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ORIGINAL ARTICLE

# Craniofacial complex specificities in five men with sex reversal syndrome

**Ivana Scepan · Branislav Glisic · Evgenija Markovic · Marko Babic**

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**Abstract** In order to clarify the role of sex chromosome constitution in craniofacial growth control, we compared craniofacial morphology of men with sex reversal syndrome (46, XX) with the morphology of normal men, Klinefelter's syndrome and normal women, using cephalometric measurements. Due to physical resemblance between men with 46, XX karyotype and men with 47, XXY karyotype, cephalometric analysis comprised parametres which had already been found to be specific for Klinefelter's syndrome, i.e. cranial base length and flexion, maxillary and mandibular base length, jaw position in relation to cranial base and sagittal jaw relationship. Linear measurements showed reduction of about 10% in maxillary base length in 46, XX men in relation to normal men. Mandibular base in men with sex reversal syndrome was also shortened for about 10% in relation to both normal men and Klinefelter's syndrome. Cranial base flexion in men with Klinefelter's syndrome and in men with sex reversal syndrome showed similarity. The basal angle was found to be more acute, for about 4°, in comparison to individuals with normal karyotype. Unlike in men with Klinefelter's syndrome, mandibular and maxillary prognathism were not registered in men with sex reversal syndrome.

I. Scepan · B. Glisic · M. Babic
Clinic of Orthodontics, School of Dentistry,
University of Belgrade,
Belgrade, Serbia

E. Markovic
Private practice,
Vancouver, Canada

I. Scepan (✉)
Dravska 2,
11000 Belgrade, Serbia
e-mail: iscepan@yahoo.com

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## Introduction

The 46, XX male syndrome is a very rare sex chromosomal disorder in men. Different pathogenic mechanisms that can lead to 46, XX sex reversal syndrome have been suggested. It usually occurs due to unequal crossing over between X and Y chromosomes during meiosis, producing two rare abnormalities: XX males and XY females. XX males are phenotypic males with 46, XX karyotype and male habitus, small testicles, azoospermia and with no evidence of uterus or ovaries [17].

The absence of Y chromosome found in males with sex reversal syndrome (46, XX chromosomal constitution) develops during the formation of germ cells in the father, when an abnormal exchange leads to the transfer of the entire pseudoautosomal region plus a portion of the Y chromosome including testis determining factor onto the X chromosome. The incidence of 46, XX male syndrome is about 1 in 20,000–25,000 male births [17].

The presence of two X chromosomes, one carrying a small translocated fragment of Y chromosome, makes men with sex reversal syndrome very similar to men with Klinefelter's syndrome. Both syndrome groups characterize eunicoid habitus, but men with sex reversal syndrome are shorter than men with Klinefelter's syndrome [18].

In the complex mechanism of growth control, both in magnitude and timing, autosomal genes, Y-chromosome genes and environmental factors are involved [9, 12]. Studies of twins have shown that body size, body shape, deposition of fat and pattern of growth are all more under genetic than environmental control [4]. Genetic factors play

a leading role in male–female growth differences. By delaying growth, the Y chromosome enables males to continue growing over a longer period of time than females, therefore making their overall growth greater.

Deviation in sex chromosome number significantly influences cranial growth and craniofacial morphology. Numerous studies on patients with X-chromosome aneuploidies showed that cranial base flexion and jaw position are affected in women with Turner's syndrome (karyotype 45, X) and in men with Klinefelter's syndrome [3, 11, 14, 16].

Our earlier investigations on men with Klinefelter's syndrome ascertained that selectively inhibited cranial growth is responsible for their specific craniofacial morphology. It was found that an extra X chromosome in men produced increased cranial base flexion, strongly expressed mandibular prognathism and deviated sagittal jaw relationships [2, 15].

This evidence inspired us to undertake comparative cephalometric analyses, in which the effects of the abnormal sex chromosome constitution in men (two X chromosomes without Y chromosome) on craniofacial morphology would be explored. To the best of our knowledge, this is the first report dealing with cephalometric analysis in XX males.

## Materials and methods

### Subjects

The data in this study were derived from lateral cephalometric radiographs of four groups of patients: five males with sex reversal syndrome (46, XX), 31 normal males (46, XY), 52 normal women, (46, XX) and 28 males with Klinefelter's syndrome (47, XXY). All participants was aged 20 to 35 residing in Belgrade and its suburbs were part of the Serbian government project for treating persons with craniofacial abnormalities, and they were invited to a dental examination that included study casts, panoramic radiographs, lateral cephalometric radiographs and facial photographs. After thorough examination, medical and dental problems of these patients have been addressed and treated.

