

# CRANIOFACIAL CHARACTERIZATION OF PATIENTS WITH MARFAN SYNDROME

Christian M. Johnson

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Approved by:

Sylvia Frazier-Bowers

Luiz Pimenta

William F. Vann

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## ABSTRACT

Christian M. Johnson: Craniofacial Characterization of Patients with Marfan Syndrome  
(Under the direction of Sylvia Frazier-Bowers)

**Background:** Marfan Syndrome (MFS) is a life-threatening connective tissue disorder with an often elusive diagnosis. Diagnosis is based on clinical findings outlined in the Ghent criteria which define hallmark features of the syndrome in the cardiovascular, ocular, and skeletal systems. The morbidity and mortality associated with MFS warrant timely diagnosis and intervention that can improve long-term prognosis. Previous research has highlighted the diagnostic value of craniofacial features in diagnosis; accordingly the aim of this study was to investigate craniofacial and dentoalveolar features in child, adolescent, and young adult patients with MFS. We hypothesized that a distinct craniofacial morphology exists for patients with MFS that can be described quantitatively and qualitatively. **Methods:** Twenty subjects with a positive diagnosis of MFS were recruited for this study (N=20). Craniofacial anthropometric measurements were made on each subject and compared to established norms of age- and sex-matched controls. The test measurements were compared to the control measurements by calculating a z-score for each test measurement; the measurements were categorized as normal or abnormal based on z-score. Lateral and frontal photographs were obtained to make qualitative assessments and describe facial features of subjects, and a clinical exam was completed to document occlusal relationships. Biometric and demographic information were obtained using a questionnaire. **Results:** The subjects were primarily female (60%) ranging in age between 4 to 25 years (mean age  $10.7 \pm 6.0$  years). Comparison of craniofacial measurements revealed that for

9 of the 12 measurements,  $\geq 65\%$  of the study population had a z-score of  $\pm 2$  and fell within the normal range for facial dimension. For 3 of the 12 measurements, over half of the subjects fell outside of the normal range (z-score  $< -2$  or  $> 2$ ) for facial dimension. Assessment of the frontal and lateral photographs revealed the most prevalent facial features were retrognathia (54%) and down-slanting palpebral fissures (62%). For occlusal relationships, 55% of subjects had a Class I molar relationship, 40% a Class II relationship, and 5% a Class III relationship. **Conclusion:** Our data suggests there are quantitative differences in the facial morphology of patients with MFS when compared to a control population.

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## TABLE OF CONTENTS

LIST OF TABLES .....	viii
LIST OF FIGURES .....	ix
LIST OF ABBREVIATIONS.....	x
LIST OF SYMBOLS .....	xi
REVIEW OF THE LITERATURE .....	1
Marfan Syndrome (MFS).....	1
Etiology of MFS .....	2
Epidemiology of MFS.....	2
Diagnostic Criteria for MFS .....	3
Challenges to Diagnosis.....	5
Diagnostic Criteria in Clinical Practice .....	7
Diagnosis and Phenotype in Children.....	9
Benefits of Early Diagnosis .....	11
Consequences of Misdiagnosis .....	12
Management of MFS .....	12
Craniofacial Characterization of MFS .....	13
Craniofacial Characterization of other Syndromes.....	15
Conclusion .....	16
References.....	18
CRANIOFACIAL CHARACTERIZATION OF MARFAN SYNDROME.....	20

Introduction.....	20
Methods.....	22
Sample.....	22
Procedures .....	23
Statistical Analysis.....	24
Results.....	25
Demographic and Biometric Results .....	25
Intraoral Examination Results.....	26
Assessment of Photographs .....	26
Craniofacial Anthropometric Measurements .....	26
Z-score Distribution by Group.....	27
Discussion .....	27
Conclusions.....	33
References.....	35
Tables.....	37
Figures.....	38
Appendix 1: Revised Ghent Nosology for MFS.....	44

## LIST OF TABLES

Table 1 – Sample Demographic Data .....	37
Table 2 – Craniofacial Measurements .....	37
Table 3 – Z-score Distribution MFS vs. Normal Population.....	37



## LIST OF FIGURES

Figure 1 – Frequency of z-score distribution for sample population vs. normal population for facial width .....	38
Figure 2 – Frequency of z-score distribution probands vs. non-probands for facial width .....	38
Figure 3 – Cardiovascular Anomalies.....	38
Figure 4 – Ocular Anomalies .....	39
Figure 5 – MFS Craniofacial Features .....	39
Figure 6 – Morphological Height of Face.....	39
Figure 7 – Physiognomical Height of the Upper Face.....	40
Figure 8 – Mandible Height.....	40
Figure 9 – Lower Face Height .....	40
Figure 10 – Nose Height .....	41
Figure 11 – Width of Nose.....	41
Figure 12 – Biocular Width .....	41
Figure 13 – Intercanthal Width.....	42
Figure 14 – Width of the Head .....	42
Figure 15 – Width of the Forehead .....	42
Figure 16 – Width of the Face .....	43
Figure 17 – Width of the Mandible.....	43

## **LIST OF ABBREVIATIONS**

MFS	Marfan Syndrome
FBN1	Fibrillin-1
SNA	Sella-Nasion-A point
SNB	Sella-Nasion- B point
ANB	A point-Nasion-B point

## LIST OF SYMBOLS

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° Degree Symbol

## **A REVIEW OF THE LITERATURE**

### **Marfan Syndrome**

Marfan Syndrome (MFS) is a life-threatening connective tissue disorder characterized by multi-system organ involvement. The syndrome was first described by Dr. Antoine Marfan, a pediatrician, in 1896 at a meeting of the Medical Society of Paris<sup>1</sup>. He presented a five-year-old girl with disproportionately long limbs that he described as arachnid-like<sup>1</sup>. It wasn't until almost fifty years later that the other hallmark cardiovascular and ocular manifestations of the syndrome were described<sup>2</sup>.

The cardinal features of MFS occur in the cardiovascular, ocular, and skeletal systems. The morbidity and mortality associated with the clinical presentation of MFS highlight the importance of early diagnosis and management<sup>3</sup>. By far, the characteristics found within the cardiovascular system are the primary source of morbidity and early mortality and include dilatation of the aorta which can progress to aortic dissection/rupture, mitral valve prolapse with/without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery<sup>3</sup>. The hallmark feature within the ocular system is ectopia lentis, dislocation of the lens of the eye, and it is observed in approximately 60% of affected individuals<sup>3</sup>. Of increasing concern and morbidity, patients with this syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation<sup>3</sup>. Within the skeletal system, patients with MFS are characterized as having excessive linear growth of long bones and joint laxity<sup>3</sup>. Excessive linear growth is demonstrated as an increased arm span to height ratio, the appearance of the

extremities being disproportionately long for the size of the trunk, and patients being abnormally tall for their age<sup>3</sup>. Other skeletal features are observed in the craniofacial region and include a long and narrow face, downward slanting of the palpebral fissures, malar hypoplasia, and a retruded chin (retrognathia); intraorally, a highly-arched palate and dental crowding have been described<sup>3</sup>. While features of MFS are present in other organ systems, the highly diagnostic and discriminating features are found within the cardiovascular, skeletal, and ocular systems.

### **Etiology of MFS**

MFS is caused by a mutation in the gene coding for the protein fibrillin-1 (FBN1) resulting in reduced amounts of functional FBN1<sup>3,4</sup>. Fibrillin-1 binds to other proteins to form microfibrils which are one of the fibers that provide flexibility and strength to connective tissue<sup>4</sup>. Microfibrils also store growth factors responsible for controlling growth and repair of tissues and organs throughout the body<sup>4</sup>. Decreased amounts of functional FBN1 lead to a decreased formation of microfibrils, resulting in the release of excess growth factors, a decrease in tissue elasticity, tissue overgrowth, and tissue instability<sup>4</sup>. The sequela of these events give rise to the clinical presentation of MFS, as the structural integrity of connective tissue is compromised<sup>2</sup>.

MFS is an autosomal dominant disorder with 75% of new cases being the direct result of inheritance from a parent, and approximately 25% of new cases result from a new mutation<sup>3,4</sup>.

### **Epidemiology**

MFS is estimated to have a prevalence of 1-2:10,000. There is no predisposition based on ethnicity, race, or gender<sup>3,5</sup>.

