# Shape of the craniofacial complex in patients with Klinefelter syndrome

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In addition to their primary role in gonadal differentiation and development, sex chromosomes are important in controlling craniofacial morphology and size.

Klinefelter syndrome is a disorder characterized by an extra X chromosome in human cells. It is manifested in numerous phenotypic differences from normal males. Secondary male sex characteristics do not develop after puberty while gynecomastia (excessive development of the male mammary glands), aspermatogenesis (absence of development of spermatozoa), and minor anomalies in the head region may occur.[1,2]

The results of cephalometric studies in true Klinefelter syndrome patients (47,XXY) indicate that the shape of the cranial base is shorter then in normal males (46,XY). Both the mandible and the maxilla differ in Klinefelter males and normal males.[3,4] Oral anomalies seem to be rare, although cleft lip and hemifacial microtia have been reported; as part of the craniofacial complex, teeth are subject to characteristic alterations in these patients[5-13]

Patients with chromosomal constitutions 48,XXXY and 49,XXXXY usually have more severe clinical aberrations than those with true Klinefelter syndrome.[14]

This cephalometric study evaluates the craniofacial morphology of adult Croatian 47,XXY males in order to provide further information on the effects of the sex chromosome imbalance on the size and shape of the craniofacial complex.

## Material and methods

Measurements were performed on 35 males with Klinefelter syndrome, 47,XXY, whose karyotypes had been determined at the Clinic for Gynecology and Obstertrics, University Hospital "Merkur", Zagreb, Croatia. Average age of the

**Abstract**

The shape and size of the craniofacial complex in 35 adults with Klinefelter syndrome (47,XXY) were analyzed cephalometrically and compared with 60 control males. Twenty-four angular and 18 linear measurements were obtained for each subject. The results showed that the 47,XXY males were different from the controls in several areas of the craniofacial skeleton. Most of the differences were located in the cranial base and the cranial base angle ($p < 0.02$). The length of the maxillary base was greater ($p < 0.05$) and more prognathic ($p < 0.01$) in the study group. The mandible was also longer and more prognathic ($p < 0.01$).

**Key Words**

Craniofacial dimensions • Klinefelter syndrome • Sex chromosomes

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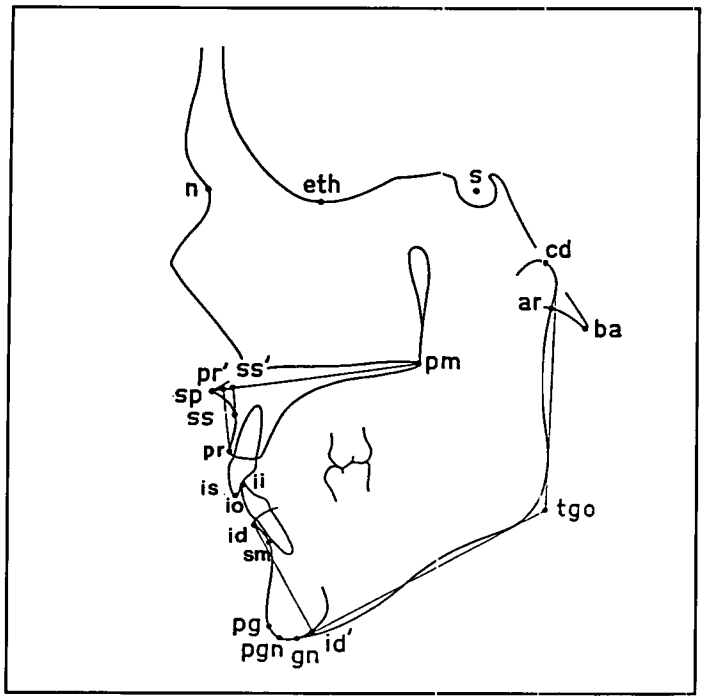


