

Chromosome Analysis in the Assessment for Gender Affirmation Process: A Retrospective Study



Arda BAĞCAZ¹, O. Koray BODUROĞLU², Koray BAŞAR³

SUMMARY

Objective: Gender dysphoria refers to the experienced discomfort related to the incongruence between gender identity and the sex assigned at birth. Current treatment approach for this clinical condition is gender affirmation procedures. International guidelines about gender affirmation do not recommend routine genetic evaluation. In Turkey, provision of health insurance for medical expenses incurred by these procedures requires genetic consultation which frequently involves chromosome analysis (karyotyping). However, the contribution of routine chromosome analysis to the assessment and management of gender dysphoria is not established. This study aims to assess the results of chromosome analysis and its effect on the management of gender dysphoria.

Method: The completed chromosome analysis results and observational records of 217 individuals among a total of 281 evaluated for gender affirmation in the psychiatry polyclinic were investigated retrospectively.

Results: The chromosome analysis results of 213 (98.2 %) of the 217 individuals investigated were congruent with the sex assigned at birth. Variations were found in the karyotypes of 4 individuals with female sex assigned at birth, only 1 of whom had been diagnosed with a disorder of sex development. In the other cases, however, chromosome analysis did not affect the diagnosis or the clinical intervention.

Conclusion: Finding that routine chromosome analysis during the assessment for gender affirmation process rarely affected the clinical diagnosis and the treatment was consistent with the reports of previous studies and supported the recommendation that chromosome analysis should be carried out only in cases where history, physical examination and the required imaging investigations suggested a disorder sex development.

Keywords: Gender reassignment procedures, gender dysphoria, karyotyping

INTRODUCTION

Gender identity is the perception and identification of oneself in a particular gender. At birth, sex is assigned on the basis of individuals' physical properties. Some individuals' gender identity is not congruent with the sex assigned at birth. Defending the existence of gender in two categories with distinct physical, mental and social aspects, determined by somatic sex characteristics, especially the genitals is defined as the gender binary (Drescher 2015). Gender binary requires the individual to self-identify within the resultant duality of male or female identity. In the societies where this way of thinking

is pervasive, gender identities and expressions diverging from the gender assumed based on physical properties are widely disapproved. The discomfort experienced due to the incongruence between the sex assigned at birth and the gender identity is called gender dysphoria (Fisk 1974).

In the classification systems of mental disorders, gender dysphoria first appeared in the DSM-III (1980), in the categories of "Transsexualism" and "Gender Identity Disorder of Childhood" (Drescher et al. 2012). The long term diagnostic use of the criteria of "Gender Identity Disorder" in DSM IV-TR and 'Transsexualism' (F64.0) in ICD-10 has been criticised for contributing to stigmatization, and

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¹Specialist, Ankara Physical Treatment and Rehabilitation Education and Research Hospital, Department of Psychiatry, ²Prof., Hacettepe University Faculty of Medicine, Department of Pediatrics, Division of Genetics, ³Assoc. Prof., Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey.

e-mail: ardabagcaz@hotmail.com

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preserving the representations of gender binary (Drescher 2015). Taking these critics into account, in DSM 5 “Gender Dysphoria” diagnosis category was defined by considering the variability of gender identity, which includes different degrees of incongruence between gender identity and sex assigned at birth (American Psychiatric Association 2013). In the recently published ICD-11, the category of “Gender Incongruence” was constituted and this diagnosis was removed from the mental disorders group and included in the conditions related to sexual health (World Health Organization 2018).

Manifestations of gender dysphoria can emerge in early childhood with the wish to dress, appear and behave in congruence with the experienced gender identity (Ristori and Steensma 2016). Within the experiences of physical, social and emotional changes which occur in adolescence, dysphoria in these individuals is often associated with both genitals and secondary sex characteristics such as facial and body hair, breast development congruent with assigned sex at birth; they either want to get rid of some of these features or wish them to change (Leibowitz and de Vries 2016). Accompanying mental difficulties also increase during this period. In adulthood, some individuals express their gender identity partially by clothing and behaviours in accordance with individual’s developmental skills, reactions from environment and opportunities (Byne et al. 2018). For this reason, conflicts often arise within the family, at school or at work usually (Başar et al. 2016). In some cases, expression of the gender identity can be deferred for long periods. Whereas some individuals try to live with gender expressions with different degrees of congruence with their gender identity, eluding traditional gender roles (Devor 2004, Başar and Yüksel 2014).