## **Diagnostic Criteria for Marfan Syndrome**

The diagnosis of MFS is a clinical diagnosis made by the observation of cardinal features in various organ systems, the presence of a family history of MFS, and/or genetic testing for a mutation of the FBN1 gene or other genes. The most recent and revised diagnostic criteria, *The Revised Ghent Nosology for the Marfan Syndrome*, were published in 2010 by Loeys *et al.*<sup>6</sup>. The need for revision from the previous criteria<sup>7</sup> arose from the observation more emphasis needed to be placed on hallmark features of MFS in the cardiovascular and ocular systems, and more consideration needed to be given to alternative diagnoses<sup>6</sup>. The alternative diagnoses have clinical features that overlap with MFS but may also include features with a higher morbidity and/or mortality than MFS<sup>6</sup>. In the revised criteria, more weight is given to two distinct features of MFS, aortic root aneurysm/dissection and ectopia lentis<sup>6</sup>. Diagnostic criteria exist for other organ systems, as discussed below, but the diagnostic finding of both aortic root enlargement/dissection and ectopia lentis confers the diagnosis of MFS in the absence of discriminating features for other syndromes<sup>6</sup>. While this is not the only pathway for being diagnosed, it highlights an important change to the diagnostic criteria. The other pathways are outlined below, and include clinical findings in other organ systems, a family history of MFS and a positive mutation in the FBN1 gene<sup>6</sup>. Additionally, there are features that are commonly observed in MFS that do not independently discriminate for MFS<sup>6</sup>. If these features exist in combination, the diagnosis of systemic involvement for MFS is given; if there is systemic involvement and another hallmark feature, the diagnosis of MFS can be inferred<sup>6</sup>.

Summary of the Diagnostic Algorithm for MFS below<sup>6</sup>:

In the absence of a family history of MFS, a patient can be diagnosed with MFS if the patient has:

- Aortic diameter  $Z \geq 2$  or dissection and ectopia lentis
- Aortic diameter  $Z \geq 2$  or dissection and mutation of FBN1
- Aortic diameter  $Z \geq 2$  or dissection and a systemic score  $\geq 7$
- Ectopia lentis, mutation of FBN1, and known aortic dilatation ( $Z \leq 2$ )

In the presence of a family history of MFS, a patient can be diagnosed with MFS if the patient has:

- Ectopia lentis
- Systemic score  $\geq 7$
- Aortic diameter  $z \geq 2$  or dissection if  $\geq 20$  years old
- Aortic diameter  $z \geq 3$  or dissection if  $\leq 20$  years old

Aortic root enlargement/dilatation is defined for MFS as having an aortic root diameter measurement, at the level of the sinuses of Valsalva, with a Z-score ( $Z$ )  $\geq 2$  when standardized for age and body size<sup>6</sup>. There are caveats to the above diagnostic criteria to rule out other syndromes. See the revised criteria for these caveats<sup>6</sup>.

The systemic score is calculated by summation of points, and a score  $\geq 7$  denotes systemic involvement:

- Wrist and thumb sign—3 points (wrist or thumb sign 1 point)
- Pectus carinatum—2 points (pectus excavatum or chest asymmetry 1 point)
- Hindfoot deformity—2 points (plain pes planus 1 point)
- Pneumothorax—2 points
- Dural ectasia—2 points
- Protrusio acetabuli—2 points

- Reduced upper segment:lower segment ratio and increased arm:height ratio and no severe scoliosis—1 point
- Scoliosis or thoracolumbar kyphosis—1 point
- Facial features (must have 3/5): dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia—1 point
- Skin striae—1 point
- Myopia > 3 diopters—1 point
- Mitral valve prolapse—1 point

As can be seen from the diagnostic criteria, emphasis is placed on those clinical features that carry the highest morbidity and mortality. All skeletal features fall under systemic involvement even though they are some of the most striking physical features. However, they don't yield high diagnostic value independently. Craniofacial features, the focus of this research, are included in the diagnostic criteria, but only reach diagnostic significance when multiple facial features are observed in combination.

### **Challenges to Diagnosis**

As previously discussed, the diagnosis of MFS is primarily a clinical diagnosis and relies on the ability of a clinician to observe/identify features specific to the syndrome. Diagnosis can be highly elusive due to the high degree of variability in clinical presentation, the age-dependent nature of some manifestations, and the host of differential diagnoses that exist<sup>3, 6, 8</sup>.

Summers *et al.* described challenges encountered in diagnosing MFS within families presenting to the Marfan Clinic at Prince Charles Hospital in Brisbane, Australia<sup>9</sup>. At the time of publication, the guidelines set forth by De Paepe *et al.*<sup>7</sup> in 1996 were being used for the diagnosis



of MFS. As an example, a family in this study had several members who were known carriers of a FBN1 mutation<sup>9</sup>. Some had been diagnosed with ectopia lentis and some children within the family required surgical repair of mitral valve prolapse<sup>9</sup>. These clinical findings would give clinical suspicion for a possible diagnosis of MFS<sup>9</sup>. However, expressivity was found to be different within the family and there was inability to predict who would be more severely affected solely on the basis of a known FBN1 mutation<sup>9</sup>. This finding is confirmed by Judge and others who noted that even when members of a family share the same mutation, phenotypic variation is prominent<sup>5, 8</sup>. A different family in the Summers' study demonstrated an occurrence of a de novo mutation in the FBN1 gene in a male child resulting in MFS<sup>9</sup>. The sibling of this proband had musculoskeletal features consistent with MFS, but the features alone did not qualify him for a positive diagnosis of MFS<sup>9</sup>. Genetic testing identified the de novo mutation in the proband and confirmed the absence of the mutation in the proband's parents and sibling<sup>9</sup>. Identification of the mutation as being spontaneous rather than inherited provided reassurance the sibling of the proband likely did not have MFS<sup>9</sup>.

Not only does there exist phenotypic variability of MFS within families, but there is also variability between ethnicities. Franken and colleagues completed a retrospective review of Asian and Caucasian patients diagnosed with MFS<sup>10</sup>. They found significant differences of clinical features in the cardiovascular, skeletal, and ocular systems between Asian and Caucasian patients<sup>10</sup>. With regard to the cardiovascular system, Asian patients were more severely affected as demonstrated by a higher z-score for aortic diameter, increasing the likelihood for an adverse cardiac event<sup>10</sup>. One explanation offered for this was under-diagnosis of MFS in Asian patients attributed to limited access to genetic testing; this results in a delay in management/treatment<sup>10</sup>. As pointed out in their article, MFS is a progressive disease and periodic monitoring is required

to allow for timely surgical intervention to slow the progression of cardiovascular defects<sup>10</sup>. If a patient with MFS does not exhibit enough physical features to be diagnosed in the absence of genetic testing, the abnormalities associated with the syndrome can progress undetected until the abnormality reaches clinical significance<sup>10</sup>. Within the skeletal system, the wrist/ thumb sign and arm span/height ratio  $>1.05$  were more prevalent in the Asian patients<sup>10</sup>. However, in the ocular system, ectopia lentis was more common in Caucasian patients<sup>10</sup>. This research not only demonstrated the phenotypic variability that exists between ethnicities, it also highlighted the importance of assessing the applicability of the diagnostic criteria to patients of different ethnicities.

### **Diagnostic Criteria in Clinical Practice**

Researchers have evaluated the application of the diagnostic criteria for MFS to populations with and without MFS to determine how well the criteria discriminates between affected and non-affected individuals. This is important as to lessen the incidences of false positives and false negatives in the diagnosis of MFS.

Sponsellar and colleagues investigated ways in which patients were recognized as needing a referral for evaluation of MFS and the prevalence of current diagnostic features of in a population of subjects with and without MFS<sup>11</sup>. They examined a population of patients attending care at a pediatric orthopedics clinic and a pediatric sports medicine clinic<sup>11</sup>. The population consisted of patients with a confirmed diagnosis of MFS (n=183) and those without MFS (n=1257)<sup>11</sup>. They examined the prevalence of physical, mostly skeletal, diagnostic features for MFS in both cases and controls<sup>11</sup>. Overall, the physical diagnostic features were more prevalent in the MFS group, but  $> 30\%$  of the control population had at least one of the described

physical features of MFS<sup>11</sup>. When evaluating sensitivity and specificity of physical features, craniofacial features were the most sensitive for MFS and when combined with the thumb and wrist sign, the most specific<sup>11</sup>. This demonstrates singular physical features of MFS are relatively prevalent within the general population, but that observed in isolation do not infer a diagnosis of MFS. However, when multiple physical features are observed in combination, the suspicion for MFS increases. Included in their research was identifying the individual responsible for initial suspicion for MFS resulting in referral for evaluation. In 26% of cases it was a pediatrician, a family member in 21%, ophthalmologist in 14%, family practitioner in 8.4%, orthopedist in 7.7%, and another contact (undefined) in 23%<sup>11</sup>. As can be seen from these findings, it is prudent practitioners from different specialties be knowledgeable about MFS.

Ting and colleagues investigated the diagnostic value of facial features in MFS to determine if commonly observed facial features could potentially be used as an early screening tool for MFS<sup>12</sup>. They evaluated specific facial features (dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, and retrognathia) in a group of patients with a confirmed diagnosis of MFS (n=76) and a group of age- and sex-matched controls (n=76)<sup>12</sup>. Each subject was assessed using frontal and lateral photographs<sup>12</sup>. Three physicians, with extensive experience evaluating patients with MFS, viewed the photographs to determine if the facial features were present or absent and recorded whether or not the facial features triggered a suspicion for MFS<sup>12</sup>. All of the facial features were significantly more prevalent in the MFS group compared to the control group<sup>12</sup>. Overall, the facial features had a sensitivity of 53.9% and a specificity of 91.2%<sup>12</sup>. The physicians were able to discriminate between subjects with MFS and controls with an accuracy of 72.6% by evaluating facial features in the frontal and lateral photographs<sup>12</sup>. Their findings also revealed the presence of more than one facial feature

increased the odds of correctly identifying a patient with MFS<sup>12</sup>. They concluded the facial features were more specific than sensitive and could be used as a tool to prioritize patients for referral for evaluation for MFS; however, they should not be relied upon as the sole metric for initial screening<sup>12</sup>.