Figure 1

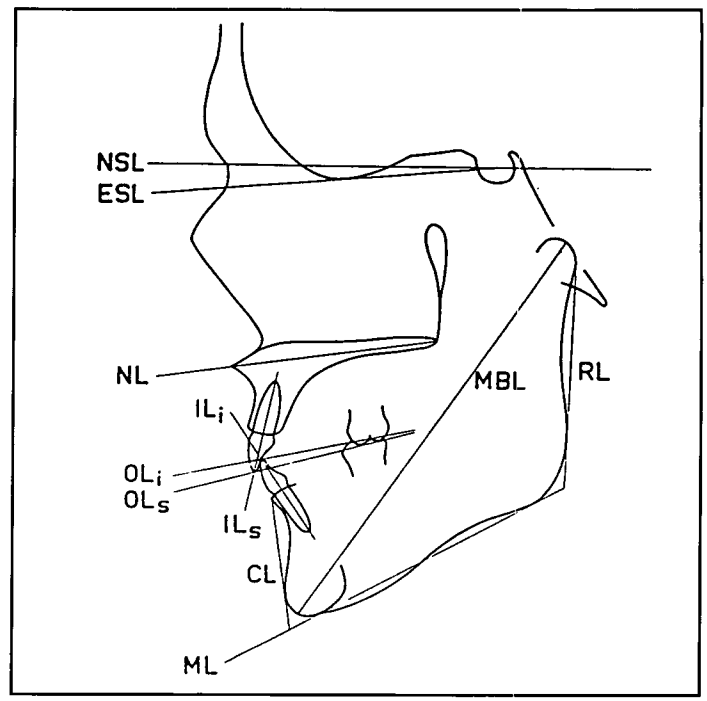


Figure 2

**Figure 1**
**Reference points on the laterial skull radiographs**

**Figure 2**
**Reference planes on the laterial skull radiographs**

study group was 27 years. The control group consisted of 60 male dental students, 21 to 27 years old.

Lateral skull radiographs were made on Ortoceph 5 "Siemens" - 80 KV and 5 mA. Radiographs taken with the jaws in habitual occlusion were used for the cephalometric measurements suggested by Solow.[15]

The cephalometric analysis consisted of 24 angular and 18 linear measurements (Figures 1 and 2). The points were marked in pencil on tracing paper and the distances measured on a sliding caliper with an accuracy of 0.5 mm. Angular measurements were made with a large protractor. The measurements were made for all variables in all the cranıograms with the following exceptions: NSL/NL, ILs/NL, OLs/ML, ILs/ILi and is-io/ii-io in the XXY males or the controls where the central incisors or the mandibular first molars were missing.

To assess reliability, three examiners measured and traced 20 radiographs twice during a 1-month period. Statistical analysis for intra- and inter-examiner reliability was performed according to the method proposed by Slatker et al.[16] and Fleiss et al.[17] Intra-examiner reliability varied from 0.89 to 0.98, depending on the measured variable, while the inter-examiner reliability varied from 0.85 to 0.94. The measurement error for each variable was calculated using Dahlberg's formula.[18] The error varied in the range of 0.015 to 0.159 for the linear measurements, and 0.158 to 0.278 for the angular measurements.

As the inter- and intra-examiner reliability was satisfactory, all further measurements were performed by the one examiner who was the most consistent in the measurements.

Means (x) and standard deviations (S.D.) were calculated for all variables, and the statistical significances of the differences were tested with the student t-test.

## Results

Statistically significant differences were found in 13 angular and eight linear measurements between the Klinefelter males and the control group. Both linear and angular measurements tended to be smaller in the 47,XXY group than in the control males. The differences were located primarily in the cranial base. The length of the cranial base (n-s), was significantly shorter in the 47,XXY group than in the controls ($p < 0.02$). The clivus (s-ba) was shorter and the cranial base angle (n-s-ba) was smaller in the 47,XXY males ($p < 0.02$). The length (s-ba) was also shorter in the males with Klinefelter's syndrome ($p < 0.05$).

The nasal bone had similar length (n-na) but was more protruded relative to nasion (s-n-na) in the 47,XXY males ($p < 0.01$).

The length of the maxillary base (sp-pm) was significantly longer in the 47,XXY group, and the maxilla was more prognathic relative to nasion (s-n-sp, s-n-ss) in the study group then in the controls ($p < 0,02$, $p < 0.01$).

