Sella Turcica Morphometrics in Subjects with Down Syndrome

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Conflict of interest

The authors declare that they have no conflict of interest

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Authors' contributions

EO, PP and contributed to the conceptualization, methodology, investigation, validation, writing—original draft, and statistical analysis. EO, PP, participated in the investigation, validation, visualization, and writing. EO, PP, played a role in the supervision, project administration, and writing—original draft. The authors read and approved the final manuscript.

ABSTRACT

Objective: Since the number of patients diagnosed with Down syndrome seeking orthodontic treatment is increasing, clinicians could contribute by applying diagnostic modalities used frequently in the orthodontic field for research purposes. Thus, The aim of the present study is to implement morphometric methods to investigate the size and shape of sella turcica in subjects with Down syndrome.

Materials and Methods: In this retrospective study, archive records of 24 individuals with Down syndrome were compared to 48 healthy controls matched for age and gender. Parameters such as sella anterior, midpoint, and posterior height were measured, as well as sella width, area, and length were calculated. Independent sample t-tests were applied for the comparison of differences in sella turcica dimensions. Geometric morphometric analysis of the sella was performed with, implementing methods such as Procrustes superimposition and principal component analysis. Statistical significance was set at $p<0.05$.

Results: Statistically significant differences were found for sella anterior height, sella midpoint height, sella posterior height, sella maximum height, sella length, and sella area. All the aforementioned values were significantly increased in the Down syndrome subjects ($p<0.05$). Principal component analysis (PCA) depicted a statistically significant difference in sella shape between patients with Down syndrome and healthy controls ($p<0.05$).

Conclusions: Subjects with Down syndrome presented significantly increased sella turcica dimensions as well statistically significant differences in shape compared to healthy controls.

Keywords: Cephalometric radiography, Down syndrome, Genetics, Geometric morphometrics, Sella turcica

INTRODUCTION

Down syndrome (DS) is a genetic disorder induced by the existence of a partial or complete third copy of chromosome 21 and comprises one of the most frequent chromosomal anomalies [1-4]. Patients with Down syndrome present specific phenotypic characteristics such as delays in growth and development, cognitive impairment, disturbances in hearing and vision, as well as thyroid gland malfunction [5-11]. The etiology of the thyroid gland malfunction could be attributed to disorders in the production of thyroid-stimulating hormone (TSH) which is secreted from the pituitary gland. The latter is located in the anatomical structure named sella turcica, which is quite important for the craniofacial complex as well as the whole body. The hormone secretion that occurs in the pituitary gland is vital for the regulation of aspects such as blood pressure, temperature, and thyroid function, as well as for producing urine and sex hormones [12,13]. According to the literature, the pituitary gland is formed in fetal life before the formation of sella turcica, while its development is closely connected with sella turcica growth. It has been reported by various researchers that individuals diagnosed with many different syndromes such as holoprosencephaly, Down syndrome, fragile X syndrome, Williams syndrome, etc. exhibit dimensional and morphological disturbances in the sella turcica region during fetal stages of growth [14-18]. Furthermore, the alterations of the sella turcica structure in some of the aforementioned conditions that are observed during fetal growth are evident postnatally as well [14-15]. In the literature, there have been many studies investigating sella turcica dimensions for disorders other than Down syndrome [18-19]. Nevertheless, to our knowledge only three studies examined the sella turcica structure in individuals with Down syndrome presenting partially similar but also controversial results [20-22]. Recently, some authors attempted to examine the size and shape of sella turcica in healthy and non-syndromic cleft lip and palate subjects by implementing geometric morphometric techniques [23,24]. This methodology

possesses the advantage of eliminating the differences that arise from the orientation of the lateral cephalometric radiographs and of the sella turcica itself, in order not to affect the measurements of sella dimensions, as well as the analysis of shape. Particularly, the application of geometric morphometrics in the analysis of lateral cephalometric radiographs could enable the researcher to avoid many of the conventional obstacles that arise during the application of traditional methods to evaluate these films [25]. Finally, an enhanced understanding of an anatomical region such as sella turcica as well as its dimensional variations, could improve existing analytic methods such as Delaire cephalometric analysis, which is widely used in orthognathic surgery, and is based on sella turcica as an anatomic landmark. Consequently, an improvement in diagnostic techniques could contribute to better clinical outcomes especially in patients with syndromic conditions [34]. For the reasons mentioned above, the present study aims to investigate the size and the shape of sella turcica in subjects with Down syndrome by the application of geometric morphometric techniques, and to compare the results with an age and gender-matched healthy control group.