### **Diagnosis and Phenotype in Children**

As mentioned, the diagnosis of MFS can be challenging due to the age-dependent nature of some physical features; these features do not manifest or become distinct for MFS until after significant growth has occurred. Research emphasis has been placed on ways to diagnose MFS sooner in life as this leads to earlier management and treatment. Several researchers have studied MFS in children/adolescents specifically to understand the phenotypic presentation in this population.

Lipscomb and colleagues evaluated 40 subjects with MFS less than 16 years of age<sup>8</sup>. Of the 40 evaluated, 10 were index cases with no prior family history of MFS<sup>8</sup>. This percentage of index cases, 25%, is in agreement with the global description of all patients, children and adults, with MFS<sup>8</sup>. For the index cases, the average age at diagnosis was  $11.4 \pm 3.95$  years and for non-index cases,  $7.31 \pm 5.23$  years<sup>8</sup>. In regard to craniofacial features of MFS, 36 of 40 subjects were described as having a highly-arched palate and 33 of 40 were noted to have mid-face hypoplasia, micrognathia, and down-sloping palpebral fissures<sup>8</sup>. When evaluating the cardiovascular system, aortic root dilatation was observed in 17 patients (42.5%) but none of the subjects had experienced an aortic dissection<sup>8</sup>. This is less than the prevalence of aortic dilatation reported by Mueller *et al.* in their examination of pediatric patients with MFS<sup>13</sup>. They found that 56% of their population had aortic dilatation but none had experienced an aortic dissection<sup>13</sup>. It is recommended patients with MFS have annual echocardiographic examinations to detect and

monitor aortic root dilatation; a delay in detection can potentially lead to adverse clinical outcomes<sup>8</sup>. As can be seen, index cases tended to be diagnosed later in childhood resulting in missed years of echocardiographic examination and delayed prophylactic intervention to manage aortic root dilatation. It highlights the need for diagnostic criteria to help identify index cases earlier in life.

Stheneur and colleagues evaluated children referred to a Marfan Clinic in France either due to the suspicion of MFS or a family history of MFS<sup>14</sup>. They sought to further document the phenotypic evolution of MFS with age in children. In adults, the phenotype has been well-described and documented, but because of the phenotypic variability and incomplete phenotypic display in children, it can be difficult to diagnose MFS in children<sup>14</sup>. It is more likely those children with severe phenotypic expression are identified earlier, while those with variable or less phenotypic expression go undetected, especially in the absence of genetic testing<sup>14</sup>. Their study population consisted of children under the age of 18 with MFS (n=259), as confirmed through meeting the Ghent I criteria and having a FBN-1 mutation, and those without MFS (n=474)<sup>14</sup>. Within each of the groups, MFS and non-MFS, the subjects were further stratified by age (0-6years; 7-9years; 10-14years; and 15-17years)<sup>14</sup>. They evaluated the presence of skeletal features, cardiovascular features and ocular features, diagnostic for MFS, in both groups<sup>14</sup>. For all age strata, children with MFS were significantly taller than the non-MFS children, and that a height >3.3SD above the mean carried a positive predictive value for MFS of 72%<sup>14</sup>. For the MFS group, an aortic root diameter >3SD from the mean was present in greater than 60%; whereas for the non-MFS, it was present in <10%<sup>14</sup>. When examining probands and non-probands within the MFS group, probands were less represented in the younger age strata and were more severely affected than non-probands when evaluating aortic diameter and the

presence of ectopia lentis<sup>14</sup>. The two most discriminating features leading to a diagnosis of MFS were aortic diameter >3SD above the mean and presence of ectopia lentis, both of which were given more weight in the most recent diagnostic criteria for MFS<sup>14</sup>. The findings in this study are in agreement with those of the Lipscomb study which showed probands are diagnosed later in life; they also demonstrated probands were more severely affected clinically.

### **Benefits of Early Diagnosis**

The morbidity associated with MFS underlines the importance of early diagnosis to improve prognosis and delay mortality. The features with the gravest clinical outcomes occur in the cardiovascular system and require early intervention to allow for favorable outcomes. Willis and colleagues evaluated outcomes in patients with MFS diagnosed in childhood (diagnosis before 18 years of age) and those diagnosed in adulthood (diagnosis after 18 years of age)<sup>15</sup>. In their study, 27 of 66 patients with MFS were diagnosed in childhood and 39 of 66 in adulthood<sup>15</sup>. Those diagnosed in adulthood had significantly greater cardiac morbidity as measured by median aortic root diameter, need for aortic surgery, aortic insufficiency, and repeat aortic surgery<sup>15</sup>. They were also more likely to require aortic root replacement on an urgent basis due to an associated aortic dissection or severe aortic insufficiency<sup>15</sup>. This highlights the importance of early diagnosis as those “who remain undiagnosed until adulthood have well-established cardiovascular pathology and a suboptimal clinical outcome<sup>15</sup>.” As previously discussed, earlier diagnosis allows for annual echocardiographic examination to monitor aortic root diameter which leads to timely intervention rather than emergent intervention which may limit the treatment options available.

## **Consequences of Misdiagnosis**

There are several consequences of misdiagnosis of MFS for a patient who indeed does not have MFS. Included are inappropriate/improper surveillance and or treatment that can be costly, discrimination by employers, or discrimination and/or difficulty with obtaining insurance<sup>9</sup>. Alternatively, a missed diagnosis of MFS infers more severe consequences as premature death can result from an aortic dissection.

## **Management of Marfan Syndrome**

The multi-system nature of MFS dictates a multidisciplinary approach to comprehensive management. For most patients, this requires a team including a cardiologist, cardiothoracic surgeon, ophthalmologist, orthopedist, and geneticist<sup>3</sup>. Annually, these patients are monitored with an echocardiogram to monitor aortic dilatation and an ophthalmologic exam to assess for ectopia lentis, cataracts, glaucoma, or retinal detachment<sup>3</sup>.

When medical professionals encounter these patients outside of the specialties outlined above, it is common for patients with MFS to present with eyeglasses for correction of myopia<sup>3</sup>,<sup>6</sup>. Aortic dilatation is usually managed by medications to reduce the hemodynamic stress placed on the aortic wall such as beta blockers<sup>3,6</sup>. For dental professionals, these patients may require antibiotic prophylaxis prior to invasive dental treatment in the presence of mitral valve or aortic valve regurgitation<sup>3</sup>.

A diagnosis of MFS infers lifestyle modifications to prevent or reduce associated morbidities and/or mortality. Some of these changes or limitations include avoiding contact sports, competitive sports, exercise to exhaustion, and isometric exercise<sup>3</sup>. However, patients can and are encouraged to participate in aerobic activities in moderation<sup>3,6</sup>. Additionally,

patients are cautioned to avoid substances that stimulate the cardiovascular system such as caffeine or decongestants<sup>3</sup>.

Although MFS is considered a rare disease, it is likely a medical professional will encounter a patient with MFS during his/her professional career. Awareness of MFS and its clinical presentation is of importance as it may have implications for the medical treatment being provided. In addition, the findings of medical practitioners from different specialties may be instrumental in enhancing the diagnostic criteria for MFS, increasing awareness, and developing new research avenues.

### **Craniofacial Characterization of Marfan Syndrome**

Research continues to focus on isolating and describing clinical/physical features that discriminate for MFS. One such area of research devoted to this is qualitatively and quantitatively describing craniofacial and dental features of patients with MFS.

De Coster and colleagues evaluated the craniofacial structure of patients with MFS using cephalometric measurements to quantitatively assess facial features that previously had only been described qualitatively<sup>16</sup>. Of interest, was characterization of the relative position of the maxilla and mandible to the cranial base by evaluating the SNA angle and SNB angle; also they wanted to evaluate the relative position of the maxilla to the mandible through the angular measurement of ANB<sup>16</sup>. The normative values for these measurements had been previously described by Steiner<sup>17</sup>. The normal angular measurement for SNA is 82° indicating a normally positioned maxilla relative to the cranial base<sup>17</sup>. A measurement greater than 82° is indicative of a prognathic maxilla and a measurement less than 82° of a retrognathic maxilla<sup>17</sup>. The normal angular measurement for SNB is 80° indicating a normally positioned mandible to the cranial



base<sup>17</sup>. A measurement greater than 80° is indicative of a prognathic mandible and less than 80° indicative of a retrognathic mandible<sup>17</sup>. For the ANB measurement, a normal Class I relationship between the maxilla and mandible exists when the angular measurement is between 2°-4°<sup>17</sup>. A measurement greater than 4° is indicative of a Class II jaw relationship and less than 2° of a Class III jaw relationship<sup>17</sup>. They also evaluated vertical skeletal relationships by assessing the S-N/Go-Gn angle; 32°=normal; greater than 32°=long face; and less than 32°=short face<sup>17</sup>. Of their population of 26 subjects with MFS, 84% were maxillary retrognathic, 88% were mandibular retrognathic, and 81% were both maxillary and mandibular retrognathic<sup>16</sup>. With respect to ANB, 44% had a normal ANB measurement while 48% had a measurement indicative of a Class II jaw relationship<sup>16</sup>. When evaluating the vertical skeletal relationship, 72% of the subjects fell into the long face category<sup>16</sup>. These findings are in agreement with the skeletal diagnostic features of MFS previously described which include dolichocephaly (long-face) and mandibular retrognathia. Their research was novel because is quantitatively described craniofacial features and provided a method and benchmark for comparison for future research.