### Cephalometric measurements

Lateral cephalometric radiographs of all participants were taken and cephalometric analysis was performed. Reference points were marked in pencil on a matt acetate film. Distances between reference points were measured with a ruler to the nearest half millimetre and angular measurements were measured to the nearest degree using a protractor. In the case of duplicated structure, reference point was marked at the midpoint.

The following linear measurements were accomplished: N–S distance (anterior cranial base), S–Ba distance (posterior cranial base), Ans–Pns distance (maxillary base length), Go–Pg' distance (mandibular base length) and Go–Cd' distance (ascending ramus length). Angular measurements were: NSBa (basal angle), SNA (maxillary prognathism), SNB (mandibular prognathism), and ANB (sagittal jaw relationship; Fig. 1).

No correction was made for the enlargement of the radiographs. Measurement errors were estimated according to Dahlberg [5]. The error of duplicate measurements was generally small.

For each variable, the mean value and standard deviation were calculated. "Microsoft Excel" computer programme was used to determine the statistically significant differences between parametres.

## Results

The results of cephalometric analysis of five men with sex reversal syndrome are summarised in Table 1. Growth retardation tendency in comparison to normal men could be seen (Table 2). Mean values of all parametres measured in men with sex reversal syndrome were decreased in relation to normal men. However, the extent of decrease varied and ranged from insignificantly small, for anterior cranial base 3% ($p$=0,252) and posterior cranial base 4% ($p$=0.089), to

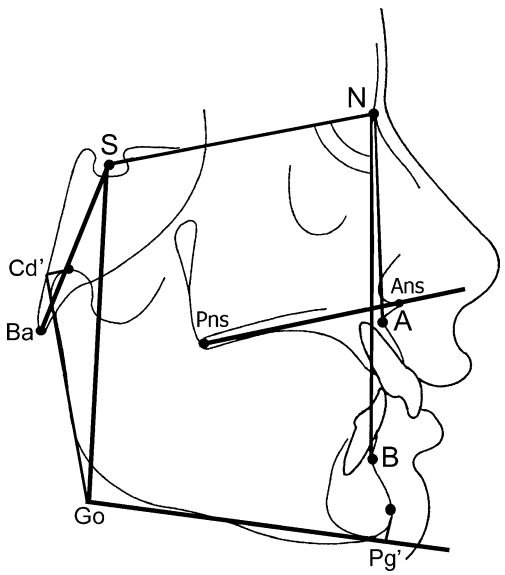


**Fig. 1** Linear and angular measurements used for cephalometric analysis: *N–S* (anterior cranial base), *S–Ba* (posterior cranial base), *Ans–Pns* (maxillary base length), *Go–Pg*' (mandibular base length), *Go–Cd*' (ascending ramus length), NSBa (basal angle), SNA (maxillary prognathism), SNB (mandibular prognathism), ANB (sagittal jaw relationship)

**Table 1** Individual measurements for men with 46, XX chromosomal constitution

| Case Measurements | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Mean value |
|---|---|---|---|---|---|---|
| N–S (mm) | 79 | 76 | 75 | 74 | 73 | 75.4 |
| S–Ba (mm) | 53 | 51.5 | 47 | 51 | 50 | 50.5 |
| Ans–Pns (mm) | 58.5 | 49 | 50.5 | 58.5 | 53.5 | 54.0 |
| Go–Pg' (mm) | 78.5 | 72.5 | 75.5 | 77.5 | 82 | 77.2 |
| Go–Cd' (mm) | 66.5 | 78.5 | 59 | 62.5 | 76 | 68.5 |
| NSBa (°) | 123 | 126 | 126 | 124 | 125 | 124.8 |
| SNA (°) | 81.5 | 77 | 78 | 80 | 81 | 79.5 |
| SNB (°) | 78 | 79.5 | 79 | 78 | 78 | 78.5 |
| ANB (°) | 3.5 | −2.5 | −1 | 2 | 3 | 1.6 |