MATERIALS AND METHODS

Patient Selection

For the present retrospective study, lateral cephalometric radiographs of subjects with Down syndrome and healthy individuals treated in the xxxx University, Faculty of Dentistry Department of Orthodontics were included. The inclusion criteria implemented for the present study were the following:

For the Down syndrome group,

- no history of any surgical operation in the craniofacial complex,
- none of the subjects were institutionalized,
- moderate to high cooperation with the clinician who was responsible for their orthodontic treatment,

- cephalometric radiographs of acceptable quality, with Frankfort horizontal plane or intention parallel to the floor level, dentition positioned in central occlusion, obtained prior to any orthodontic treatment.

For the healthy control group,

- dental and skeletal Class I relationships,
- exact matching for age and sex with the Down syndrome group,
- availability of cephalometric radiographs obtained prior to the initiation of any orthodontic treatment,
- absence of any pathological growth conditions, hormonal treatment, signs of growth impairment (short stature), absence of cleft lip and/or palate, malformations, and syndromic diseases.

Lateral cephalometric radiographs were acquired on Promax device (Planmeca Oy, 0080 Helsinki, Finland), with the use of a cephalostat, and by applying the following parameters: 75 kV, 4.1 seconds, 10 mA.

The size of the sample for the present study was calculated by looking at the sella anterior height, sella midpoint height, sella area, and sella maximum height between subjects with Down syndrome and healthy controls, with differences in the mean diameter of 1.46 mm, 1.13 mm, 11.53 mm^2, and 1.27 mm respectively, and differences in the standard deviation of 0.08 mm, 0.01 mm, 1.04 mm^2, and 0.06 mm respectively, alpha of 0.05 and power 90%. The necessary number of subjects to meet the aforementioned criteria in order to conduct the present study were 22 patients with Down Syndrome.

In agreement with the protocol of the xxxx University, Faculty of Dentistry Department of Orthodontics, parents or legal guardians of the individuals included in the present study signed the informed consent forms. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee of ... University, Faculty of Dentistry (protocol code XXX and date of approval, …, …).

Data Assessment

The cephalometric radiographs were imported into Viewbox 4 cephalometric software (dHAL Software, Kifissia, Greece). The methodology of the present study was based on a combination of the methods of Andreadaki et al., and Antonarakis et al. (Figure 1) [23,24]. Furthermore, the main investigator of the present research was an orthodontist, with the assistance of senior faculty member (assistant professor).

First of all, the contour of sella turcica was traced, starting from the posterior clinoid process (PClin) and reaching to tuberculum sella (TS). Nine extra points were outlined by the cephalometric software along the contour of sella turcica. Furthermore, within the sella turcica contour, the most posteriorly (SP: sella posterior) and anteriorly (SA: sella anterior) points were defined, as well as the most deeply located point (SF: sella floor). The aforementioned points were outlined by the cephalometric software by implementing the Frankfort horizontal plane (FH) as a reference plane, and the following measurements were calculated: 1) Sella width: The largest sagittal dimension measured from sella posterior (SP) to sella anterior (SA) parallel to Frankfort horizontal plane (FH). 2) Sella anterior height: The distance from tuberculum sella (TS) to the sella floor (SF) perpendicular to FH. 3) Sella midpoint height: The distance from the midpoint between posterior clinoid process (PClin) to tuberculum sella (TS) to sella floor (SF) perpendicular to FH. 4) Sella height posterior: The distance from posterior clinoid process (PClin) to sella floor (SF) perpendicular to FH. 5) Sella length: The distance from posterior clinoid process (PClin) to tuberculum sella (TS). 6) Sella maximum height: The distance from the most superiorly located point to the sella floor (SF) perpendicular to FH. 7) Sella area: The area located within the contour of sella turcica and capped by a line from posterior clinoid process (PClin) reaching tuberculum sella (TS).