Staufenbiel and colleagues investigated the periodontal health of patients with MFS<sup>18</sup>. Considering that the periodontal ligament is comprised of elastic fibers and that MFS is a connective tissue disorder, they sought to find out if patients with MFS are more susceptible to periodontal disease<sup>18</sup>. The sample included 51 patients with MFS, average age of 40.2±15.3 years, and 31 controls, average age 40.29±13.9 years<sup>18</sup>. The periodontal examination of each subject recorded probing pocket depth, gingival recession, clinical attachment level, and bleeding on probing assessed at six sites per tooth<sup>18</sup>. They found no significant difference between the MFS subjects and the control subjects in any of the periodontal parameters evaluated<sup>18</sup>. As a part of the study, the subjects with MFS completed a questionnaire inquiring about

temporomandibular disorders and previous orthodontic treatment<sup>18</sup>. Disorders of the temporomandibular joint were reported by 39.2% of the MFS subjects and 62% had previous orthodontic treatment<sup>18</sup>. It is expected that all patients with MFS would be encouraged to receive routine dental care with a primary dentist, but it is also likely these patients will be evaluated and/or treated by dental specialists for either temporomandibular disorders or for orthodontic treatment. As such, dental professionals may be in a unique position to identify patients with MFS and aid in further research on craniofacial and dental characterization of patients with MFS.

### **Craniofacial Characterization of other Syndromes**

There are several medical syndromes that include craniofacial anomalies. The facial anomalies associated with each syndrome can be highly discriminating for the syndrome and as such, are used in diagnosis. Leslie Farkas recognized this, and sought to develop a method for evaluating and quantifying craniofacial characteristics of syndromes with distinct facial features such as Down's Syndrome and Apert's Syndrome<sup>19, 20</sup>. He found the facial features observed were described qualitatively in the literature but without quantification and/or comparison to controls/normative data<sup>19, 20</sup>.

Farkas' previous research evaluating the facial anatomy of normal subjects, using anthropometric measurements, provided the normative data needed as a control population<sup>21</sup>. His population for establishing the norms consisted of normal, healthy, North American children in Canada; subjects were recruited from schools and summer camps<sup>21</sup>. He sought to achieve a sample population of male and female subjects between the ages of 0-25 years<sup>21</sup>. He made anthropometric measurements on the head and face of each subject; from this data, a mean and SD for each measurement, by age group and sex, were calculated to establish the norm for the anthropometric measurement<sup>21</sup>.

His quantitative investigation of the facial anatomy of patients with Down's Syndrome included making select craniofacial anthropometric measurements on a test population of subjects with Down's Syndrome<sup>19</sup>. He selected the measurements based on previous research that identified specific facial features commonly observed in patients with Down's Syndrome<sup>22</sup>. The measurements from the subjects with Down's Syndrome were then compared to normative data by calculating a z-score for each measurement<sup>19</sup>. He categorized the measurements based on z-score as listed below<sup>19</sup>:

z score  $\pm 1$ : optimal facial measurement

z score  $< -1$  but  $> -2$  or  $> 1$  but  $< 2$ : normal facial measurement

z score  $< -2$  or  $> 2$ : subnormal or supernormal facial measurement

z score  $< -3$  or  $> 3$ : severe facial abnormality

The results from this study provided quantitative evidence for qualitatively described differences in craniofacial morphology of patients with Down's Syndrome. This method of research provided a framework for future research in quantitatively describing facial features of syndromes with known craniofacial anomalies<sup>19</sup>.

## **Conclusion**

While research continues to evolve in regard to treatment strategies for MFS to improve quality of life and prognosis, these findings are most beneficial when implemented early. Early diagnosis is dependent upon careful observation and identification of the clinical features associated with this syndrome. The challenges to observing the clinical features in younger populations have been outlined and a focus in research has been to discover, or further define,

clinical features of MFS in the child/adolescent population. As such, this research project aims to quantitatively and qualitatively describe craniofacial features in child/adolescent patients with MFS by, 1) making select craniofacial anthropometric measurements on each subject and comparing these measurements to normative data and 2) evaluating clinical photographs of subjects with MFS to identify discriminating features.

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## **CRANIOFACIAL CHARACTERIZATION OF MARFAN SYNDROME**

### **Introduction**

Marfan Syndrome (MFS) is a life-threatening connective tissue disorder characterized by multi-system organ involvement with cardinal features occurring in the cardiovascular, ocular, and skeletal systems<sup>1</sup>. It is caused by a mutation in the gene coding for the protein fibrillin-1 (FBN1)<sup>2</sup>. The morbidity and mortality associated with the clinical presentation of MFS highlight the importance of early diagnosis and management. The characteristics found within the cardiovascular system (aortic dilatation and/or aortic dissection) are the primary source of morbidity and early mortality<sup>1</sup>, and it has been noted that undiagnosed adult patients have well-established cardiovascular pathology and suboptimal clinical outcomes<sup>3</sup>. Within the ocular system, the hallmark feature is ectopia lentis (dislocation of the lens of the eye), a condition seen in approximately 60% of patients<sup>1</sup>. While the features in the skeletal system are not a major source of morbidity/mortality and do not account for sudden or premature death, they are fundamental in diagnosis<sup>4</sup>. Skeletal features are the most striking physical features of MFS and may lead to a suspicion for this syndrome in undiagnosed patients. These features include excessive linear growth of long bones, increased arm span to height ratio, and distinct craniofacial features (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures)<sup>1</sup>. While features of MFS occur in other organ systems, the observation of discriminating features in these three systems often leads to the diagnosis of MFS.

The diagnosis of MFS is a clinical diagnosis, and the diagnostic criteria are outlined in *The Revised Ghent Nosology for the Marfan Syndrome* published by Loeys *et al.* in 2010 (see Appendix 1). The criteria set forth objective clinical requirements that must be observed to infer the diagnosis of MFS; consideration is given to clinical findings in various organ systems, a family history of MFS, and a positive mutation of the FBN1 gene <sup>5</sup>.

Prior research has highlighted the value of early diagnosis as a prerequisite for improved clinical outcomes <sup>3</sup>; however, diagnosis can be highly elusive due the high degree of variability in clinical presentation and the age-dependent nature of some features <sup>1, 5, 6</sup>. Additionally, the hallmark features, aortic dilatation/aneurysm and ectopia lentis, require more advanced diagnostic tests than are routinely prescribed for the general population<sup>7</sup>. This underscores the need for a method to objectively assess other readily observable features as a screening tool for MFS. Studies have evaluated the application of the diagnostic criteria in populations consisting of MFS subjects and non-MFS subjects to determine how well the criteria discriminate between affected and non-affected individuals; these studies found that facial features, as outlined in the MFS diagnostic criteria, are valuable in diagnosis. Ting and colleagues utilized frontal and lateral photographs to evaluate facial features of patients with a confirmed diagnosis of MFS and age- and sex-matched controls<sup>8</sup>. Three physicians with extensive experience treating patients with MFS evaluated all photographs for the presence of the five diagnostic craniofacial features<sup>8</sup>. The physicians were able to discriminate between subjects and controls with an accuracy of 72.6% solely on the basis of assessing facial features<sup>8</sup>. Similarly, Sponseller and colleagues evaluated the diagnostic sensitivity and accuracy of the presence of not only craniofacial features, but also other skeletal features, finding that craniofacial features were the most sensitive discriminator between individuals with and without MFS <sup>7</sup>. Also, the combination of



craniofacial features with a positive thumb sign provided the highest diagnostic accuracy<sup>7</sup>. Of equal importance, was their finding that 19% of MFS patients had zero or one skeletal feature and that in very young patients, it may take time for the full phenotype to evolve<sup>7</sup>. The authors concluded that further studies are needed to objectively define and describe craniofacial features as currently, they are only subjectively defined<sup>7</sup>. In summary, current literature demonstrates the pivotal role craniofacial features may play in the diagnosis of MFS, especially in the absence of a family history of MFS, genetic testing, or other discriminating features.

