses in males were larger than in females. Previous studies have found that neurofibromin mRNA and protein have been detected in human osteoclasts and osteocytes (Kuorilehto et al 2004)¹¹. Additionally, research has found that an increase in the Ras-pathway activity enhances osteoclast-mediated resorption and reduces osteogenesis (Dulai et al 2007)¹³. Tucker et al (2009)¹⁷ stated that “evidence from NF1 mouse models suggests that the Ras-pathway plays a key role in both osteoclast and osteoblast biology.” Since osteoclasts and osteoblasts are not functioning properly in patients with NF1, they may not get proper resorption and

deposition of bone at the nasion point. This might account for nasion remaining at a higher point which might account for the increased Ba-SN angle seen in this study.

Heerva et al (2011)¹ found that patients with NF1 often have osseous dysplasia, including macrocephaly. “Macrocephaly, determined by occipito-frontal circumference, is a common characteristic in NF1 and can be detected in approximately 25% of North American patients with NF1.” The enlarged circumference of the occipito-frontal region might account for the increase in Ba-SN angle found in NF1 patients compared to the healthy controls seen in this study.

It is known that patients with NF1 have bony changes including sphenoid wing dysplasia and tibial dysplasia. These bony changes often appear in early childhood. Heerva et al (2011)¹ stated that the osseous dysplasia that is seen in approximately half of the patients with NF1 include “macrocephaly, sphenoid wing dysplasia, short stature, reduced bone mineral density, scoliosis, lytic bone lesions and congenital bowing and psuedoarthrosis of the tibia.” They also found that “Ten percent of patients with NF1 have facial asymmetries with associated sphenoid wing dysplasia.” The sphenoid bone is a midline craniofacial bone and is formed by endochondral ossification. Due to the defect in the neurofibromin protein and thus an increase in RAS-pathway activity in patients with NF1, the properties and function of the osteoclasts and osteoblasts, which are needed to remodel the cartilaginous precursors into bone, may be defective. This may account for the sphenoid bone dysplasia and may explain the increase in the Ba-SN angle seen in this study.

Moss et al (1955)²² explained that the axis of cranial flexure passes through the body of the sphenoid bone. “Change in the form or position of the components of the sphenoid bone complex will greatly influence the angular rotation of the skull base.” Patients with NF1 are known to have sphenoid wing dysplasia. Since the sphenoid bone is the axis for the cranial base flexure, this might explain the increased cranial base flexure (Ba-SN angle) seen in pediatric NF1 patients in this study.

Pre-pubertal NF1 vs Control

When comparing the 19 pre-pubertal NF1 with the 19 healthy pre-pubertal group, no measurements were statistically significant. However, three measurements were approaching significance; CoGo, mandibular length and Ba-SN.

In this study, NF1 pre-pubertal patients showed a larger Ba-SN angle and a smaller mandibular length measurement. A number of reasons may explain the smaller mandibular length measurement. The mutation of the *NF1* gene and thus the increase in RAS activation might decrease the proper osteoblast and osteoclast functioning. This might account for the smaller mandibular length measurement seen in pre-pubertal NF1 patients. As stated earlier, the mandible forms by endochondrial ossification. It requires a cartilaginous precursor to subsequently form bone by the use of osteoclasts and osteoblasts. Therefore, if this process is not working properly in patients with NF1, this might explain the decreased mandibular length found in pre-pubertal NF1 patients.

Another possible explanation for the smaller mandibular length found in NF1 pre-pubertal patients compared to their matched controls could be due to a delay in growth of

these patients. NF1 patients have decreased bone density, increased likelihood of scoliosis, and are known to be shorter in stature. It is known that the peak height velocity of a person coincides with the peak in craniofacial growth. If NF1 patients have their peak height velocity later on than their healthy controls, this might explain the smaller mandibular length at the time of this study. NF1 pediatric patients may be delayed in both the timing of their height and their craniofacial growth potential.

Moss et al (1955)²² and Klocke et al (2002)²³ found that patients with an increased cranial base flexure tend to have skeletal class II relationships. They both indicated that there is a relationship between the cranial base angle and certain types of dental malocclusions. This might account for the smaller mandibular length found in NF1 pre-pubertal patients compared to their matched healthy controls. If this is the case, it might allow orthodontists and practitioners to be able to predict the type of dental malocclusion in patients with NF1 with a larger than average cranial base flexure angle.

