

# 3D Craniofacial Morphometric Analysis of Young Subjects with Marfan Syndrome: A Preliminary Report

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## Abstract

Marfan syndrome (MFS) is a rare autosomic dominant disease of connective tissues mostly due to mutations in the fibrillin 1 gene. Clinical manifestations of MFS include a variety of signs and symptoms, mainly affecting the heart, blood vessels, bones, joints and eyes, and comprising craniofacial alterations. At present, diagnosis of MFS is largely based on clinical signs and family history. However, it could be difficult, as its manifestations vary greatly and they are not always present right away. Since a life-threatening complication of MFS is aortic dissection, an early diagnosis of the disorder is essential. We aim to better describe the face of patients with MFS, identifying new quantitative morphological features which could facilitate the early diagnosis of the disease. In the current preliminary study, a group of young subjects with MFS was investigated. Three-dimensional facial images of 3 girls and 8 boys aged 5-15 years were collected by stereophotogrammetry. From the coordinates of 50 anatomical facial landmarks, linear distances and angles were measured; z score values were calculated through the comparison with data obtained from 556 control subjects matched for gender, age, and ethnicity. All subjects with MFS showed a longer face than controls, mainly due to an increased middle third (mean z score = 1.7). They also showed a longer mandibular body (mean z score = 1.4) with a shorter ramus (mean z score = -1.4) and a greater facial divergence (mean z score = 2.2). The assessment of facial features of subjects with MFS pointed out some morphometric characteristics that had never been reported in literature, alongside with other well known alterations, and suggests the usefulness of a three-dimensional quantitative approach for the recognition of facial phenotypic features of the syndrome. Nevertheless, they need to be confirmed extending the study on more patients.

**Keywords:** Stereophotogrammetry, face, Marfan syndrome (MFS)

## 1. Introduction

Marfan syndrome (MFS, OMIM #154700) is an autosomic dominant disease of connective tissues due to mutations in the fibrillin 1 gene (FBN1) in more than 95% of cases, but also to mutations in the transforming growth factor beta receptor 1 and 2 genes (TGF- $\beta$ 1, TGF- $\beta$ 2) or in other still unknown genes. The resulting dysregulation of the TGF- $\beta$  signalling affects structural integrity of extracellular matrix. The syndrome is rare, with a prevalence estimated at 1 per 5,000 individuals in the general population, without any racial or gender predilection. Clinical manifestations of MFS reflect the damage to the connective tissues; they include a variety of signs and symptoms, mainly affecting the heart, blood vessels, bones, joints and eyes, and comprising alterations of the craniofacial district [1-3].

At present, diagnosis of MFS is based mainly on clinical signs and familiar history, according to international criteria defined in 2010 (Ghent's criteria) [4]. However, establishing a diagnosis of MFS may be difficult, as its phenotypic expression can vary greatly and the features of the disorder are not always present right away. Moreover, genetic testing for mutations in FBN1 and other genes can help in the diagnosis of MFS but it could be not conclusive.

The most serious clinical and life-threatening complications of MFS result from pathologic changes in the cardiovascular system. In particular the aorta can weaken and stretch with an increasing risk of dissection. For this reason an early and accurate diagnosis of the disease is essential [5]. For most people, MFS is not diagnosed until later in childhood or in adulthood. The MFS phenotype is evolutive, and the peculiar somatic traits of the syndrome are often the first signs suggestive of a diagnosis [6].

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With particular reference to the craniofacial district, the clinical manifestations of MFS may include dolichocephaly, enophthalmos, palpebral downslanting, malar hypoplasia and retrognathia. These characteristics are comprised among the criteria applied for the diagnosis of MFS and they are usually evaluated through a clinical inspection or cranial X-ray examination [7-9]. Subjects with MFS may also have narrow jaws, high-arched palate, which can create dental and orthodontic problems such as teeth crowding, posterior crossbite and malocclusion [10-15]. Sponseller et al. included craniofacial features of MFS among highly specific signs that musculoskeletal clinicians should be aware to improve the clinical recognition of the syndrome [16].