Few studies have attempted to quantify the facial features described for MFS in the Ghent Nosology as most have been qualitative studies. The quantitative studies that have been conducted have used lateral cephalometric radiographs to compare craniofacial findings from MFS patients to control subjects<sup>9,10</sup>. We report here the first anthropometric study of patients affected with MFS in order to: 1) quantify craniofacial features in a cohort of child, adolescent, and young adult patients with a confirmed diagnosis of MFS and compare them to a control population, 2) qualitatively examine subjects for the presence of diagnostic facial features, 3) document occlusal relationships, and 4) collect relevant demographic and biometric information.

## **Methods:**

This cross-sectional study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

## **Sample:**

Subjects were recruited during the Marfan Foundation Annual Conference in Chicago, IL in 2015 and in Rochester, MN in 2016. The study population included twenty (N=20) individuals with a confirmed diagnosis of MFS. The mean age of the study population was

10.7±6.0years (age range 4-25 years). The subjects were primarily female (60%) and white (70%) (see Table 1 for complete demographic data).

#### Inclusion Criteria:

Confirmed diagnosis of MFS and subject age between 4-25 years.

#### Procedures:

##### Craniofacial Assessment:

Twelve craniofacial anthropometric measurements (see Table 2 for craniofacial measurements) were obtained on each subject using spreading and sliding calipers as described by Farkas<sup>11</sup>. The test measurements were compared to age- and sex-matched controls from previously published normative data by calculating a z-score for each measurement<sup>11</sup>. Z-scores were categorized using a classification system describing facial dimensions that was developed by Farkas and colleagues<sup>12</sup>.

Categorization of z-scores was as follows<sup>12</sup>:

z-score±1: optimal facial measurement

z-score: <-1 but >-2 or >1 but <2: normal facial measurement

z-score: <-2 or >2: subnormal or supernormal facial measurement

z-score: <-3 or >3: severe facial abnormality

Photographs including a lateral, frontal in repose, and frontal smiling were obtained to document and qualitatively describe facial features. Each subject was assessed for the presence/absence of the five craniofacial diagnostic criteria for MFS: dolichocephaly, malar

hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures<sup>5</sup>. The definition of these facial features, as outlined by the National Human Genome Research Institute, was used as a rubric to complete this part of our analysis<sup>13, 14</sup>. Two examiners evaluated all photographs independently and recorded his/her clinical judgment of the presence/absence of each facial feature. When disagreement occurred between the examiners, a consensus diagnosis was reached after discussion.

#### Intraoral Examination:

A clinical exam was completed to document occlusal relationships. For those subjects with erupted first permanent molars, the Angle Classification System, Class I, Class II, and Class III dental malocclusion, was used to document molar and canine relationships<sup>15</sup>. For those in the primary dentition, molar classification was recorded as mesial step, distal step, or flush terminal plane<sup>15</sup>.

#### Questionnaire:

Each subject or subject's guardian completed a questionnaire to obtain biometric and demographic information.

#### Statistical Analysis:

Statistical analysis were undertaken using Microsoft Excel 2013 (version 15.0.4885.1000) and Statistical Analysis System (SAS) version 9.3 (Cary, NC). Individual z-scores were calculated in Microsoft Excel for each test measurement using the mean measurement and standard deviation of age- and sex-matched controls<sup>11</sup>.

The z-scores were grouped as described by Farkas<sup>12</sup>. In SAS, a Fisher's exact test, using a level of significance of  $p=.05$ , was completed for each craniofacial anthropometric measurement to compare the observed frequency of z-score distribution to an expected frequency of z-score distribution of a normal population (see Figure 1).

Data was stratified by family history (proband vs non-proband), cardiovascular diagnosis (cardiovascular anomaly vs no cardiovascular anomaly) and by age (5-9; 10-14; 15-18; and 19-25). A Fisher's exact test, ( $p=.05$ ), was completed to compare frequency of z-score distribution between the groups. For these groups, we evaluated only the frequency of z-score distribution for z-scores outside of the normal range ( $z<-2$  or  $z>2$ ) (see Figure 2).

The remaining data from the clinical exam, photographic exam and questionnaire are presented as percentages.

## **Results:**

### Demographic and Biometric Results:

Our analysis of the demographic and biometric data revealed fifty percent of subjects had no family history of MFS (probands) and fifty percent had a family history of MFS (non-probands). The average age at diagnosis for the entire sample was  $5.9\pm4.6$  years. For probands, the average age at diagnosis was  $6.7\pm5.1$  years and non-probands,  $5.1\pm4.0$  years. The average age at diagnosis was not statistically different between probands and non-probands ( $p=0.47$ ).

Forty percent of subjects reported one or more cardiovascular anomalies (see Figure 3), and sixty percent reported no cardiovascular anomalies. The most prevalent cardiovascular anomaly was aortic dilatation (35%).

Eighty percent of subjects reported one or more ocular anomalies (see Figure 4), and twenty percent reported no ocular anomalies. The most prevalent ocular anomaly was ectopia lentis (35%).

Thirty-five percent of subjects reported current or a past history of orthodontic treatment, while 55% reported no history of orthodontic treatment. Two subjects/guardians did not provide an answer to this question.

#### Intraoral Examination Results:

Fifty percent of subjects had a Class I molar relationship, 40% Class II, and 5% Class III.

#### Assessment of Lateral and Frontal Photographs:

All facial features described in the diagnostic criteria were observed in our subjects (see Figure 5). The most prevalent facial features observed were retrognathia (54%) and down-slanting palpebral fissures (62%).

#### Craniofacial Anthropometric Measurements:

For all 12 craniofacial anthropometric measurements, the frequency of z-score distribution for our MFS sample was significantly different from the distribution expected in a normal population,  $p=.05$  (see Table 3). Our subjects tended to be under-represented in the optimal/normal categories and over-represented in the subnormal, supernormal, and abnormal categories.

For 9 of the 12 craniofacial measurements, the majority of subjects ( $\geq 65\%$ ) fell within the normal range for facial dimension with a z-score of  $\pm 2$ . For 3 of the 12 measurements, biocular

width, facial width, and width of the nose, the majority of subjects fell outside the normal range for facial dimension (see Figures 6-17).

#### Frequency of z-score Distribution by Groups

There was no statistically significant difference in frequency of z-score distribution for craniofacial measurements for probands vs. non-probands, those with or without a cardiovascular anomaly, or by age ( $p=.05$ ).

#### **Discussion:**

In this cross-sectional study, we evaluated biometric and demographic markers, occlusal relationships and craniofacial morphology in child, adolescent and young adult patients with MFS. We sought to discover if quantifiable differences in facial morphology existed in our subjects when compared to a control population, and to determine if biometric markers could be correlated to facial morphology. Our aim was to enhance the current body of literature related to the diagnostic value of craniofacial findings in patients with MFS by quantifying differences in facial features which may aid in earlier recognition and diagnosis.

In regard to biometric data collected, many of our findings agree with previously published research. For age at diagnosis, though not statistically different, we found that probands tended to be diagnosed later in life than non-probands. Lipscomb *et al.* and of Stheneur *et al.* had similar findings<sup>6, 16</sup>. Lipscomb and colleagues evaluated pediatric patients with MFS (N=40) and found the average age at diagnosis for probands was  $11.4 \pm 3.95$  and for non-probands,  $7.31 \pm 5.23$  years<sup>6</sup>. The morbidity and mortality associated with MFS emphasize the importance of early diagnosis and intervention as the main barrier to optimal outcomes is lack of timely diagnosis<sup>3</sup>. Those with a family history of MFS, non-probands, are early on the

radar to be evaluated for MFS, as it is known this syndrome is inherited in an autosomal dominant pattern. Whereas for probands, there must be a compelling clinical finding or adverse clinical event for a diagnostic evaluation for MFS to be pursued. The recommended annual echocardiographic and ocular examination for patients with MFS or suspected MFS should be implemented as early as possible to assess for the presence/progression of aortic dilatation and ectopia lentis<sup>1</sup>. This yearly surveillance is delayed in implementation for undiagnosed probands and has the potential to lead to adverse clinical outcomes. There are several reported incidences of the diagnosis of MFS being made post-mortem in individuals who died suddenly as a direct result of cardiovascular complications related to MFS<sup>17, 18</sup>. To avoid these types of outcomes, diagnostic strategies have to focus on identifying probands at an earlier age to allow for prophylactic medical intervention.

When evaluating cardiovascular morbidity associated with MFS, 40% of our subjects reported at least one cardiovascular anomaly and some reported multiple anomalies. The cardiovascular anomaly that carries significant diagnostic weight for MFS is aortic root dilatation; however, for diagnostic significance, the aortic dilatation must meet a threshold (z-score) based on the patient's age and body size<sup>5</sup>. We only evaluated for the presence of aortic dilatation and did not assess the degree of dilatation. We found that 35% of subjects reported aortic dilatation which is less than that reported in previous studies by Lipscomb *et al.* and Mueller *et al.* who found that 42.5% and 56% of their pediatric MFS populations, respectively, had aortic dilatation<sup>6, 19</sup>. Stheneur and colleagues evaluated pediatric patients with and without MFS and found that >60% of subjects with MFS had an aortic root diameter >3 SD from the mean (corrected for height and weight) compared to only 10% of subjects without MFS<sup>16</sup>. When the most recent diagnostic criteria for MFS were published in 2010, increased emphasis

was placed on aortic dilatation as a hallmark feature as it is not observed frequently in the general population <sup>5</sup>. It has been noted that many manifestations of MFS are age-dependent which may explain the lower prevalence found in our younger study population <sup>1,5</sup>. It is possible that aortic dilatation had not yet manifested in our subjects resulting in a lower reported prevalence.