No measurements in this group were found to be statistically significant. This might be due to the small sample in this study. It might also be due to the fact that some differences seen between NF1 patients and healthy controls may not be evident until later on in life. They may appear after puberty or later into adulthood. Fadda et al (2007)¹⁰ found that “the tumors seen in NF1 patients may be present at birth; however they usually don’t begin to appear until puberty and continue to slowly develop through adulthood.” In some patients, the tumors are not present early on, and therefore, other craniofacial differences may not be seen until later in life as well.

Post-pubertal NF1 vs Control

When comparing nine post-pubertal NF1 and nine post-pubertal healthy control subjects, there were no comparisons that were statistically significant; however three analyses were approaching significance. These analyses were LFH/TFH, LAFH, Ba-SN. Due to the small sample size in this group, comparisons that were approaching significance and that were clinically relevant were indicated. NF1 post-pubertal patients showed a larger LFH/TFH and a larger LAFH compared to their healthy controls. They also showed the increase in their Ba-SN angle that was seen in the prior analyses. The longer lower anterior facial height might be due to the decrease in bone resorption and deposition at the condyle area. This may lead to a shorter posterior facial height, and thus increase the dimensions of the lower anterior facial height. The condyle and the posterior ramus are areas of constant remodeling with resorption and deposition of bone by the use of osteoclasts and osteoblasts. If those components are not functioning properly in NF1 patients, this may lead to a disproportionately smaller PFH, making their LAFH larger.

Lieberman et al (1998)²⁴ found that “shortening of the sphenoid influences human cranial shape primarily by altering the spatial relationships between the face, cranial base, and neurocranium in the sagittal plane, which together determine the degree of facial projection.” This might account for the differences seen in the facial proportions of post-pubertal NF1 patients compared to their healthy matched controls.

Male NF1 vs Male Control

There were 18 male NF1 patients and 18 male control subjects that were analyzed. One comparison in this study was statistically significant. When looking at the groups based on male gender, it was found that male NF1 patients had a larger Ba-Sn measurement compared to the control. Again, this can be explained by their larger head circumference and larger frontal sinus, with less anterior and inferior migration of the nasion point with growth. Leiberman et al (2008)²⁵ found that there was a relationship between brain size, face size, width and length of the cranial base. He proposed that this accounts for a large percentage of variations in the cranial base angle. This article discussed possible reasons for a smaller or larger cranial base flexure angle. Therefore the larger cranial base angle seen in NF1 patients might be due to a decrease in brain size. The basicranium forms by endochondrial ossification. It first forms a set of cartilaginous precursors and then continues to increase from expansion within synchondroses. “The synchondrosis can be defined as a cartilaginous joint between two immovable bones that serves to allow growth until the cartilage is converted into bone before or during early adult life” (Bassed at al 2010)²⁶. The cartilage is then converted into bone by osteoclasts and osteoblasts. When the brain size is larger, it puts pressure on the floor of the cranial base, and expands the cranial base leading to a smaller cranial base angle. When the brain size is smaller, it exerts less pressure on the skull base, and thus increases the cranial base angle (Ba-SN angle).

Moore et al (2000)²⁷ found that children with NF1 are more likely to have learning disabilities, however they have been found to have larger brain volume than the healthy controls. This would disprove the theory of a smaller brain volume putting less

pressure on the cranial base, leading to a larger cranial base flexure angle. However, since NF1 children are found to have larger brain volumes and a larger skull circumference, this may lead to the increase in the Ba-SN angle found in this group of patients.

There were no other differences observed between male NF1 patients and their matched male healthy controls. The differences seen between these two groups may not be evident until later on in life. Males with NF1 might go through peak height velocity and their growth spurt at a later time than male control patients. If we looked at male NF1 compared with male control patients in adulthood, there may be differences seen. Other significant differences may not have been found due to the small sample size in this study and due to the data being used for multiple analyses.

Female NF1 vs Female Control

There were ten female NF1 patients and ten healthy female subjects in this study. The analyses that were statistically significant were PFH/AFH, posterior cranial base and SN-GoGn. SNB was approaching significance and can be considered clinically relevant. NF1 females were found to have a smaller PFH/AFH, SNB and posterior cranial base compared to the female control group. They were also found to have a larger Sn-GoGn angle compared to their matched healthy control group.