The current treatment approach for gender dysphoria, gender affirmation process, is to align the physical sex characteristics to the individual’s gender identity through a multidisciplinary process including detailed mental, physical and social evaluation (Coleman et al. 2012). During the gender affirmation process, long-term hormone treatment and surgical interventions are implemented in a comprehensive transition plan which is developed to be optimally appropriate for the individual by evaluating individual’s demands, medical conditions, the legal process, personal and environmental opportunities and restrictions (Başar and Yüksel 2014). Mental health professionals play an important role in every step of this process. The practices of health professionals during gender affirmation processes are regulated by international guidelines. The most common used guideline is the “Standards of Care”, which is periodically updated and published by the World Professional Association for Transgender Health (WPATH) (Coleman et al. 2012). Standards of Care recommends that gender dysphoria should be evaluated comprehensively by a mental health professional with specific qualities or another health professional with

sufficient training on mental disorders if working within a team. Gender Dysphoria is a clinical diagnosis for which there is not any recommended laboratory study or genetic analysis (Coleman et al. 2012). Apart from the diagnostic interviews, the assessment includes exploring the individual’s gender identity, managing the adverse effects of gender dysphoria and of stigmatization on mental health, ensuring awareness of the internalized transphobia, increasing social support, and psychological practices targeting improvement in the individual’s body image and resilience. Based on this assessment and transition plan, hormone treatment to change physical appearance, surgical interventions for changing primary and secondary sex characteristics (for breasts, internal and external genitals, facial features and body shape) are applied (Coleman et al. 2012). Most recent guideline on endocrinological approach to the transition process was prepared by the American Endocrine Society (Hembree et al. 2017). In this guideline as well, specific laboratory evaluations have not been outlined for assessment.

The diagnosis of “Gender Identity Disorder” according to DSM IV-TR and ‘Transsexualism’ (F64.0) according to ICD-10 (American Psychiatric Association 2000, World Health Organization 1992) require the absence of any disorder of sex development. However, if there is an accompanying disorder of sex development, it is only noted as a specifier for the diagnosis according to “Gender Dysphoria” category of DSM 5 (American Psychiatric Association 2013).

Disorders of sex development encompass congenitally acquired chromosomal, gonadal or anatomically atypical physical features related to sex (Hughes 2008). The classification proposed for disorders of sex development is shown in Table 1. While there is only limited data about the prevalence of disorders of sex development diagnosed with chromosome analysis, the incidence have been reported as 1:20000 for 46,XY disorders of sex development, 1:14.000-15.000 for 46,XX disorders of sex development, 1:10000 for testicular or mixed gonadal dysgenesis, approximately 1:2500 for Turner syndrome, between the range of 1:5000 and 1:10000 live birth for Klinefelter syndrome (Lee et al. 2016). When all disorders of sex development are included, the prevalence is predicted to reach to 1.7% (Fausto-Sterling 2000).

Since the development of the external genitalia differ from those expected for the two genders, a significant number of the disorders of sex development can be recognized with ultrasonography during pregnancy or soon after birth. The rest are frequently diagnosed during adolescence as secondary sex characteristics do not follow their expected developmental course. It is known that this diagnosis could often have been made until adulthood (Lee et al. 2016).

Table 1. The Classification of Disorders of Sex Development (DSD)

Sex Chromosome DSD	46, XY DSD	46, XX DSD
47,XXY (Klinefelter Syndrome and variants)	Disorders of testicular development (Gonadal dysgenesis)	Disorders of ovarian development (Gonadal dysgenesis)
45,X (Turner Syndrome and variants)	Disorders of androgen synthesis or action (e.g. Androgen Insensitivity Syndrome)	Androgen excess (e.g. Congenital Adrenal Hyperplasia)
45,X/46,XY (Mixed gonadal dysgenesis)	Other (Syndromic associations, anatomic or endocrine anomalies)	Other (Syndromic associations, anatomic or endocrine anomalies)
46,XX/46,XY (Chimerism)		

(This is the classification proposed at the Chicago Consensus with the contribution of the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society in 2005. The table is adapted from Hughes, 2008.)