When evaluating ocular morbidity, 80% of subjects reported at least one ocular anomaly and some reported multiple anomalies. The ocular anomaly that is highly specific for MFS is ectopia lentis and is reported to occur in 60% of patients with MFS <sup>1,16</sup>. In our population, 35% of subjects reported ectopia lentis and 10% lens removal which is a treatment modality for severe cases of ectopia lentis <sup>20</sup>. Once again, our decreased prevalence could be due to our younger sample population and this condition not yet manifesting.

In our questionnaire, we inquired about each subject's history of orthodontic treatment. Thirty-five percent of subjects reported a prior history of orthodontic treatment. While no clinical dental findings are included in the most recent diagnostic criteria for MFS, they were included in the previous diagnostic criteria published in 1996<sup>21</sup>. Several studies and case reports have reported on dental findings in patients with MFS focusing on palatal vault height, palatal width, and dental crowding <sup>10, 22, 23</sup>. Docimo *et al.* evaluated pediatric patients with MFS (N=32) and found that 56% of subjects had a crossbite (mono- or bilateral) and 69% had evidence of an ogival (high and arched) palate; they estimated the prevalence of crossbite in their MFS population was 2.5 to seven times more frequent than the normal population<sup>10</sup>. We found 25% of our subjects reported maxillary expansion as a part of their orthodontic treatment. It is unknown if maxillary expansion was prescribed due to a narrow palate and/or crossbite, but maxillary expansion is a treatment modality for these malocclusions. Staufenbiel and colleagues



reported on the prevalence of orthodontic treatment among subjects with MFS and found that 62% (N=51) had a previous history of orthodontic treatment. Their study population was older (mean age  $40.2 \pm 15.4$  years) than our population which could account for the discrepancy in orthodontic treatment prevalence<sup>24</sup>. Orthodontic treatment is rarely indicated in the primary dentition and is not routinely recommended in the mixed dentition stage. It is likely some subjects in our sample were not at a developmental stage to warrant orthodontic treatment at the time they were included in our study.

In this report, we also evaluated occlusal relationships to determine if certain features were characteristic of MFS patients. We found that 40% of our subjects had a Class II or mesial step molar occlusion. Previous studies have reported on Class II molar relationships and excess overjet in patients with MFS<sup>22, 25, 26</sup>. However, these features are not highly discriminate for MFS and occur in the general population. The recommended treatment to address this malocclusion would not differ significantly for patients with MFS when compared to the general orthodontic population.

Clinical photographs were taken on thirteen subjects and assessed for the facial features outlined in the most recent diagnostic criteria. Lateral photographs taken on six subjects were undiagnostic for assessment for dolichocephaly, and therefore, the assessment for the presence of dolichocephaly was completed on only 7 subjects. We found that 43% of subjects presented with dolichocephaly which is slightly less than reported in a study by Docimo *et al.* who found that 47% of pediatric patients with MFS had dolichocephaly; their sample size (N=32) was much larger than ours<sup>10</sup>. Retrognathia and down-slanting palpebral fissures were the two most prevalent facial features in our population being observed in 54% and 62% of our sample population respectively. When compared to a previous study of pediatric MFS patients, the

presence of retrognathia was reported as 56%<sup>10</sup>. Ting and colleagues evaluated facial features in an older population of MFS patients (N=76; mean age=18 years, age range 1-55 years), and found dolichocephaly in 60%<sup>8</sup>. It could be speculated the decreased prevalence of facial features in pediatric populations exists because the subjects have not “grown into” these features<sup>1, 6, 9</sup>. A longitudinal assessment of facial features of pediatric MFS patients would allow for investigation to determine if facial features become more prevalent with age.

For 9 of the 12 craniofacial anthropometric measurements, the majority of subjects ( $\geq 65\%$ ) fell within the normal range (z-score  $\pm 2$ ) for facial dimension. When compared to age- and sex-matched controls, the facial features of our sample population did not vary significantly from the control mean. De Paepe *et al.* noted the nature of the phenotype of MFS is a continuum that at the mild end of the spectrum, merges with the normal population<sup>21</sup>. The historical literature for MFS reports that some musculoskeletal features are absent or less evident during growth, and diagnosis in children or teenagers can be difficult<sup>4</sup> which likely accounts for our findings. For three of the measurements, biocular width, facial width, and width of the nose, the majority of our subjects fell outside of the normal range. For biocular width, our subjects had a super normal/abnormally wide biocular width. Down-slanting palpebral fissures has been well documented in patients with MFS and is a part of the current diagnostic criteria<sup>5</sup>. Down-slanting of the palpebral fissures appears as a downward drop of the lateral aspect of the eye fold; this results in a more pronounced elliptical shape of the eye which may account for this finding. For facial width, our subjects had a subnormal/abnormally narrow facial width; malar hypoplasia is prevalent in MFS<sup>5</sup> and likely explains this finding. When considering width of the nose, we found that 25% had a subnormal/abnormally narrow nose and 30% had a supernormal/abnormally wide nose. A narrow width of the nose may follow an overall narrow

width of the face. However, there have been not previous reports of increased nasal width in MFS patients. The only explanation we can provide is normal variation that exists within a population. We could not find any other studies that utilized craniofacial anthropometric measurements to assess facial features in MFS and therefore cannot compare our findings to other studies.

We evaluated frequency of z-score distribution for all craniofacial measurements between probands and non-probands, those with and without cardiovascular anomalies, and by age. Our purpose in doing so was to determine if probands showed more deviation from the norm than non-probands which could have potentially led to a suspicion for MFS. For cardiovascular anomalies, we aimed to determine if those who reported a cardiovascular anomaly were more severely affected globally in other organ systems such as the skeletal system. By stratifying our sample by age, we sought to find out if craniofacial morphology became more abnormal as age increased. For all of our analyses, we found there was no statistically significant difference in frequency of z-score distribution between the groups. Studies have reported the phenotypic expression of MFS is unpredictable<sup>27, 28</sup> which possibly explains our finding of no difference between groups. It has also been noted that phenotypic variation is prevalent in families with MFS carrying the same genetic mutation, and attempts to find genotype-phenotype correlations have been met with limited success<sup>16, 28-30</sup>. While this may partly explain our findings, our small sample size is likely a contributing factor too; we simply may not have recruited enough subjects to detect differences.

Overall, our sample of child, adolescent and young adult patients with MFS demonstrated quantifiable differences in three craniofacial features when compared to age- and sex-matched controls. However for nine of twelve measurements, the majority of subjects did not

demonstrate a quantifiable difference in craniofacial morphology. This does not mean a difference does not exist, but that continued research with larger sample sizes needs to be pursued. It is also likely that the use of published norms, with large standard deviations, was a less sensitive tool to detect meaningful differences. We could not find any other studies that utilized our method of analysis to which our findings could have been compared, underscoring that this study represents the first time craniofacial features of MFS have been assessed with anthropometric analysis.

### **Conclusions:**

- 1.) Probands tended to be diagnosed later in life than non-probands.
- 2.) Aortic dilatation and ectopia lentis were present in our study population but not as prevalent as reported in previous studies.
- 3.) Retrognathia and down-slanting palpebral fissures were the two most prevalent diagnostic facial features in our study population.
- 4.) Our hypothesis of quantifiable, distinct craniofacial features for MFS was rejected for 9 of 12 craniofacial measurements, as the majority of subjects fell within the normal range for facial morphology. However it was accepted for 3 of the 12 measurements (binocular width, facial width, and width of the nose), as the majority of subjects fell outside the normal range.
- 5.) There was no statistically significant difference in frequency of z-score distribution for craniofacial anthropometric measurements between probands vs. non-probands, subjects with or without a cardiovascular anomaly, or by age.

### **Limitations:**

The age- and sex-matched controls were historical controls being established nearly 20-30 years ago. It is unknown if facial dimensions have evolved over time. Also, the control sample consisted of only North American whites. Our sample included Hispanic and Asian subjects and facial morphology may be different between races.

The craniofacial anthropometric measurements made on each subject require correct landmark identification and accuracy when making the measurements. There could have been error introduced into the measurements due to incorrect landmark identification or due to inaccurate measurements.

The biometric data obtained using the questionnaire was not verified by referencing the subject's medical chart. This could have resulted in under- or over-reporting.

#### Future Directions:

Future directions for research on quantifying facial features for MFS include use of 3D photography and/or cone-beam computed tomography. Both of these techniques allow for repeated measures to be made on test subjects, archiving of data, and require less time and cooperation for each subject.