Kloche et al (2002)²³ found that there was a relationship between the cranial base flexure (Ba-SN) and the skeletal patterns of the jaws. He found that an increased cranial base angle is associated with a decrease in the SNA and SNB angles. This would lead to an increase in skeletal class II malocclusions and an increase in the ANB angle. This

would explain the smaller PFH/AFH, SNB and posterior cranial base found in the female NF1 patients. This would also explain the larger SN-GoGn angle found. Due to the smaller posterior facial height and the smaller posterior cranial base, the mandible is likely to swing slightly downward and back, leading to a decrease in the SNB angle, and an increase in the ANB angle. More research should be done to determine if the skeletal bases of NF1 patients are more likely to be in a skeletal class II relationship.

Male NF1 vs Female NF1

When analyzing the groups based on gender, there were 18 male NF1 patients and ten female NF1 patients. The comparisons that were statistically significant were PFH/AFH, posterior cranial base and PFH. The analyses that approached significance were PNS-ANS and CoGo. All the measurements for the male NF1 group were larger than the female NF1 group. According to Ochoa et al (2004)¹⁹, the growth of the face is closely related to the growth of the body as a whole. He also found that there were larger changes in males compared to females. He concluded that “the male sample overall developed two years longer than the female sample and also grew relatively more... The female sample had less incremental growth and duration of growth of the mandible.”

There have been many studies done comparing the gender differences in growth and development. Ursi et al (1993)²¹ found “On average, the craniofacial complex is between 5% and 9% larger in males than females.” He also found that these differences are not apparent until the age of approximately 14 years. He found that before 14 years of age, the “effective lengths of the maxilla and mandible were similar in both sexes...”

thereafter in females this length remained relatively constant while in males it increased.” He also found that the anterior cranial base was larger in males when compared to females.

Hunter et al (1966)²⁸ found that there is a “period of accelerated growth, called adolescence or pubertal growth spurt, that occurs approximately two years earlier in girls than in boys... and that during the adolescent period, there was a greater absolute facial growth and a greater rate of facial growth in males than females.” This would explain why NF1 males were found to have larger measurements compared to NF1 females in this study.

Male Control vs Female Control

There were 18 male healthy control patients and ten female healthy control patients analyzed in this study. The comparisons that were statistically significant were mandibular length, Ba-SN, SN, posterior cranial base, LAFH and UAFH. The analyses that were approaching significance were maxillary unit length and PFH. All the measurements for the male control were larger than for the female control group, except for Ba-SN. Females have their growth spurt earlier than males, and their growth is complete within two years. Males, however, have their peak height velocity at a later age, but continue to grow for a longer period of time than females. This might explain why males have larger measurements for all the comparisons that were statistically significant or approaching significance. This might also explain why females have a larger Ba-SN angle compared to males. Since males continue to grow past the females cessation of

growth, their nasion point may continue to migrate downward and forward with the growth of the face, and thus decrease the males Ba-SN cranial base angle when compared to females.

A number of studies have found that males grow larger in size and growth continues over a longer period of time as compared with females. Ferrario et al (1993)²⁹ explained that “the face was wider and longer in men than in women...this finding could be related to the well-known time differences in craniofacial growth: males as a group grow for a longer period of time and to a larger size than females.” Christie et al (1977)³⁰ also explained that men grow larger than females. He summarized that “boys grow later, longer and larger than girls... in other words, boys achieve more growth over a longer period of time and they begin this growth at a later time relative to chronological age.” Darwis et al (2003)³¹ also found males were larger than females. He explained that “growth patterns were similar for both genders until age 11 years, and then differed significantly thereafter. A growth spurt in facial volume was evident in females by 11 to 12 years then growth declined rapidly and ceased by 14 to 15 years. In males, the growth spurt was evident by 11 to 12 years and continued at a similar rate to 16 to 17 years. Facial volumes were always larger in males than females in all age groups.” Therefore it is not surprising that in the analyses of male vs female NF1 and controls, males were found to have larger measurements when compared to females.