The shape analysis of sella turcica was also performed with the application of geometric morphometric methods and particularly with Procrustes superimposition and principal component analysis (PCA) through Viewbox 4 software [23,24,25]. Initially, Procrustes superimposition was implemented for the registration of all the tracings depicting the contour of sella turcica in order to the calculate of the average shape for the Down syndrome subject group and the control group. Moreover,

principal component analysis (PCA) was used to the point coordinate residuals for the extraction of the principal components (PCs). Finally for every cephalometric tracing the centroid size calculation was carried out.

Statistical Analysis

Python 3.7 Software (package stats from SciPy v1.6.0 Library) was implemented for conducting the statistical analysis of the data of the present study. Independent sample t-tests were applied for the comparison of differences in sella turcica dimensions. Furthermore, dissimilarities between the shapes of sella turcica in subjects with Down syndrome in comparison with the overall population of the present study were attained by permutation tests. These tests were implemented to calculate the Procrustes distance among groups with the Procrustes distance between group means and were performed by the Viewbox 4 software. The error of the present study method was assessed by repeating the cephalometric analysis of the radiographs by the same examiner 2 weeks after the initial measurements. The systematic error was investigated by the application of paired t-tests, whereas the random error was calculated by the implementation of Dahlberg's formula [26]. Statistical significance was set at $p<0.05$.

RESULTS

Sample Demographics

The present study consisted of 24 patients with Down syndrome (12 males and 12 females) aged between 8 and 13 years (mean age of 11.72 years), and 48 (24 males and 24 females; mean age of 11.68 years) gender and age-matched healthy subjects serving as a control group. The reason for doubling the number of the control group was to eliminate variations in the normal population.

Sella Size Analysis

In Table 1, the descriptive statistical analysis of the conventional measurements implemented for the sella size investigation is depicted. Statistically significant differences were found between Down syndrome subjects and healthy controls in relation to sella anterior height, sella midpoint height, sella posterior height, sella

maximum height, sella length, and sella area, which showed significantly increased values in the Down syndrome subjects.

Table 1: Sella size statistical comparison of Down syndrome subjects with healthy controls

	Control group			**Down syndrome group**			
	Mean (SD)	**Minimum**	**Maximum**	**Mean (SD)**	**Minimum**	**Maximum**	**P value**
Sella anterior height (mm)	6,4 (1,3)	3,9	9,6	7,9 (1,2)	4,4	10,2	**< 0,001***
Sella midpoint height (mm)	6,6 (1,1)	4,6	9,2	7,7 (1,1)	4,6	10,1	**< 0,001***
Sella posterior height (mm)	6,8 (1,2)	4,7	9,3	7,6 (1,3)	4,9	9,8	**0,01***
Sella maximum height (mm)	7 (1,2)	4,7	9,6	8,3 (1,2)	4,9	10,2	**< 0,001***
Sella width (mm)	7,7 (1,4)	5,2	11	8 (1,1)	4,5	9,9	0,24
Sella length (mm)	3 (1,4)	1	6	3,7 (1,2)	0,6	5,6	**0,03***
Sella area (mm^2)	38,4 (13,2)	15,7	66,9	49,9 (12,2)	15,7	70,9	**< 0,001***

1) Independent sample t-tests, 2) Bold values are statistical significance

Sella Shape Analysis

Principal component analysis (PCA) generated an amount of 22 principal components (PCs) for the 11 points that were implemented for the tracing of the sella turcica contour. The first three principal components (PCs) accounted for 84,6% of the variability of the total samples as shown in Table 2.

Principal Component (PC)	Variance (%)	Cumulative variance (%)
PC1	36,2	36,2
PC2	28,3	64,5
PC3	20,1	84,6
PC4	7,2	91,8
PC5	4,5	96,3
PC6	1,5	97,8
PC7	0,8	98,6
PC8	0,6	99,2
PC9	0,3	99,5
PC10	0,2	99,6

Table 2: Variance and cumulative variance of the first 10 PCs of shape in percentages.