When individuals diagnosed with disorders of sex development early in life are followed up, variations are observed in gender identity development. For example, it is expected that 95% of 46,XX disorders of sex development develop female gender identity, also people with androgen insensitivity syndrome and 46,XY luteinizing hormone (LH) deficiency often develop female gender identity (Lee et al. 2016). It is reported that among people with 5 α -reductase deficiency 60% experience male, 40% experience female gender identity, more than half of people with 17 β -hydroxysteroid dehydrogenase 3 (17 β -HSD3) deficiency identify as male (Lee et al. 2016). Due to this variability in the course of gender identity development, in people diagnosed with disorders of sex development at childhood, early surgical interventions and bringing up styles towards a particular gender may end up with gender incongruence (Meyer-Bahlburg et al. 2004). It was reported that gender dysphoria accompanies 5% of those diagnosed with disorders of sex development (Kreukels et al. 2018). Whereas gender identity related issues are very rare in congenital adrenal hyperplasia in which virilization is apparent and the condition is expected to be diagnosed at childhood or puberty as they lead to distinct anatomic changes, in 5 α -reductase and 17 β -HSD3 enzyme deficiencies gender dysphoria may be prevalent, upto rates of 63% (Furtado et al. 2012). In mixed gonadal dysgenesis, the outcomes related to gender identity cannot be accurately estimated as the cases are very rarely seen.

The prevalence of gender dysphoria is lower in disorders of sex development where the diagnosis of the condition can be delayed to adolescence and early adulthood, in contrast with disorders of sex development which can be diagnosed early in life. There are only case reports about gender dysphoria accompanying androgen insensitivity syndrome and sex chromosome anomalies such as Turner syndrome or Klinefelter syndrome (James et al. 1972, T'Sjoen et al. 2011). When reported cases of gender dysphoria in individuals with DSD who were not diagnosed in their childhood or puberty were assessed in detail, it was seen that there were apparent signifiers of disorders of sex development in anamnesis, physical examination or hormone levels during their

presentation at early adulthood. For example; an individual with Klinefelter syndrome might be assigned male at birth, cryptorchidism and micropenis could be seen at childhood or there could be no recognized anatomic difference. However, there could be clues for identifying these cases at adulthood with medical history and physical examination such as neural/motor development disorders since early childhood, late and less developed or undeveloped secondary sex characteristics like facial or body hairing, gynecomastia, testicular atrophy or hypergonadotropic hypogonadism in laboratory findings (Groth et al. 2013). Cases of Turner syndrome with assigned female at birth, can be detected at the early period of life with delayed puberty, primary or secondary amenorrhoea, physical features such as short stature and webbed neck, comorbidities especially associated with the cardiovascular system and hypergonadotropic hypogonadism in laboratory findings (Saenger et al. 2001).

Chromosome analysis is needed for diagnosing disorders of sex development (Hughes 2008). Whereas, gender identity is a subjective experience of an individual and the declaration of individual is enough for diagnosis of Gender Dysphoria. Mental health specialists have the key role for the problems about gender identity and at this point, anamnesis taken by them is crucial for differential diagnosis. Particularly the individuals whose disorders of sex development diagnosis was missed at childhood or puberty, can apply to mental health specialists for gender identity problems at adulthood (James et al. 1972, Buhrich et al. 1978). In addition to individuals' gender identity, history of sexual development and sexual function must be taken by mental health specialists. In suspected cases with clues of sexual development differing from the expected, with the collaboration of endocrinology specialist, laboratory studies, necessary radiological examination and chromosome analysis when needed, disorders of sex development can be distinguished.

It is known that in European countries such as France and Germany, for the assessment of individuals with gender dysphoria, chromosome analysis is done in addition to physical examination, endocrinological investigation and

imaging methods (Inoubli et al. 2014, Weyers et al. 2009). It was reported that the practical contribution of chromosome analysis which is done routinely in these countries was not known (Auer et al. 2013). Also in Turkey, genetic evaluation and chromosome analysis is done as a part of assessment for gender affirmation process. Costs of the various surgical procedures performed are met by national health insurance system on the basis of presenting a multidisciplinary medical board decision which includes a report by the specialist geneticist, which is perceived as justification for the routine chromosome analysis without ascertained cost-effectiveness and benefits for each case.

In this study, it was aimed to examine the results of chromosome analysis done as a part of the assessment for gender affirmation procedures and its effects on the medical decision process. For this purpose, the results of chromosome analysis done routinely for gender affirmation process were reviewed retrospectively and its effects on clinical assessment and follow-up were evaluated.

