Erciyes Med J 2021; 43(2): 166–9 • DOI: 10.14744/etd.2020.67915
ORIGINAL ARTICLE – OPEN ACCESS

Chromosomal Evaluation Results for Transgender Individuals and Questioning the Necessity of Karyotyping

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ABSTRACT

Objective: Gender dysphoria is a condition where an individual is discontent with their assigned gender. Karyotyping is a part of the transition period before hormone therapy to detect the biological gender for most professionals in many countries. Thus, we discussed the requirements for chromosomal analysis of individuals with gender dysphoria considering clinical and genetic findings.

Materials and Methods: Karyotype analyses were used to evaluate 67 unrelated individuals.

Results: Five individuals transitioned from male to female, and the rest transitioned from female to male. No chromosomal abnormalities and/or chromosomal rearrangements were observed, except for an individual who had mosaic Turner syndrome.

Conclusion: This study evaluates the results of chromosomal analysis of individuals with gender dysphoria. From the findings of this study and the literature, we suggest that chromosomal analysis is unnecessary unless evidence for another disorder of sex development is found alongside clinical, laboratory, and radiological findings.

Keywords: Transgenderism, karyotyping, genetics, sex chromosome disorders

Cite this article as: Çankaya T, Onur Cura D, Özkalaycı H, Ülgenalp A. Chromosomal Evaluation Results for Transgender Individuals and Questioning the Necessity of Karyotyping. Erciyes Med J 2021; 43(2): 166-9.

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Submitted 14.07.2020

Accepted 05.10.2020

Available Online Date 08.02.2021

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INTRODUCTION

Gender dysphoria (GD) is a condition in which an individual is discontent with their assigned gender. The prevalence is 4.6 in 100,000 individuals; 6.8 for natal males and 2.6 for natal females (1). Karyotyping is a part of the transition period before hormone therapy for most professionals. Chromosomal investigation is required to separate genetically determined intersex from GD in many countries. Besides, the probability of other chromosomal abnormalities has been the subject of curiosity in these individuals (2). Therefore, this study assesses the need for chromosomal analysis of individuals with GD considering clinical and genetic findings.

MATERIALS and METHODS

Participants

Out of a total of 97 individuals who applied to our clinic for chromosomal analysis before gender reassignment surgery, 67 were karyotyped. The medical history and physical examination findings were recorded. They were informed about this genetic analysis and gave written informed consent. This study was approved by the Clinical Research Ethics Committee of Dokuz Eylül University İzmir, Turkey.

Genetic Analysis

Peripheral blood samples were collected into Vacutainer sodium heparin tubes. Lymphocytes were cultured in a RPMI 1640 Medium (Gibco™; Thermo Fisher Scientific, Massachusetts, USA) supplemented with 15% fetal calf serum, phytohemagglutinin, L-glutamine, and penicillin/streptomycin. On the second day of culture, thymidine was added for the synchronization of the cells, and the next day, colcemid was applied to elongate chromosomes after washing using phosphate-buffered saline. Hypotonic treatment was performed using 0.075-M potassium chloride. Fixation was performed using Carnoy's solution. The chromosomes were banded using the G-banding method, and at least 25 metaphases were analyzed between 500 and 700 band level resolutions for each individual.

Statistical Analysis

The data were statistically analyzed using Statistical Package for the Social Sciences (version 24; IBM Corp., Armonk, NY, USA). Statistical comparison of the results was performed using the Mann–Whitney U-test. P values of <0.05 were used to denote statistical significance.