The gonial angle (ML/RL) was larger and the mandible was more prognathic (s-n-pg, s-n-id) in

**Table 1**
**Linear cephalometric measurements performed on the 47,XXY males and the controls (Student t-test)**

| | 47,XXY | | | Control Males | | | |
|---|---|---|---|---|---|---|---|
| Dimension | n | $\bar{x}$ | SD | n | $\bar{x}$ | SD | p |
| s - f | 35 | 92.53 | 4.10 | 60 | 93.70 | 4.28 | 1.32 |
| n - s | 35 | 75.07 | 4.14 | 60 | 77.07 | 3.21 | 2.45 ** |
| s - ba | 35 | 49.36 | 4.25 | 60 | 51.39 | 3.99 | 2.30 ** |
| ba - pm | 35 | 47.96 | 3.73 | 60 | 48.31 | 4.08 | 0.42 |
| n - na | 35 | 26.45 | 4.76 | 60 | 24.61 | 3.92 | 1.93 |
| sp - pm | 35 | 57.98 | 3.64 | 60 | 59.98 | 5.45 | 2.12 * |
| n - sp | 35 | 56.12 | 5.37 | 60 | 57.52 | 4.16 | 1.33 |
| s - pm | 35 | 54.59 | 3.45 | 60 | 54.08 | 3.97 | 0.65 |
| sp - is | 35 | 30.76 | 6.64 | 60 | 31.03 | 4.02 | 0.28 |
| pr - pr' | 35 | 16.89 | 4.51 | 60 | 16.72 | 3.56 | 0.19 |
| pgn - cd | 35 | 131.74 | 4.11 | 60 | 129.41 | 4.09 | 2.70 *** |
| sp - gn | 35 | 74.54 | 6.94 | 60 | 75.06 | 6.23 | 0.37 |
| s - ar | 35 | 39.34 | 3.77 | 60 | 42.82 | 4.40 | 4.09 *** |
| s - tgo | 35 | 89.18 | 6.33 | 60 | 95.37 | 7.99 | 4.18 *** |
| cd'- tgo | 35 | 61.72 | 6.66 | 60 | 65.89 | 5.47 | 3.11 *** |
| id - id' | 35 | 35.03 | 3.07 | 60 | 35.36 | 3.10 | 0.50 |
| is - io | 34 | 2.57 | 1.36 | 58 | 2.17 | 1.17 | 1.48 |
| ii - io | 34 | 3.64 | 1.65 | 58 | 2.90 | 1.51 | 2.17 * |

$\underline{n}$ - number of measurements,
$\bar{x}$ - arithmetic mean,
SD - standard deviation,
* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$

the 47,XXY males, ($p < 0.01$), but the posterior vertical dimension (cd-tgo) was smaller, ($p < 0.01$). The length of the mandible (pgn-cd) was significantly larger in the 47,XXY males, ($p < 0.01$).

Both the maxilla and the mandible seem to be located farther forward in relation to the cranial base in the 47,XXY males.

## Discussion

Variations in craniofacial form are determined by genetics and environmental factors. According to Scott[19] the parts of the skull which show the greatest amount of genetic control are those which are developmentally most closely related to the chondrocranial and chondrofacial skeleton, namely the midline cranial base and the lower border of the mandible.

It is obvious from these results that the anterior cranial base length was significantly shorter in the males with an extra X chromosome than in the males with normal chromosomes. A short anterior cranial base has also been reported earlier by Ingerslev and Kreiborg[20] and Babic et al.[21]

A recent cephalometric investigation of 30 adults with Turner's syndrome (45,X) revealed that the cranial base is these women tended to be flatter than in controls.[22] Peltomaki et al.[23] reported short posterior cranial base in 45,X females and a slight increase in cranial base angle.

In a comparative study of humans with sex chromosomal aneuploidi, Gorlin et al. proposed a correlation between the presence of the X chromosome and mandibular retrognathism or prognathism.