10.5% for maxillary base length ($p$=0.005), 9.4% for mandibular base length ($p$=0.023) and 5.5% ($p$<0.001) for ascending ramus length (Fig. 2). In comparison to men with Klinefelter's syndrome, no significant difference was found in linear dimensions, with one exception; mandibular base length was shorter for about 10% ($p$<0.001) in men with sex reversal syndrome (Fig. 2). In relation to normal women who possess the same chromosomal constitution as men with sex reversal syndrome, cranial base lengths, both anterior and posterior, were increased in the syndrome group, 4.3% ($p$<0.001) and 6.4% ($p$<0.001), respectively (Fig. 2). Ascending ramus length was longer for about 10% in the syndrome group ($p$<0.001), but negligible differences were found in the length of maxillary ($p$=0.935) and mandibular base ($p$=0.658) between men and women with 46, XX karyotype (Fig. 2).

Angular measurements showed that the basal angle was smaller in the syndrome group than in normal men ($p$=0.015) and women ($p$=0.018), mean value of 124.8±1.3° (Table 2). This value was very similar to that in men with Klinefelter's syndrome, mean value, 123.3±6.0°. Craniofacial characteristics typical for men with Klinefelter's syndrome, such as maxillary prognathism (SNA angle), mandibular prognathism (SNB angle), and deviated sagittal jaw relationship (ANB angle), were absent in men with sex reversal syndrome (Table 2).

## Discussion

Studies dealing with craniofacial morphology in individuals with sex chromosome aneuploidies are rare in orthodontic literature. The majority of published papers are focused on the analysis of Turner's syndrome characteristics as an interesting abnormality in chromosomal constitution [3, 4, 11, 16].

Only a few articles examining aetiologic factors of sex reversal syndrome were published [6–8, 10, 18]. Craniofacial development in these individuals was rarely investigated, although there are some findings indicating smaller permanent teeth in XX males compared to control group of men and resemblance in tooth size with normal females [15]. Fechner et al. [10], Alvesalo and de la Chapelle [1], Micic et al. [13] and Varrela [18] found that most of the anthropometric dimensions of men with sex reversal syndrome are smaller than those of normal males.

Due to rare occurrence of sex reversal syndrome in population (1 in 20,000–25,000 male births), only five persons were included in this study. Although the size of the sample is statistically inadequate, results obtained in this study could be a valuable contribution to better understanding of growth tendencies in males with sex reversal syndrome. Namely, a comparative study involving men with 46, XX karyotype, men with Klinefelter's syndrome and normal men and women could be helpful

**Table 2** Linear and angular measurements used in cephalometric analysis

| Measurements | 46, XY male | 46, XX male | 47, XXY male | 46, XX female | Error of measurement |
|---|---|---|---|---|---|
| N–S (mm) | 77.3±3.5 | 75.4±2.3 | 74.5±3.2 | 71.5±2.8 | 0.51 |
| S–Ba (mm) | 51.7±3.4 | 50.5±2.2 | 50.8±3.3 | 46.6±2.9 | 0.57 |
| Ans–Pns (mm) | 60.3±4.0 | 54.0±3.9 | 55.0±3.9 | 54.7±2.5 | 0.42 |
| Go–Pg' (mm) | 85.2±5.9 | 77.2±3.6 | 85.7±3.9 | 79.6±4.4 | 0.49 |
| Go–Cd' (mm) | 72.5±3.3 | 68.5±6.4 | 67.5±4.7 | 62.5±4.7 | 0.59 |
| NSBa (°) | 128.7±4.9 | 124.8±1.3 | 123.3±6.0 | 130.8±5.5 | 0.66 |
| SNA (°) | 81.9±3.7 | 79.4±2.2 | 85.2±3.7 | 81.4±3.6 | 0.37 |
| SNB (°) | 79.2±3.5 | 78.5±2.1 | 85.5±4.4 | 78.7±3.6 | 0.73 |
| ANB (°) | 2.8±2.4 | 1.6±2.1 | −0.3±3.1 | 2.7±2.4 | 0.10 |