Today the two-dimensional assessment of craniofacial features on photographs and radiographic projections can be improved by means of the application of modern three-dimensional image acquisition systems which provide a detailed reconstruction of anatomic structures. Three-dimensional images are becoming a daily reality in several clinical and research contexts all over the world. Both volumetric (CT, MR) and surface (optical) imaging systems are currently being applied for the qualitative and quantitative assessments of craniofacial structures. In particular, instruments allowing a not invasive assessment of facial morphology such as stereophotogrammetry are of special interest, as they significantly improve the cost-benefit ratio of clinical analyses [17,18].

The three-dimensional morphometric facial analysis through stereophotogrammetry may highlight alterations of facial parameters which may be not detected by a clinical examination based on the mere inspection of the patients, and therefore give a contribution to the early diagnosis of the disease when the facial phenotype of MFS is not clearly evident or has not yet been clearly expressed. This is the key task for a correct strategy in preventing complications.

For instance, Kohler et al. hypothesized that the high occurrence of craniofacial dysmorphisms and an increased upper airway collapsibility could predispose to an increased prevalence of obstructive sleep apnoea (OSA) in MFS. Moreover, they demonstrated an association between OSA and aortic dilatation in MFS [19]. On the basis of clinical assessment of the orofacial phenotype of MFS, a recent study highlighted a correlation between a group of oral defects and systemic alterations of the syndrome, such as an aortic dilatation [9].

We aim to better describe the facial characteristics of patients with MFS, identifying new common quantitative morphological features which could facilitate the early diagnosis of the disease, in order to prevent the most serious complications of the syndrome. In the current preliminary study, a group of young Italian subjects with MFS was investigated.

## 2. Method

### 2.1. Patients and control subjects

Three girls and eight boys, fulfilling the Ghent criteria for MFS referred by the Rare Diseases Center – MarfanClinic – Milan, were recruited for the study. We also examined 556 healthy subjects from the local population, matched with patients for gender, age, and ethnicity, to serve as controls. Participants were chosen among Italian Caucasoid subjects without history of facial surgical treatment or trauma. Details of the analyzed subjects are shown in Table 1.

Parents or legal guardians of involved subjects signed the written consent to the participation in the study, after explanation of its nature; verbal agreement was also provided from subjects themselves. All procedures were not invasive and not dangerous, were performed according to the tenets of the Declaration of Helsinki, and were preventively approved by the local ethic committee.

*Table 1. Subjects analyzed in the current study.*

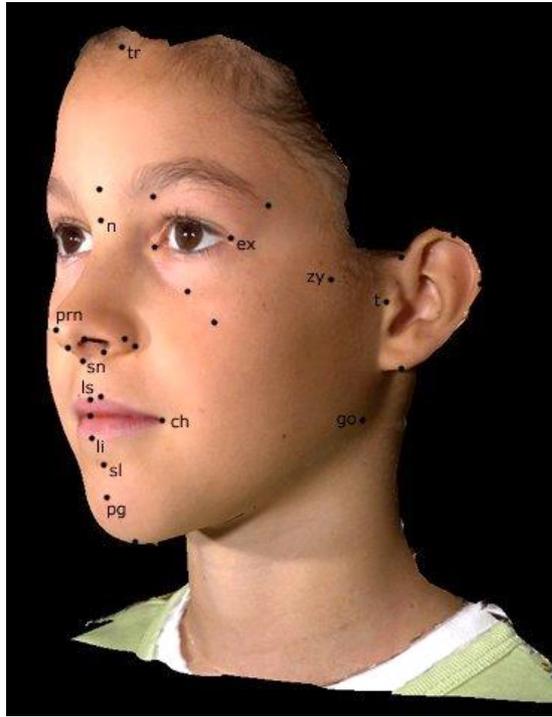
Age (yr)	Gender	MFS	Controls
4-5	male	2	98
8-11	male	4	131
12-15	male	2	195
12-15	female	3	132

### 2.2. Data collection and analysis

For each subject, the facial image was acquired using a three-dimensional stereophotogrammetric system (VECTRA M3, Canfield Scientific Inc, Fairfield, NJ, USA). The instrument has a 1.2 mm geometry resolution and can reproduce three-dimensional facial morphology with a capture time of 3.5 milliseconds.