In the present study, the first three principal components were investigated to a greater extent, due to the fact that they were the only PCs that were located clearly above the scree point when the screen plot was assessed.

Principal component analysis (PCA) depicted a statistically significant difference (P=0.0489, 10.000 permutations) in sella shape between patients with Down syndrome and healthy controls.

Furthermore, the average sella shape for both the Down syndrome and the control groups as produced from Procrustes superimposition is depicted in Figure 2.

The differences in sella shape between the Down syndrome patients and the control group are visualized as well in the PCA plots in Figure 3.

Finally, a graphic representation of the first three principal components (PCs) of the whole sample is depicted in Figure 4. The effect of every principal component on the sella shape is visualized on every row by three standard deviations (SD) in both directions.

DISCUSSION

The present study presents a comparison regarding the dimensions and shape of sella turcica between Down syndrome subjects and healthy controls. According to the literature, numerous researchers studied the craniofacial morphology of Down syndrome subjects but there are only three studies up to this date that investigated the morphology of sella turcica [14,20,21,22,27,28]. Moreover, the existing literature is scarce regarding the evaluation of the shape of sella turcica in patients diagnosed with Down syndrome. To our knowledge, the present study is the only one up to this date that investigated the shape of sella turcica by implementing geometric morphometric techniques.

Application of Geometric Morphometric Techniques

According to recently conducted research regarding the dimensions of sella turica in subjects with Down syndrome, the present is the only one which implemented geometric morphometric techniques such as Procrustes superimposition and principal component analysis. These techniques present some considerable advantages, which are discussed, bellow [25]:

1. Evaluation of the craniofacial shape with a decreased amount of measurements, which are not conflicting due to the fact they are not statistically related with each other.
2. Morphometric techniques are relatively insensitive to errors in the identification of landmarks.
3. The degree of variation from the average can be evaluated with more ease and precision.
4. The shape between subjects can be compared with greater ease (with Procrustes distance).
5. A more precise selection of subjects for research projects in relation to homogeneity of the sample.

The previously mentioned advantages of the geometric morphometric modalities could enhance cephalometric analysis and enable the researcher to reach more precise and clinically valuable conclusions.

Sella Dimensions Related to Systemic Conditions

Although sella turcica and pituitary gland begin to form during the 7th week of embryonic life, the initiation of pituitary gland formation precedes the one of sella. It needs to be highlighted that any abnormality occurring in this region during embryonic growth, persists for the entire life of the individual [15,29,30]. This fact is evident during prenatal investigations of sella turcica in subjects diagnosed with conditions such as lumbosacral myelomeningocele, Down syndrome, and fragile X syndrome, where the same disturbances are evident after birth [15,16]. Moreover, abnormalities in both sella turcica and the pituitary gland are evident postnatally in individuals diagnosed with holoprosencephaly [14]. Still, it is not clear in the existing literature if disturbances in the dimensions or shape of sella turcica in subjects with Down syndrome affect the activity of the pituitary gland. However, there have been reports of hypothyroidism in patients with Down syndrome with increased levels of thyroid-stimulating hormone (TSH) and thyroid microsomal antibodies [5-7,10].

Sella Size

According to Korayem and AlKofide, sella depth (which is analogous to sella height in the present research) and sella diameter were significantly increased in patients with Down syndrome, whereas sella length did not differ from healthy controls [21]. These results come partially in agreement with the present study, in relation to the sella height values (anterior, midpoint, and maximum height) which were significantly increased. However, while the sella diameter differed significantly between the groups according to the study of Korayem and Alkofide [21], the sella width did not exhibit any significant differences between the subjects of the present study, which might be due to the differentiation in the methods which were incorporated for measuring. In 2019, Hasan et al. investigated three-dimensionally the morphology of sella turcica in Malay subjects by assessing computed tomography scans [22]. They reported significant differences between patients with Down syndrome and healthy controls in the majority of the measurements they conducted except for sella anterior and midpoint height, as well as sella area. However, it is worthwhile mentioning that in the study of Hasan et al. the subjects presented significantly decreased sella dimensions compared with the healthy controls,[22] in contrast with the present study where the Down syndrome group presented significantly increased sella dimensions in comparison with the healthy population. When sella turcica was examined in subjects with other pathological conditions either syndromic (e.g., Williams syndrome) or with multifactorial etiology (e.g., cleft lip and palate) significant dimensional differences were evident [18,24]. On the contrary to the present study, sella turcica in the aformentioned conditions presented decreased sized in comparison with healthy controls [18, 24].