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**Table 1. Sample demographic data**

	N=20
Males	8 (40%)
Females	12 (60%)
White	14 (70%)
Hispanic	4 (20%)
Asian	2 (10%)

**Table 2. Craniofacial measurements**

Craniofacial Measurement	Landmarks
Morphological Height of Face	N-Gn
Physiognomical Height of Upper Face	N-Sto
Mandible Height	Sto-Gn
Lower Face Height	Sn-Gn
Nose Height	N-Sn
Width of Nose	Al-Al
Biocular Width	Ex-Ex
Intercanthal Width	En-En
Width of Head	Eu-Eu
Width of Forehead	Ft-Ft
Width of Face	Zy-Zy
Width of Mandible	Go-Go

**Table 3: p-values for frequency of z-score distribution MFS population vs. normal population**

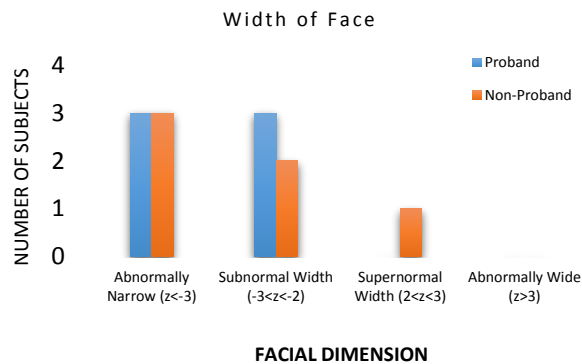
Craniofacial Measurement	p-value
Morphological Height of Face	.0103
Physiognomical Height of Upper Face	.0131
Mandible Height	.0011
Lower Face Height	.0079
Nose Height	.0023
Width of Nose	<.0001
Biocular Width	<.0001
Intercanthal Width	<.0001
Width of Head	.0008
Width of Forehead	.0081
Width of Face	<.0001
Width of Mandible	.0091



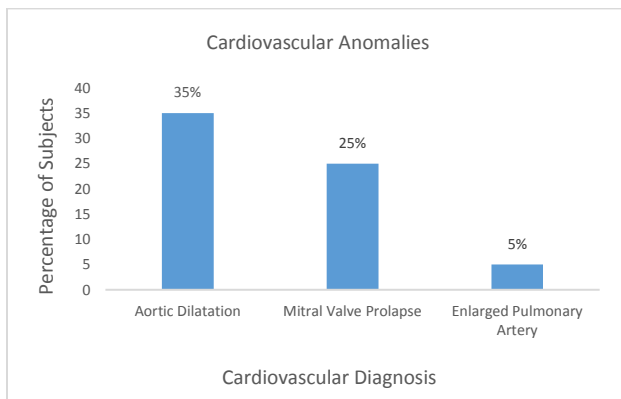
**Figure 1. Frequency of z-score distribution for sample population vs. normal population for facial width**

	Abnormal ( $z < -3$ )	Subnormal ( $-3 < z < -2$ )	Normal ( $-2 < z < -1$ )	Optimal ( $-1 < z < 1$ )	Normal ( $1 < z < 2$ )	Supernormal ( $2 < z < 3$ )	Abnormal ( $z > 3$ )
Null	0.03 (0.13%)	0.43 (2.14%)	2.72 (13.59%)	13.65 (68.27%)	2.72 (13.59%)	0.43 (2.14%)	0.03 (0.13%)
MFS Subjects	6 (30%)	5 (25%)	5 (25%)	3 (15%)	0 (0%)	1 (5%)	0 (0%)

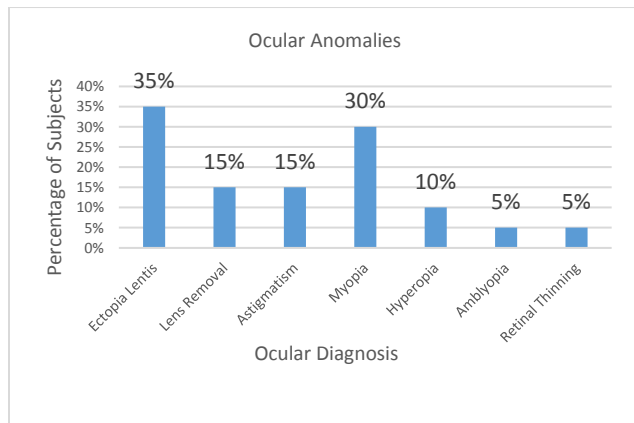
**Figure 2. Frequency of z-score distribution probands vs. non-probands for facial width**



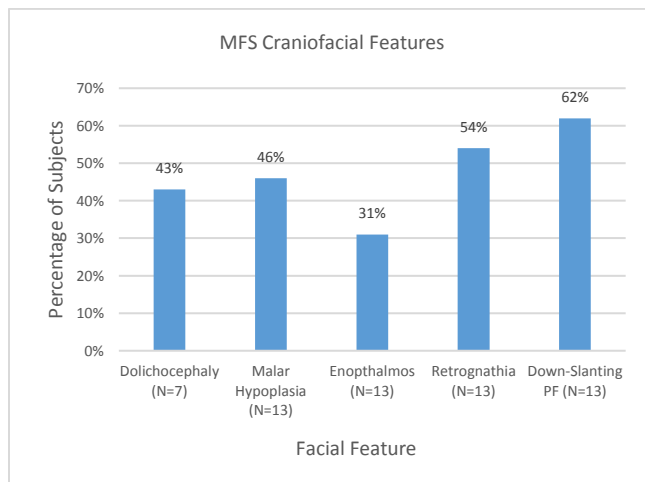
**Figure 3. Cardiovascular anomalies**



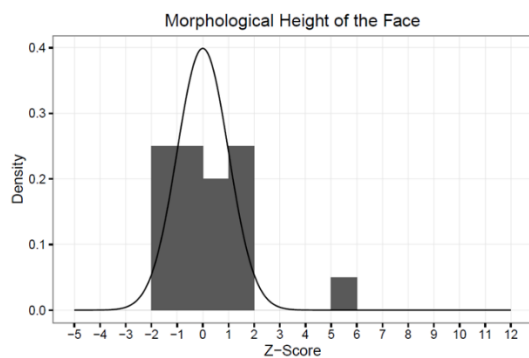
**Figure 4. Ocular anomalies**



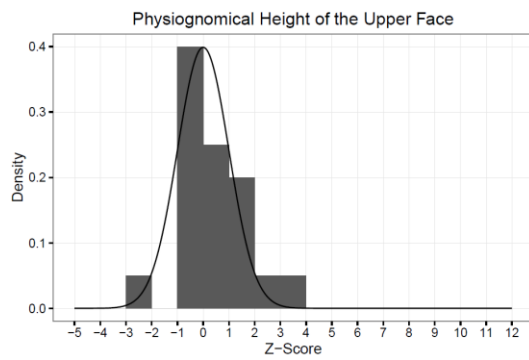
**Figure 5. MFS craniofacial features**



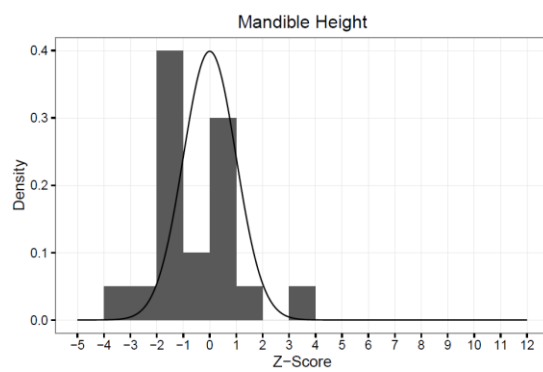
**Figure 6. Morphological height of face**



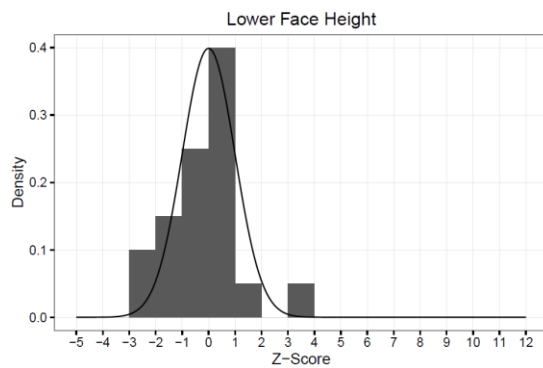
**Figure 7. Physiognomical height of the upper face**