Before each acquisition, 50 soft-tissue facial anthropometric landmarks were identified through inspection or palpation by an experienced examiner (Figure 1), according to international criteria and a

specific experimental protocol developed and widely used by our laboratory in investigating facial dysmorphism also associated to genetic syndromes [20-27]. Each landmark was highlighted by a common commercial eyeliner, whose possible hypersensitivity or intolerance were ascertained. The whole procedure took about 20 minutes.



*Fig. 1. Landmarks identified and digitized on all the subjects. Landmarks used in the current study are associated with their names.*

Using dedicated software, three-dimensional facial reconstructions were obtained. Data elaboration was performed off-line and was based on the three-dimensional coordinates of the digitized anthropometric landmarks, which allowed to obtain a geometric model of the face. Among the standard 50 landmarks, a subset of 8 selected midline landmarks and 5 paired landmarks described in Table 2 were considered in the current study.

*Table 2. Facial landmarks used in the current study and relevant definitions.*

<b>Midline landmarks</b>		
tr	trichion	on the hairline in the middle of the forehead
n	nasion	at the suture between forehead and nose
prn	pronasale	the most protruded point of the nasal apex
sn	subnasale	at the end of the columella
ls	labiale superius	midpoint of the vermilion line of the upper lip
li	labiale inferior	midpoint of the vermilion line of the lower lip
sl	sublabiale	in the midline of the mentolabial sulcus
pg	pogonion	most anterior point of the chin
<b>Paired landmarks</b>		
ex	exocanthion	external commissura of the eye fissure
zy	zygion	most lateral point of the zygomatic arch
t	tragion	in the middle of the tragus
ch	cheilion	outer labial commissura
go	gonion	most lateral point of the mandibular angle

For each subject 13 facial linear distances and 15 facial angles were calculated by custom computer programs. Table 3 shows the performed measurements.

Table 3. Analyzed distances and angles (*r* = right, *l* = left, *m* = mid-landmark).

<b>Linear distances</b>	
Vertical distances	
tr-n	length of the upper third of the face
n-sn	length of the middle third of the face
sn-pg	length of the lower third of the face
Horizontal distances	
ex <sub>r</sub> -ex <sub>l</sub>	biocular width
zy <sub>r</sub> -zy <sub>l</sub>	face width
t <sub>r</sub> -t <sub>l</sub>	skull base width
ch <sub>r</sub> -ch <sub>l</sub>	mouth width
go <sub>r</sub> -go <sub>l</sub>	mandibular width
Sagittal distances	
t <sub>m</sub> -n	upper facial depth
t <sub>m</sub> -sn	mid facial depth
t <sub>m</sub> -pg	lower facial depth
pg-go <sub>m</sub>	mandibular body length
t <sub>m</sub> -go <sub>m</sub>	mandibular ramus length
<b>Angles</b>	
Angles in the sagittal plane	
n-sn-pg	facial convexity, except nose
n-prn-pg	facial convexity, including nose
sn-n-prn	nasal convexity
sl-n-sn	maxillary prominence
t <sub>r</sub> -go <sub>r</sub> -pg, t <sub>l</sub> -go <sub>l</sub> -pg	mandibular angles (right and left)
(t <sub>m</sub> -n)-(go <sub>m</sub> -pg)	facial divergence (midfacial to mandibular plane angle)
prn-sn-ls	nasolabial angle
li-sl-pg	mentolabial angle
(sn-ls)-(li-pg)	interlabial angle
Angles in the horizontal plane	
t <sub>r</sub> -n-t <sub>l</sub>	upper facial convexity
t <sub>r</sub> -prn-t <sub>l</sub>	middle facial convexity
t <sub>r</sub> -pg-t <sub>l</sub>	lower facial convexity
go <sub>r</sub> -pg-go <sub>l</sub>	mandibular convexity
ex <sub>r</sub> -n-ex <sub>l</sub>	relative position of exocanthia and nasion