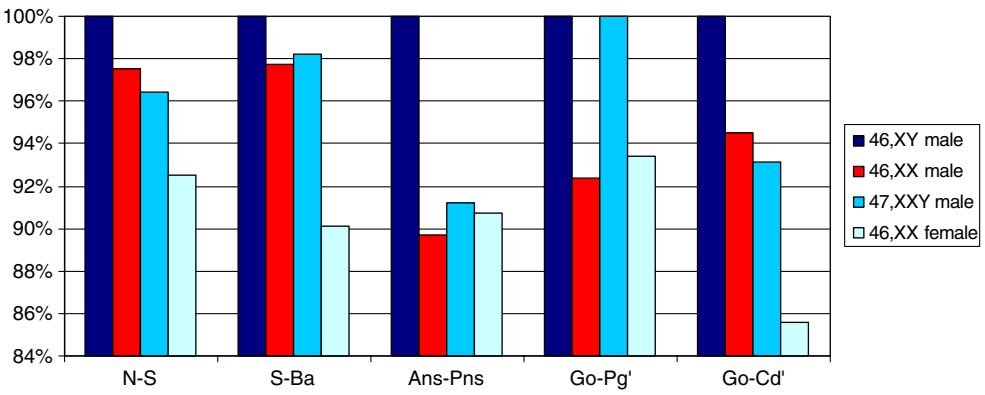


**Fig. 2** Graphic presentation of linear measurements in percentages

in clarifying the role of sex chromosomes in controlling craniofacial morphology.

Variation of the same linear and angular dimensions measured within the group of men with sex reversal syndrome could be explained by the fact that craniofacial morphology is a polygenic trait, with complex growth control in which various genetic as well as environmental factors are involved. There was no important scattering of the analysed parametres within the group of men with 46, XX karyotype, with the exception for ascending ramus length.

Mean values of length of both anterior and posterior cranial base in men with sex reversal syndrome were found to be between mean values of normal men and women and were very similar to those in men with Klinefelter's syndrome (Table 2). This finding, together with increased flexion of cranial base found in both men with 46, XX and 47, XXY karyotype, leads us to the conclusion that two X chromosomes in men, regardless of Y chromosome presence or absence, represent a dominant factor in controlling cranial base morphology.

Dimensions of both upper ($p$=0.005) and lower jaws ($p$=0.023) in men with sex reversal syndrome were decreased for about 10% when compared to normal men. However, very similar mean values of maxillary and mandibular base length in men with sex reversal syndrome and normal women were registered, suggesting the importance of sex chromosome constitution in controlling the capacity of jaw growth.

The presence of a Y chromosome could be considered responsible for increased growth potential. In the case of mandibular base length, the growth stimulatory effect of Y chromosome remains preserved regardless of the number of X chromosomes (one or two). This is supported by the fact that mean values of mandibular base length are almost identical in men with 46, XY and in 47, XXY karyotype. On the other hand, in the case of maxillary base length, growth stimulatory effect of the Y chromosome seemed neutralised because negligible difference was found in the length of maxillary base within groups of men with sex reversal syndrome (46, XX), normal women (46, XX) and men with Klinefelter's syndrome (47, XXY). Although ascending ramus length was shortened in men with sex reversal syndrome in relation to normal men ($p$<0.001), due to large individual variations within the group, the results obtained are not taken into consideration.

The increased cranial base flexion found in men with 46, XX karyotype, when compared to the relationship between cranial base flexion and jaw position in normal individuals [4] and in patients with X-chromosome aneuploidy [3], would point to prognathism. However, both maxilla and mandible were mainly orthognathic in men with sex reversal syndrome.

Our comparative cephalometric study revealed no distinct craniofacial characteristics, except for the increased cranial base flexion, in men with sex reversal syndrome. Despite resemblance of physical properties between men with sex reversal syndrome and men with Klinefelter's syndrome, major craniofacial characteristics of men with 47, XXY karyotype, such as bimaxillary prognathism and deviated sagittal jaw relationship, were absent in men with 46, XX karyotype. This can be explained by the fact that specific craniofacial morphology arises due to sex chromosome imbalance rather than the presence of two X chromosomes in men.

## Conclusion

A clear tendency of reduction in almost all linear and angular cephalometric measurements in five males with 46, XX chromosomal constitution in comparison to men with normal (46, XY) chromosomal constitution and decrease of SNA and SNB angles compared to the group with Klinefelter's syndrome could be observed.

Our results suggest that variations in craniofacial dimensions between groups are connected to changes in the number and constitution of X and Y chromosomes.

Although a common growth pattern in patients with sex reversal syndrome is found in this study, no valid conclusion regarding this subject can be made due to inadequate size of the sample.

In order to come to statistically relevant conclusions regarding the influence of sex chromosomes on craniofacial morphology, more studies on larger samples are still needed.

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