Sella Shape

The shape of sella turcica in subjects with Down syndrome has been investigated in the studies of Russel and Kjaer, Korayem and AlKofide, and Hasan et al. according to the literature [20-22]. The aforementioned studies presented significant differences in the sella shape of Down syndrome subjects compared to healthy controls which come in agreement with the results of the present study. However, a direct comparison of

our results is difficult due to the differences in the methodology incorporated for the evaluation of sella shape. It is worthwhile mentioning that these studies incorporated more subjective criteria for the assessment of the shape variability and abnormalities in comparison with the present study where a geometric morphometric evaluation was implemented, which is considered more objective. Thus, the choice of applying geometric morphometrics for shape investigation in the present study was made aiming for an evaluation with less bias, increased objectivity, and easier repeatability if incorporated by researchers in future studies. Finally, it is interesting that the results related to the principal components (PCs) present differences from the studies on sella shape of Antonarakis et al. and Andreadaki et al. on unilateral cleft lip and palate subjects and non-cleft and non-syndromic individuals respectively [23,24]. In the first study conducted by Antonarakis et al. the variance of PC1, PC2 and PC3 were 57.8 %, 26.9%, and 8.6% respectively, whereas Andreadaki et al. presented similar values between each other [23,24]. Interestingly in the present study the first three PC presented more evenly distributed variance.

Sella turcica size and shape of subjects with Down syndrome differed significantly from healthy controls, however, the clinical significance of the findings of the present study needs to be further investigated. According to a recently conducted research, the patients with Down syndrome present distinctive characteristics of the morphology of the craniofacial complex such as Angle Class III skeletal malocclusion (mainly due to maxillary hypoplasia and midface deficiency) and increased lower anterior facial height [28]. So, the size or the shape of sella turcica in such individuals might be associated with maxillofacial growth in the sagittal and/or vertical dimensions. Nonetheless, this hypothesis still needs to be elucidated. Appraisal of the growing tendency of the craniofacial complex in individuals with Down syndrome could be valuable for improving treatment planning, prognosis, and outcome, and the implementation of sella turcica as an index for the potential growth tendency could serve as an invaluable tool in the hands of the clinician. Even if the increased dimensions or the differentiated shape of sella turcica of Down syndrome subjects are attributed to the variations of the anatomical structures when compared to healthy controls, or due to pathological conditions of the pituitary gland further investigation

is necessary. Since the number of patients diagnosed with Down syndrome seeking orthodontic or a combination of orthognathic surgery and orthodontic treatment is increasing, clinicians who are familiar with the shape variations of this specific anatomical regions could improve the precision of their diagnostic and treatment planning modalities, contributing to more favorable treatment outcomes [35,36]. Moreover, if sella turcica morphology is thoroughly investigated could serve as a histological and neuroradiological marker for pathologic conditions or developmental malformations of the pituitary gland which are present in many syndromic on non-syndromic diseases [37]. Since such conditions frequently require an interdisciplinary approach, if the clinicians of multiple specialties (maxillofacial surgeons, orthodontists etc.) are familiar with variations of such anatomical landmarks and its associations, the treatment approaches of specific conditions such as Down syndrome could be benefited.

It is worthwhile mentioning that there have been researchers investigating the morphology of sella turcica implementing three-dimensional (3D) imaging techniques, which could provide a comprehensive evaluation of the anatomical features of this region [31-33]. Future studies with an increased sample size of both Down syndrome subjects, and healthy controls, with different imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT), accompanied by geometric morphometric analysis and endocrinological investigations could elucidate the previously mentioned questions, and provide more insight in the understanding of the morphological variations of sella turcica regions.