Each measurement was expressed as z score value, calculated through the comparison with corresponding data obtained from control subjects (patient value minus mean value in the control subjects divided by the SD of the control subjects). The average z scores and their standard deviations were then calculated. Since by definition the average z score of control groups is = 0 and its standard deviation is = 1, we considered remarkable those mean patient z scores that differed at least 1.4 SD from the control values.

### 3. Results

Figure 2 shows examples of geometrical reconstruction of the face, starting from the three-dimensional coordinates of anatomical landmarks. The face of a 10-year-old boy with MFS and the average face of the group of healthy control subjects of the same age and sex are compared.

#### 3.1. Linear distances

All subjects with MFS showed a longer face than controls, mainly due to an increase of the middle third (mean z score = 1.7, SD = 0.7). Also the lower third of the face was longer (mean z score = 1.6, SD = 0.4), while the upper third was not different.

In comparison with control subjects, MFS patients showed different mandibular dimensions. In particular, a longer mandibular body was observed (mean z score = 1.4, SD = 0.4), while the mandibular ramus length was reduced (mean z score = -1.4, SD = 0.9). Upper, mid and lower facial depths were similar in subjects with MFS and controls.

All analyzed facial dimensions in the horizontal plane did not show apparent differences between MFS patients and control subjects.

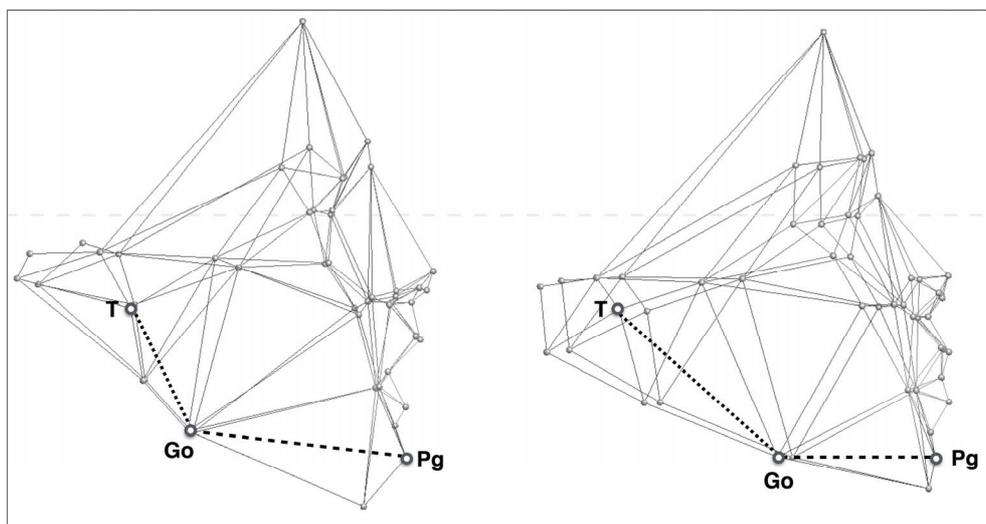


Fig. 2. Examples of 3D geometrical reconstruction of the face. The highlighted pogonion (pg)-gonion (go) and trago (t)-gonion (go) distances correspond to the mandibular body and ramus respectively. Left: patient with MFS. Right: mean facial profile of 30 control subjects. All subjects are, male, 10 years old.

### 3.2. Angles

In the sagittal plane, all subjects with MFS showed a greater facial divergence (midfacial to mandibular plane angle) when compared to controls (mean z score = 2.2, SD = 0.7).

MFS patients did not show any remarkable differences in all the other analyzed angles in the three spatial dimensions. Nonetheless, a reduced upper facial convexity (mean z score = -1.2, SD = 0.7) and an increased lower facial convexity (mean z score = 1.1, SD = 0.8) in the horizontal plane were pointed out.