METHOD

The medical records of 281 individuals who consulted to Hacettepe University Hospitals Psychiatry Department between January 2008 and August 2017 for gender affirmation procedures were examined retrospectively. Peripheral blood samples, obtained after evaluation of the applicants at the Genetics Department, were analysed by the 400-band resolution GTG staining technique to detect numerical and structural anomalies of autosomal and sex chromosomes. Since 64 out of 281 individuals examined had not completed genetic consultation, it was possible to reach the chromosome analysis results of 217 individuals, 154 female and 63 male assigned at birth.

The files and records of those with chromosome analysis results not congruent with the sex assigned at birth or with

additional chromosomal aberrations were investigated. In these cases, it was investigated whether or not the diagnosis of sexual development disorder could be based on the patient history, the physical examination, imaging examinations and laboratory tests made prior to chromosome analysis. Also, the effects of chromosome analysis results on the clinical diagnoses and the gender affirmation process were evaluated.

RESULTS

The median age of the 217 applicants with completed genetic assessment was 24 years (min-max:17-53) and the median age of the 64 applicants with incomplete genetic assessment was 23 years (min-max:17-46). There was no significant age difference between two groups (U:6040.5, $p=0.113$). The groups also did not significantly differ on the basis of gender distribution ($\chi^2=0.010$, $p=0.919$).

The chromosome analysis results of 213 (98.2%) applicants were congruent with their sex assigned at birth; 150 (97.4%) being 46,XX females and 63 (100%) being 46,XX males at birth. Only 4 cases who were assigned female at birth had variations in their karyotypes (Table 2). Two of these individuals had extra chromosomal segments; one of the karyotype 46,XY, incongruent with the sex assigned at birth and SRY gene deletion detected with further analysis; and one had autosomal translocation.

The medical records of these cases were examined. The chromosomal features detected in three cases did not have any effect on the gender affirmation procedure and it was concluded that chromosome analysis results were without significance to indicate any clinical intervention. In conclusion, among the 217 cases applying for gender affirmation process, only one of them (0.5%) had different sex chromosome structure from the sex assigned at birth and diagnosed as disorder of sex development. Additional clinical and laboratory findings were found in the file reports on this

Table 2. The Cases with Aberrant Results in Chromosome Analysis

Sex Assigned at Birth	Age	Karyotype	Advanced Genetic Investigation	Additional Clinical Findings
Female	22	47,XX, +mar	FISH: marker chromosome belonging to the X chromosome detected.	None
Female	32	47,XX,+ idic(15)(q12) Extra isodicentric 15. chromosome	FISH: Extra isodicentric chromosome does not contain Prader Willi/AS sequence.	None
Female	31	46,XX, t(3;5;6)(q11;q11.1;p11.1)	None	None
Female*	21	46,XY	PCR: SRY (+)	Primary amenorrhoea, increased free testosterone level, absent uterus and ovaries with ultrasonography, presence of bilateral tissues at mons pubis level compatible with testicle parenchyma.

*Disorder of Sex Development (Androgen Insensitivity Syndrome).

FISH: Fluorescence In Situ Hybridization, PCR: Polymerase Chain Reaction

case (Table 2). This individual had applied to psychiatry clinic with gender dysphoria at the age of 21. History of sexual development was noted to reveal that this individual never had menstruation. Endocrinological tests had detected a serum testosterone level above that expected for females. The subsequent ultrasonographic investigation had not detected uterus and ovaries but bilateral tissues compatible with testicular parenchyma were observed at the level of mons pubis. This case had been followed with a preliminary diagnosis of androgen insensitivity syndrome; chromosome analysis had shown the 46,XY karyotype and, finally, the SRY gene was detected by PCR, thereby confirming the diagnosis of androgen insensitivity syndrome. None of the chromosome analysis data on the applicants investigated in this study had effects on the clinical procedures.

DISCUSSION

The results of the chromosome analyses made between the indicated dates in this study had not changed the diagnoses or clinical interventions on the individuals attending psychiatry clinic for gender affirmation procedure except for the single individual who was diagnosed with a disorder of sex development. In adults, developmental history especially on physical changes in puberty, physical examination and laboratory findings can facilitate the diagnosis of disorders of sex development. Therefore, it is believed that advanced genetic analyses performed selectively after clinical evaluation would enable diagnosis in such cases.