CONCLUSION

- Subjects with Down syndrome present significantly increased sella turcica dimensions when compared with age- and gender-matched healthy population in the aspects of sella anterior height, sella midpoint height, sella posterior height, sella maximum height, sella length, and sella area.

- The application of geometric morphometric techniques for the shape evaluation of sella turcica in subjects with Down syndrome presented significantly different shape pattern of the sella area when compared with age- and gender-matched healthy population.

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FIGURE LEGENDS

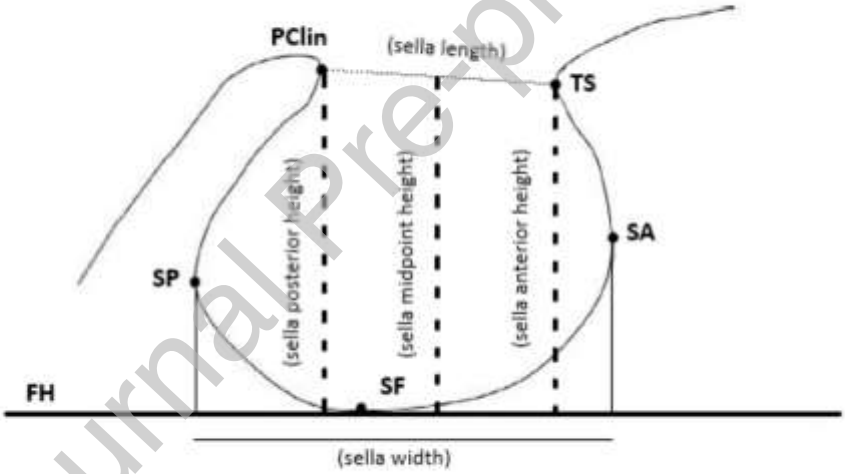

Figure 1: Tracing of sella turcica contour with the definition of the following anatomical landmarks and planes: posterior clinoid process (PClin), tuberculum sella (TS), sella posterior (SP), sella anterior (SA), sella floor (SF), Frankfort plane (FH). The following linear measurements were calculated: sella width (SP to SA, parallel to FH), sella anterior height (TS to SF, perpendicular to FH), sella midpoint height (midpoint between PClin and TS to SF, perpendicular to FH), sella posterior height (PClin to SF, perpendicular to FH), sella length (PClin to TS).