RESULTS

We were able to perform karyotyping on 69% of 97 unrelated individuals. Chromosome analyses of all applicants were normal, except for an individual who had mosaic Turner syndrome. The patient was 165 cm tall and weighed 56 kg, and her physical examination was normal. Hormone levels measured were within the normal reference range. The patient did not have any symptoms of mosaic Turner syndrome, such as ovarian hypofunction and premature ovarian failure. Only five individuals transitioned from male to female (MtF), and the rest transitioned from female to male (FtM). The mean age of the individuals was 24.64±5.13 years (range, 18–41 years). No statistically significant difference in age was observed between the two groups (p=0.227) (Table 1). Medical histories of the applicants showed that pubertal developmental processes were normal. One individual had a primer amenorrhea, and another had hypo-oligomenorrhea. Menstrual irregularity was present in 22.6% of FtM individuals (Table 2). The physical examination findings of all but one individual were normal. The karyotype of this individual was 46,XY, and the individual had gynecomastia, sparse facial and body hair, and micropenis. No participants had any hormonal abnormalities, and most were taking uncontrolled hormone therapy.

Table 1. Mean age status in groups

Gender	n	%	Age, Mean±SD	Sig.
FtM	62	92.5	24.32±4.83	p>0.05
MtF	5	7.5	28.6±7.56	

FtM: Female to male; MtF: Male to female; SD: Standard deviation; n: number; %: Percent; Sig: Significance

Table 2. Menarche age, age, and menstrual cycle irregularities in FtM individuals

	n	%
Menarche age, Age, Mean±SD		
Menstrual irregularity		
Present	14	22.6
Absent	22	35.5
Not available	26	41.9

FtM: Female to male; SD: Standard deviation; n: number; %: Percent

DISCUSSION

Information on karyotype analysis for transgender people is lacking. A review of studies in the literature is shown in Table 3 (2–10).

Recent studies have shown that the ratio of MtF individuals to FtM individuals is 2.6:1, with an increase in the prevalence of transgender individuals (1). In this study, the number of MtF individuals was lesser than that of FtM individuals. This may be due to the male-dominated nature of our country; MtF individuals may have more difficulty in revealing their sexual identity than FtM individuals. Because of social judgment, individuals may question this decision again and postpone realization.

So far, we have learned from studies that Klinefelter syndrome (KS) is the most noteworthy chromosomal aberration (6–9, 11). The prevalence of KS is 223 in 100,000 male births (12). Inoubli et al., Auer et al., Fernandez et al., and Davies et al. have found that 47,XXY chromosomal situation was frequent in the general population (1.2%, 1.2%, 1.13%, and 1.5%, respectively) (6–9). KS is a well-known sex chromosome abnormality, which has been described by Harry Klinefelter with a group of distinct features (13). Most patients show clinical symptoms such as hypospadias, small phallus or cryptorchidism, and gynecomastia. In this study, we could not detect KS. This may be due to the small number of MtF individuals in this study.

In the FtM group in this study, an individual had mosaic Turner syndrome. The karyotype result was consistent with 46,XX-[47]/45,X[3], and the result has been evaluated as low-level mosaicism. The presence of the 45,X cell line in phenotypically normal women makes interpretation difficult. X aneuploidy detected in peripheral blood cells below 10% has been reported to generate no reproducible problems in these women (14). Furthermore, mosaicism rates display tissue-specific differences (15). Because of this situation, we planned to perform chromosome analysis from a different tissue.

The fact that most individuals in this study have begun using hormone therapy without consulting physicians is an indication of their severe dissatisfaction with their appearance and determination. Before hormone therapy, the reason for chromosome analysis to seek gender reassignment is the need to exclude chromosomal abnormalities such as KS, which is a predisposing factor for hormone-sensitive tumors, and another reason for karyotyping is to exclude disorders of sex development (DSD) (1), whereas detailed physical examination, laboratory and radiological evaluation, and history of pubertal development are instructive in many cases.

There are some rules in approaching balanced chromosomal rearrangements such as inversions and translocations. Parents should be assessed and analyzed to clarify the situation. If one of the parents carries the same chromosomes, it can be considered low risk. In addition, genetic counseling is needed due the risk of the child having unbalanced chromosomes. Fernandez et al. have detected pericentric inversions of chromosome 2 in three individuals. This inversion is not associated with an increased risk of live births with mental retardation and/or congenital abnormalities, but a twofold risk of spontaneous miscarriage was associated with unbalanced chromosome segregation (16). Furthermore, they found two pericentric inversions of chromosome 12 and five pericentric inversions of chromosome 9. However, they did not mention the parental origin of these rearrangements and the clinical background of the individuals. Additionally, in the study by Bağcaz et al. (10), an individual with a complex chromosomal rearrangement containing three separate chromosomes was reported.