Research Limitations

One limitation of this study was the small sample size. Some radiographs from the NF1 were not diagnostic and needed to be discarded from the study. This reduced the sample size even more. Another limitation was the control sample selected for this study. The control group was taken from The University of Maryland dental school, orthodontic department. Existing radiographs that were available were used because it is unethical to randomly take radiographs on a sample of patients. It would be unethical to use a prospective study and select patients with normal occlusions to take lateral cephalometric radiographs.

Another limitation was that the control sample that was selected had varying degrees of malocclusion. It would have been best to use a control group that had ideal orthognathic faces; with proper overbite, overjet and a class I angle classification. However, patients in this sample had malocclusions including open bites, deep bites, cleft palate, crossbites, some were dolichocephalic and others were brachycephalic. For future research, it would be best to include more inclusion and exclusion criteria in this study. Future research could be improved by using patients with an ideal occlusion and balanced facial proportions for the control group. Our control group was more representative of the general Caucasian population, however it is best to use an ideal occlusion to establish norms for which other groups can be compared. However, most patients who seek orthodontic treatment have dental malocclusions, and therefore those are the patients that these radiographs would be taken on at the dental school.

Another limitation was that the patient heights and head circumferences were not known. Heerva et al 2011¹ found that “short children with NF1 have short jaws and short cranial base, but in adulthood, a patient with NF1 may have short jaws and short cranial base, irrespective of height.” Therefore he concluded that there may be some form of growth disorder during puberty in NF1 patients. If the heights and head circumferences of the NF1 patients and their matched controls were known, their relationship could be compared to the growth and development of their craniofacial structures in both children and adults.

Future Research

Future research should include a larger pediatric NF1 sample size. It may also be beneficial to use controls from previous growth studies as opposed to using matched controls from the dental school. However, there are statistical problems with comparing our group to previous growth studies. The data available from growth studies is usually only the mean and standard deviations. The raw data is usually not available, and therefore the groups cannot be statistically analyzed. If the raw data were accessible, it cannot be statistically analyzed for this study because the data was collected by a different investigator at a different period of time and therefore the data may have not been collected the same way. As a result, the analysis would not be statistically valid. One might also look into a prospective study to gain a larger sample size.

Another future research interest might be the use of 3D cone beam imaging to analyze the craniofacial structures in all the dimensions of space. This would give more accurate measurements of the sagittal, transverse and vertical aspects of the craniofacial

structures. The NIH has some 3D cone beam imaging on the NF1 patients, however, The University of Maryland rarely takes 3D imaging on healthy patients due to increased radiation exposure.

Patients with NF1 have issues with bone formation and metabolism due to the effects on osteoblasts and osteoclasts from their abnormality in the *NF1 gene* and RAS pathway. It might be useful to evaluate other intraoral bone defects, including tori, possible periodontal defects, alveolar ridge defects and TMJ abnormalities.

Previous studies found a relationship between the cranial base flexure and the skeletal patterns of the jaws. More research should be done to determine if patients with NF1 are more likely to have a skeletal class II relationship due to their increased cranial base flexure found in this study.

The height and head circumferences have also been studied in NF1 patients. It has been found that height and head circumference correlates to short jaws and short cranial bases in children. However this correlation is not found in adults. If the heights and head circumferences of the NF1 pediatric patients and their matched controls were known, the correlation between these measurements and their craniofacial structures can be analyzed in future research.

Another area that might be evaluated is the use of bisphosphonates in the treatment of NF1 patients. Dulai et al (2007)¹³ stated that “bisphosphonates have been used to treat osteopenic segments after surgery on NF1 patients.” This may be an issue with orthodontic tooth movement since teeth move at a much slower rate in patients taking bisphosphonates.

Conclusion

The purpose of this study was to cephalometrically analyze and compare the craniofacial regions, including the morphology of the cranial base and the sphenoid bone, in pediatric patients with neurofibromatosis type I and a gender- and age-matched healthy controls. Based on the results of this study, it can be concluded that there are very few statistically significant differences found between the two groups studied. These differences are unlikely to have an effect on the orthodontic and orthopedic treatments performed on NF1 pediatric patients by their clinicians. Therefore, pediatric NF1 patients should be offered the same type of orthodontic and orthopedic treatment options as their matched healthy controls.

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