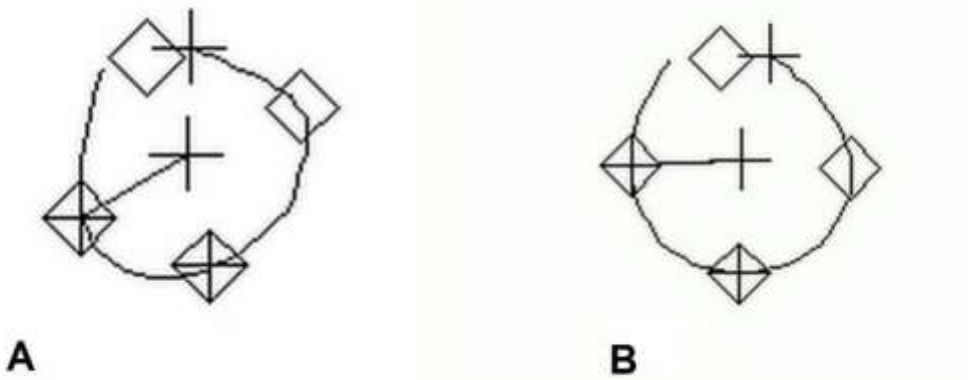

Figure 2: Average sella shape of (A) control group, and (B) Down syndrome group

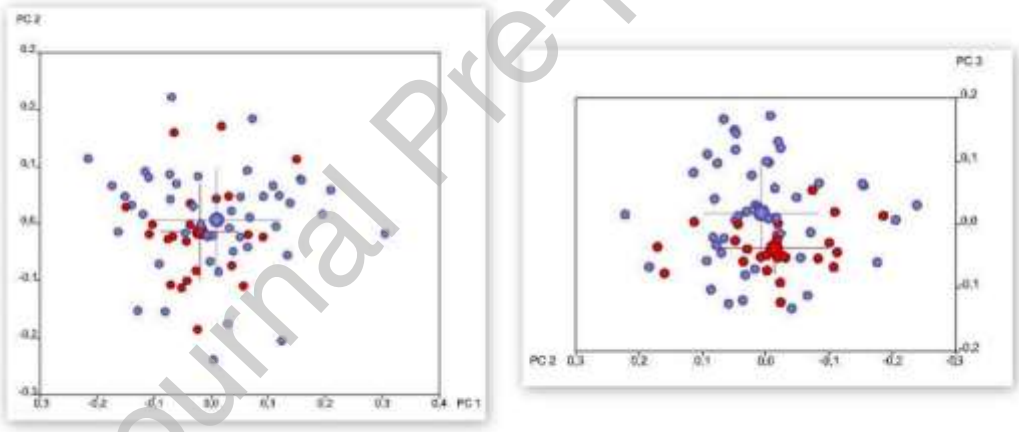

Figure 3: Principal component analysis (PCA) plot for PC1 - PC2 and PC2 – PC3. (Red: Down syndrome subjects, Blue: control group) generated from Viewbox 4 software

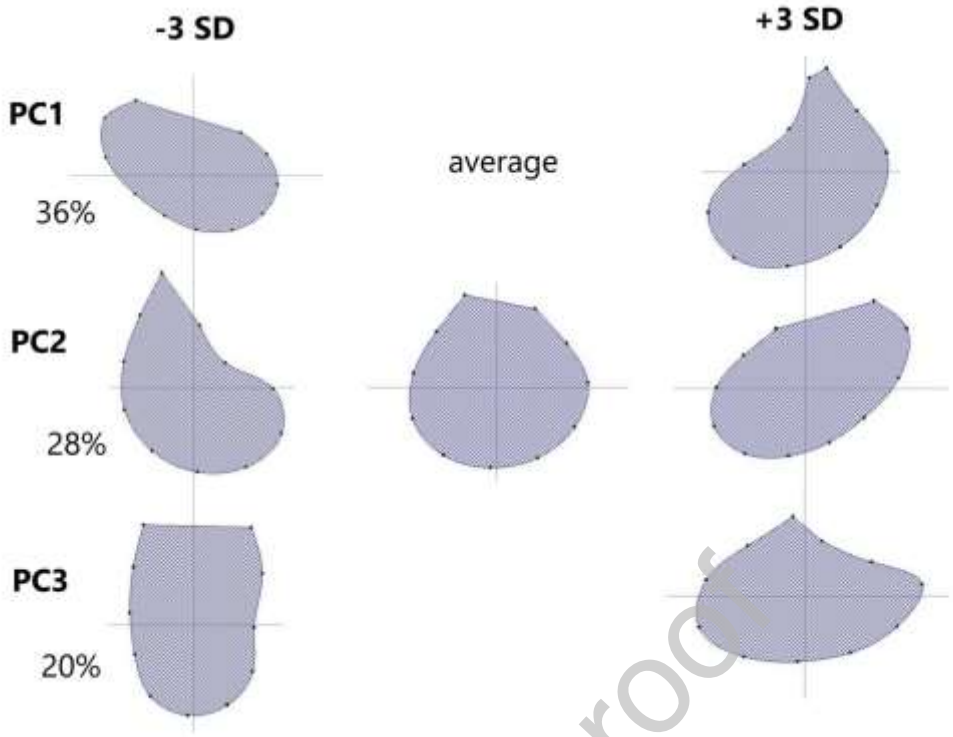

Figure 4: Variability of sella turcica shape of the whole sample as affected from the first three PCs. Average shape is located in the center and the effects of each PC on sella shape in the extremes by 3 standard deviations (+/- 3 SD) on the left and right.