## 4. Discussion

People born with MFS may not notice any features until later childhood or adulthood, but actually an early diagnosis of the syndrome is essential to prevent its life-threatening complications. Today, the evaluation of facial dysmorphism associated with MFS remains largely descriptive and almost based on subjective clinical impressions of the craniofacial features.

A recent study by Ting et al. analyzed the diagnostic value of facial features for MFS, concluding that the recognition of a specific facial phenotype can be used as an initial screening test. However, the study performed only a qualitative evaluation of two-dimensional photographs, in frontal and lateral views [28]. Anthropometry allows for a safe and non-invasive detailed qualitative and quantitative assessment of facial morphology and could help in the early diagnosis of the syndrome in clinical practice.

Beyond conventional direct anthropometry, which needs the direct contact with the subjects and exposes to the deformation of soft tissues, several procedures are now available for capturing and quantifying human three-dimensional facial surface morphology [29]. These include stereophotogrammetric systems, which are among the most appropriate for the definition of morphometric facial phenotypes, both in healthy subjects and in patients with different syndromes [17,18]. The high level of precision and repeatability of these systems is verified [30] and, due to the very short time required for the acquisition of the facial image, are appropriate for three-dimensional data collection even in children or disabled persons [17,18]. Moreover, they are easy to use and with practically no running costs.

Marking the landmarks of interest on the skin before the acquisition allows for capturing the position of those landmarks that can be efficaciously identified only by palpation of the underlying bone surface, thus increasing the instrument precision [18].

In the current preliminary study we evaluated the three-dimensional facial features of a small group of young subjects with MFS. Since the MFS phenotype is evolutive, the identification of specific facial features even in juvenile patients strengthens their usefulness for an early diagnosis of the syndrome. Facial linear distances and angles of subjects with MFS were compared to those obtained in healthy control subjects using z scores. Z scores values are well suitable for morphometric analyses, and they are widely used in clinical anthropometry to assess single patients [8,23,25].

Some of the current findings are in good agreement with literature reports: the increased facial divergence can well explain the retrognathia listed among the typical facial features of subjects with MFS [7-9], even if we did not find actually reduced facial dimensions in the anteroposterior direction. Indeed, maxillo-mandibular reciprocal positions were found to be very variable in previous cephalometric studies [8], without significant modifications of the ANB angle [7], the skeletal equivalent of the current maxillary prominence angle. An actual increment in facial divergence was also reported by both Cistulli et al. [7] and De Coster et al. [8].

A longer face was previously reported for both Belgian and Australian subjects with MFS [7,8]. The increased palatal height found in English MFS subjects can also contribute to this vertical increment [19].

The present finding of an increased mandibular body length contrasts with previous cephalometric data, where the opposite result was reported [8]. Indeed, the use of two-dimensional radiographic projections, and the different age range of the analyzed subjects could partly explain the difference, even if further investigations are necessary. Additionally, no modifications in mandibular ramus length were previously listed [7,8].

It has to be mentioned that the current investigation assessed facial soft tissues only, and no evaluations of the hard tissues were made. In contrast, previous studies used cephalometric analyses of head x rays [7,9,19]. Additionally, we analyzed children and adolescent patients only, and compared their data with those of normal subjects of the same age, sex and ethnicity, while literature mainly reports data about adults [7,19] or used reference values collected in other countries [8].

The quantitative assessment of facial features of subjects with MFS pointed out some morphometric characteristics that had never been reported in literature, alongside with other well known alterations: the current group of MFS patients showed a longer face due to an increase of its middle and lower thirds, a mandible with a longer body and a shorter ramus, and a greater facial divergence. These preliminary findings suggest the usefulness of a three-dimensional quantitative approach for the recognition of facial phenotypic features of MFS and encourage the evaluation of further anthropometric facial features. Nevertheless, they need to be confirmed extending the study on more patients.

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