One of the results of Fernandez et al. was mosaic t(9;22), which is related to chronic myeloid leukemia (CML). The relationship of this translocation with CML rather than GD is a condition that should not be overlooked during clinical management.

Table 3. Chromosome evaluations in the literature and our results

Publication	Number of people	Abnormal karyotypesMtF	Abnormal karyotypes FtM	Frequency of chromosomal abnormalities (%) MtF/FtM /Total
Hengstschläger et al. (2003) (2)	61 (30 MtF/31FtM)	46,XY,t(6;17)(p21.3;q23)	–	3.34/0/1.64
Bearman et al. (2007) (3)	400	?	?	-/-/2.5
Wylie and Steward (2008) (4)	52 (46 MtF/6 FtM)	47,XYY[42]/46,XY[8]	–	2.17/0/1.92
Vujovic et al. (2009) (5)	147 (71MtF/76 FtM)	-	–	0/0/0
Inoubli et al. (2011) (6)	368 (251 MtF/117 FtM)	47,XXY (3 cases) 45,XY,der(14;21) 45,XY,t(14q22q) 47,XY,+mar[4]/46,XY[6] 46,XY,t(1,8)(q42;q24.3)[12]/46,XY[5] 46,XY,dup(3)(q25.31q26.31)	46,XX,t(5;14)(q11.2;q13)	3.19 /0.85/2.45
Auer et al. (2013) (7)	139 (83 MtF/56 FtM)	47,XXY	45,X[10]/47,XXX[6]/46,XX[98] 45,XXder(14;22)(q10;q10) (2 cases)	1.2/5.36/2.88
Davies et al. (2018) (8)	200 MtF	47,XXY (3 cases)	–	1.5/-/1.5
Fernández et al. (2018) (9)	717 (444 MtF/273 FtM)	47,XXY (3 cases) 46,XY/47,XXY (60%/40%) 47,XYY/48,XXYY (90%/10%) 46,XY,Yqh- (2 cases) 46,XY, inv(9)(p11q12) 46,XY, inv(2)(p11q13) 45,XY, t(13;14)(q10:q10) 46,XY/46,XY, t(9;22)(q34;q11) (60%/40%)	46,XX, inv(12)(p11q21) (2 cases) 46,XX, inv(9)(p11q12) (4 cases) 46,XX, inv(2)(p11q13) (2 cases)	2.48/2.93/2.65
Bağcaz et al. (2019) (10)	217 (63 MtF/154 FtM)	–	47,XX,+mar 47,XX,+ idic(15)(q12) 46,XX, t(3;5;6)(q11;q11.1;p11.1) 46,XY	0/2.6/1.84
Our results	67 (5 MtF/62FtM)	-	46,XX[47]/45,X[3]	0/1.61/1.49

CONCLUSION

As Bağcaz et al. have emphasize (10), we also suggest that no chromosomal analysis is necessary unless there is an evidence for another sex development disorder, as clinical, laboratory, and radiological findings are sufficient to assess the biological gender of individuals. The necessity of chromosome analysis for these individuals should be evaluated again in terms of financial burden and work force.

Ethics Committee Approval: The Dokuz Eylül University Clinical Research Ethics Committee granted approval for this study (date: 24.05.2018, number: 2018/13-09).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – TÇ, DOC, HÖ, AÜ; Design – TÇ, DOC, HÖ, AÜ; Supervision – TÇ, DOC, HÖ, AÜ; Materials – TÇ, DOC, HÖ; Data Collection and/or Processing – DOC, HÖ; Analysis and/or Interpretation – TÇ, DOC; Literature Search – DOC, HÖ; Writing – TÇ, DOC, HÖ; Critical Reviews – TÇ, AÜ.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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