The results of cephalometric studies in Turner syndrome patients indicated that the mandible and the maxilla were shorter than in normal females. The face has been described as being rotated posteriorly, which gives a retrognathic impression.[22-24]

The hypotheses that the lack of an X chromosome causes mandibular retrognathism and that an extra X chromosome causes mandibular prog-

**Table 2**
**Angular cephalometric measurements performed on the 47,XXY males and the controls (Student t-test)**

| Angle | 47,XXY n | 47,XXY x̄ | 47,XXY SD | Control Males n | Control Males x̄ | Control Males SD | p |
|---|---|---|---|---|---|---|---|
| n-s-ba | 35 | 124.80 | 4.47 | 60 | 127.45 | 5.90 | 2.47 ** |
| eth-s-ba | 35 | 123.05 | 5.81 | 60 | 123.73 | 5.57 | 0.56 |
| n-s-cd | 35 | 127.57 | 5.89 | 60 | 130.10 | 6.99 | 1.88 |
| n-s-ar | 35 | 119.48 | 5.90 | 60 | 123.23 | 5.69 | 3.04 *** |
| n-s-pm | 35 | 70.08 | 3.27 | 60 | 71.31 | 5.24 | 1.40 |
| pm-s-ba | 35 | 54.91 | 4.74 | 60 | 56.35 | 6.84 | 1.00 |
| s-n-na | 35 | 122.71 | 5.69 | 60 | 118.70 | 6.75 | 3.09 *** |
| s-n-sp | 35 | 90.85 | 4.52 | 60 | 88.48 | 4.01 | 2.57 ** |
| s-n-ss | 35 | 85.31 | 4.02 | 60 | 83.06 | 3.37 | 2.80 *** |
| s-n-pr | 35 | 87.45 | 3.82 | 60 | 85.41 | 4.69 | 2.31 * |
| s-n-pg | 35 | 85.34 | 3.66 | 60 | 82.58 | 3.75 | 3.51 *** |
| s-n-id | 35 | 85.51 | 4.22 | 60 | 81.86 | 3.13 | 4.50 *** |
| s-n-tgo | 35 | 96.74 | 7.53 | 60 | 99.90 | 8.88 | 2.48 ** |
| ss-n-pg | 35 | 2.71 | 2.26 | 60 | 1.95 | 1.83 | 1.72 |
| NSL/NL | 30 | 8.26 | 3.03 | 60 | 7.23 | 3.54 | 0.71 |
| ILs/NL | 33 | 110.03 | 7.78 | 60 | 108.63 | 6.54 | 0.88 |
| OLs/ML | 24 | 9.54 | 3.84 | 60 | 7.73 | 3.49 | 2.01 |
| NSL/ML | 35 | 31.08 | 6.75 | 60 | 27.31 | 6.99 | 2.60 ** |
| NSL-MBL | 35 | 52.20 | 4.93 | 60 | 51.73 | 4.78 | 0.43 |
| ML/RL | 35 | 127.70 | 6.32 | 60 | 120.86 | 10.36 | 4.04 *** |
| ILi/ML | 35 | 85.11 | 8.48 | 60 | 93.08 | 6.58 | 4.80 *** |
| CL/ML | 35 | 64.65 | 6.21 | 60 | 66.41 | 6.60 | 1.30 |
| NL/ML | 35 | 24.54 | 7.63 | 60 | 23.26 | 6.72 | 1.47 |
| ILs/ILi | 34 | 137.64 | 9.31 | 60 | 134.71 | 8.92 | 1.49 |

n - number of measurements,
x̄ - arithmetic mean,
SD - standard deviation
* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$

nathism has been supported by Ingerslev and Kreiborg,[20] Peltomaki et al.,[23] Jensen,[24] Brkic,[25] and Brown et al.[26] Thus, males with Klinefelter syndrome should exhibit increased facial prognathism, whereas patients with Turner syndrome should exhibit facial retrognathism. In the present study, craniofacial patterns were particularly distinctive in the mandible which, on average, displayed a shorter ramus, longer body, larger gonial angle and greater prognathism relative to the cranial base and maxilla. These findings are consistent with Lyon's[27] hypothesis that the X chromosome has an effect on mandibular growth in relation to the development of the maxilla.

Craniofacial dimensions in the adult 47,XXY male are smaller and the viscerocranium is more prognathic than in the controls. These findings confirm the hypothesis of Gorlin, Redman and

Shapiro: "The retrognathism and prognathism are probably also related to the shape of the cranial base, and it might be hypothesized that loss or addition of an X-chromosome influences the shape of the cranial base and thereby the measurement of facial prognathism."

However, the characteristic craniofacial morphology of 47,XXY males evidently cannot be compensated for by the many environmental factors influencing the growth and development of the head.

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