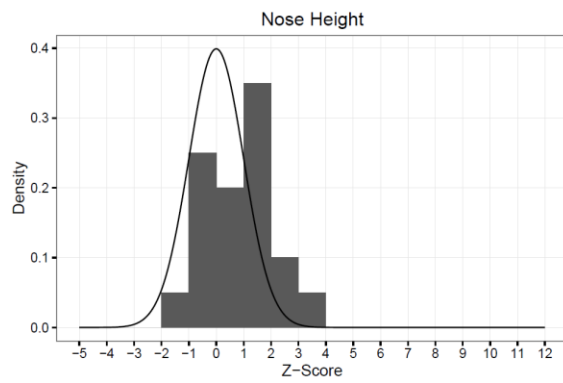
**Figure 8. Mandible height**



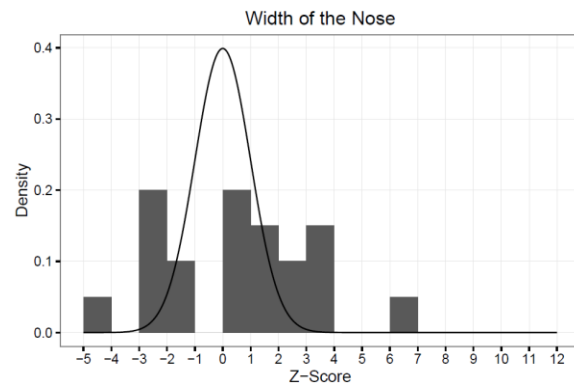
**Figure 9. Lower face height**



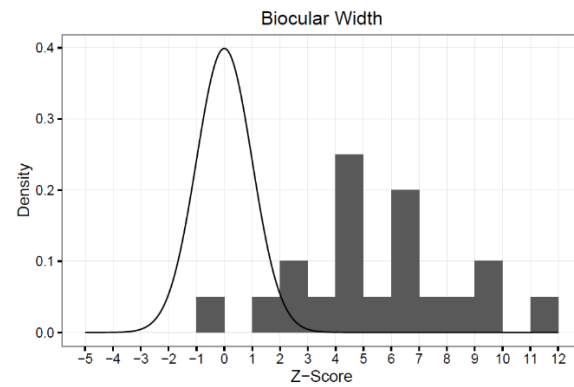
**Figure 10. Nose height**



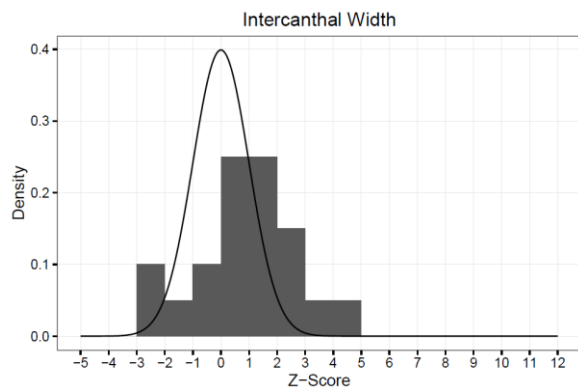
**Figure 11. Width of nose**



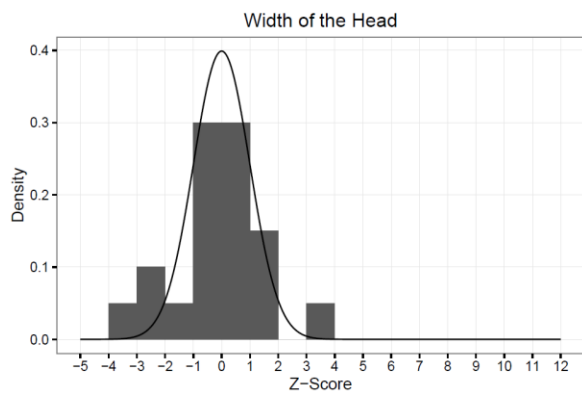
**Figure 12. Biocular width**



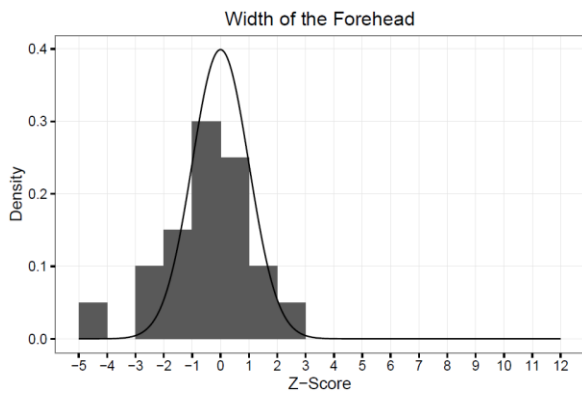
**Figure 13. Intercanthal width**



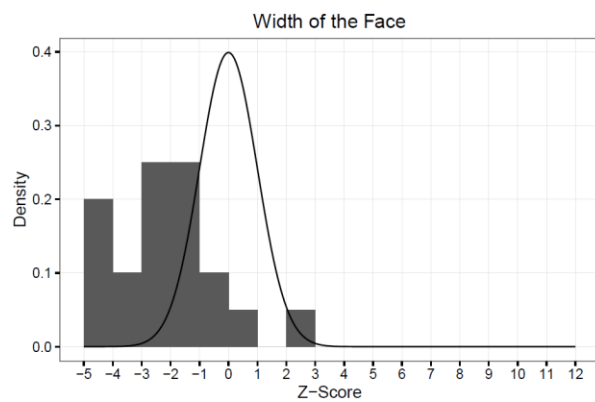
**Figure 14. Width of the head**



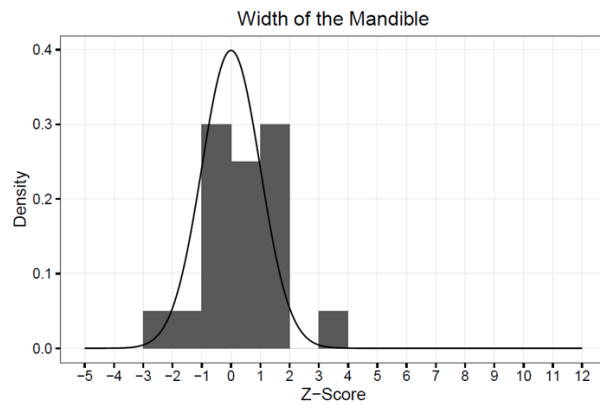
**Figure 15. Width of the forehead**



**Figure 16. Width of the face**



**Figure 17. Width of the mandible**



## APPENDIX 1. REVISED GHENT NOSOLOGY FOR THE MARFAN SYNDROME

### Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:

- (1) Ao ( $Z \geq 2$ ) AND EL=MFS\*
- (2) Ao ( $Z \geq 2$ ) AND *FBN1*=MFS
- (3) Ao ( $Z \geq 2$ ) AND Syst ( $\geq 7$ pts)=MFS\*
- (4) EL AND *FBN1* with known Ao=MFS

EL with or without Syst AND with an *FBN1* not known with Ao or no *FBN1*=ELS

Ao ( $Z < 2$ ) AND Syst ( $\geq 5$  with at least one skeletal feature) without EL=MASS

MVP AND Ao ( $Z < 2$ ) AND Syst ( $< 5$ ) without EL=MVPS

In the presence of family history:

- (5) EL AND FH of MFS (as defined above)=MFS
- (6) Syst ( $\geq 7$  pts) AND FH of MFS (as defined above)=MFS\*
- (7) Ao ( $Z \geq 2$  above 20 years old,  $\geq 3$  below 20 years) + FH of MFS (as defined above)=MFS\*

\* Caveat: without discriminating features of SGS, LDS or vEDS (as defined in table 1) AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated. Other conditions/genes will emerge with time.

Ao, aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; *FBN1*, fibrillin-1 mutation (as defined in box 3); *FBN1* not known with Ao, *FBN1* mutation that has not previously been associated aortic root aneurysm/dissection; *FBN1* with known Ao, *FBN1* mutation that has been identified in an individual with aortic aneurysm; MASS, myopia, mitral valve prolapse, borderline ( $Z < 2$ ) aortic root dilatation, striae, skeletal findings phenotype; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; Syst, systemic score (see box 2); and Z, Z-score.

### Box 2 Scoring of systemic features

- ▶ Wrist AND thumb sign — 3 (wrist OR thumb sign — 1)
- ▶ Pectus carinatum deformity — 2 (pectus excavatum or chest asymmetry — 1)
- ▶ Hindfoot deformity — 2 (plain pes planus — 1)
- ▶ Pneumothorax — 2
- ▶ Dural ectasia — 2
- ▶ Protrusio acetabuli — 2
- ▶ Reduced US/LS AND increased arm/height AND no severe scoliosis — 1
- ▶ Scoliosis or thoracolumbar kyphosis — 1
- ▶ Reduced elbow extension — 1
- ▶ Facial features (3/5) — 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- ▶ Skin striae — 1
- ▶ Myopia  $> 3$  diopters — 1
- ▶ Mitral valve prolapse (all types) — 1

Maximum total: 20 points; score  $\geq 7$  indicates systemic involvement; US/LS, upper segment/lower segment ratio.

### Box 3 Criteria for causal *FBN1* mutation

- ▶ Mutation previously shown to segregate in Marfan family
- ▶ De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
  - ▶ Nonsense mutation
  - ▶ Inframe and out of frame deletion/insertion
  - ▶ Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
  - ▶ Missense affecting/creating cysteine residues
  - ▶ Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
- ▶ Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
- ▶ Linkage of haplotype for  $n \geq 6$  meioses to the *FBN1* locus