In the literature, the study on the subject with the largest population sample, similar to the present study, was reported from Belgium (Inoubli et al. 2011). In this study, applications for gender transition in adulthood were also examined retrospectively, due to the observations that chromosome analysis has limited effect on the process, but their sample differs from the present study as their sample's two thirds consisted of individuals assigned male at birth. In 97.55% of the 363 adults with gender dysphoria, karyotyping was as expected and chromosome analysis showed atypic results in only 9 individuals, of whom 3 had Klinefelter syndrome. Two cases had been diagnosed with Klinefelter syndrome before psychiatric consultation, and one had the preliminary diagnosis of hypogonadism before chromosome analysis. The chromosomal anomalies of the remaining 6 individuals were not associated with disorders of sex development.

In another similar study, chromosome analyses on 270 individuals, 165 of whom were assigned male and 105 assigned female at birth, were reviewed and atypical chromosomal findings were found at the rate of 2.45%, only two cases were diagnosed with disorders of sex development, one having Klinefelter syndrome and the other Turner syndrome with mosaicism (Auer et al. 2013). In this study, the limited

contribution of chromosome analysis to gender affirmation and the identification of the patients requiring chromosome analysis by clinical and endocrinological evaluations were reported. Similar results have been reported in the literature by other studies with less number of participants. In one study, chromosomal aberrations were not detected in a total of 147 participants (Vujovic et al. 2009); and only 1 participant was diagnosed with a disorder of sex development in another study with 52 participants (Hengstschlager et al. 2003). Our results are consistent with these findings.

There are case reports on the comorbidity of gender dysphoria and disorders of sex development including reports of additional symptoms and findings in the medical history, physical examination, hormone levels or ultrasonography of all the cases (T'Sjoen et al. 2011).

In individuals with gender dysphoria, chromosome analysis may be necessary for the purposes of evaluating the diagnosis of sexual development disorders and to achieve differential diagnosis (Hughes 2008). International guidelines on medical practice about gender affirmation procedures do not recommend routine genetic evaluation (Coleman et al. 2012, Hembree et al. 2017). Studies made on individuals with gender dysphoria report that chromosomal anomalies are not frequently found in this group (Futterweit et al. 1986). Also, since the disorders of sex development are often identified at adolescence or earlier, the detailed history taken by the mental health specialist, the laboratory and imaging techniques required before both the hormone therapy and surgical treatments for gender affirmation at adulthood, suggest that routine genetic evaluation is not a necessity.

In Turkey, the view of the consultant geneticist is required to be included in the medical board decision to ensure the support of health insurance for various surgical interventions within the context of gender affirmation. Based on this requirement, routine chromosome analysis is often performed for genetic evaluation. Not only does routine chromosome analysis has limited contribution to patient assessment independently of the clinical history, examination and investigations, but also may have adverse outcomes by subjecting the applicants to unnecessary medical evaluation, and thereby incurring time and financial losses, increasing the burden on the limited laboratory facilities in Turkey and resulting in unnecessary expenditure of national health insurance funds. Finally, although gender dysphoria has no genetic basis which can be detected by chromosome analysis, this practice triggers false expectations and hope in some applicants and family members, especially those who experience difficulty in accepting gender affirmation procedures. For example, doing analysis can give rise to hopes of attributing the present experience about gender identity or expression to a genetic problem or a disease. Subsequently, the failure in detecting

a “disease” or a “genetic problem”, not infrequently, leads to the thoughts of abandoning gender affirmation procedures.

Considering the costs versus benefits, regulations requiring routine chromosome analysis for each adult with gender dysphoria should be revised, due to lack of evidence for the clinical benefits and likely adverse consequences. Moreover, genetic evaluation based on existing regulations does not specifically enforce routine chromosome analysis. Hence, it can be seen that, whether new regulations about chromosome analysis are introduced or not, the approach to act on the view of the expert geneticist without routine chromosome analysis, unless seen necessary after clinical evaluation, appears to be an adequate and cost-effective strategy.

CONCLUSION

The results of this study are consistent with earlier reports, indicating that chromosome analysis rarely has an influence on the diagnosis or clinical interventions included in the gender affirmation procedures at adulthood. It seems to be a more appropriate approach not to perform chromosome analysis routinely, unless the medical history, and the results of physical examination and necessary radiological investigation suggest a disorder of sex development during the assessment for gender affirmation procedures in adulthood.

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