ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

Karyotyping, Is It Worthwhile in Transsexualism?

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ABSTRACT

Introduction. Karyotyping is often performed in transsexual individuals.
Aim. Quantification and characterization of karyotype findings and abnormalities in transsexual persons.
Main Outcome Measures. Karyotypes were listed both in male-to-female and in female-to-male transsexual persons.
Methods. The data were collected through a retrospective study.
Results. Karyotypes of 368 transsexual individuals (251 male-to-female, 117 female-to-male) are described. Normal findings were found in 97.55%. Prevalence of abnormal karyotypes was 3.19% among male-to-female, and 0.85% among female-to-male transsexuals. Nine karyotypes showed variations; Klinefelter syndrome was confirmed in three persons, whereas others displayed autosomal aberrations.
Conclusion. Karyotyping is only of very limited information in the transsexual population. **Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, and T'Sjoen G. Karyotyping, is it worthwhile in transsexualism? J Sex Med 2011;8:475–478.**

Key Words. Karyotyping; Transsexualism; Prevalence; Chromosomal Abnormalities; Klinefelter Syndrome; Disorders of Sexual Differentiation

Introduction

Gender identity disorder (GID) is often a self-diagnosis, confirmed by one or more mental health professionals. In most centers, the diagnostic phase includes contact with the endocrinologist, even before hormonal treatment is started. At the Ghent University Hospital, Belgium, as in many other centers around the world, baseline analyses performed in transsexual individuals typically include clinical examination, endocrinological testing, and karyotyping [1]. Exclusion of chromosomal abnormalities is included in the three criteria proposed by ICD-10 for the diagnosis of transsexualism; this being the reason karyotyping is frequently included in the baseline work-up [2]. The management of persons with disorders of sexual differentiation (DSD) is obviously different than that of persons with GID [3].

Karyotyping has recently officially been recommended in France [4]. However, few karyotype variations have been observed in transsexual populations [5–8]. The current retrospective study describes karyotypes of 368 transsexual individuals.

Methods

Data Collection

The data were collected through the retrospective study of patients' files. The selection of the files was based on a diagnosis of transsexualism in

Table 1 Abnormal karyotypes and clinical background

N = 368; Normal karyotypes: 359 = 243[46,XY]+116[46,XX]

Patient	Transsexualism	Birth year	Karyotype	Clinical background
Patient 1	MtF	1966	47,XXY	Klinefelter syndrome, morbid obesity.
Patient 2	MtF	1977	47,XXY	Klinefelter syndrome.
Patient 3	MtF	1979	45,XY,der(14;21)	Gastric ulcerations, automutilation.
Patient 4	MtF	1961	45,XY,t(14q22q)	
Patient 5	FtM	1983	46,XX,t(5;14)(q11.2;q13)	
Patient 6	MtF	1977	47,XY,+mar[4]/46,XY[6]	Learning and behavior problems, ADHD.
Patient 7	MtF	1961	46,XY,t(1,8)(q42;q24.3) [12]/46,XY[5]	Type 1 diabetes, hypertension, arterial stenosis right leg, gastric ulcerations.
Patient 8	MtF	1985	46,XY,dup(3)(q25.31q26.31)	Strabismus, cryptorchidism, autism, hearing impairment.
Patient 9	MtF	1953	47,XXY	Klinefelter syndrome.

MtF = male-to-female transsexual person; FtM = female-to-male transsexual person; ADHD = attention-deficit hyperactivity disorder.

accordance with International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Only the files containing karyotype results were included in this study.

The study was approved by the Ethical Committee of the Ghent University Hospital.

Karyotyping

All karyotypes were examined in the Center for Medical Genetics of the Ghent University Hospital. Standard chromosome analysis was performed in those patients on cultured lymphocytes with G banding techniques at a resolution of 500–550 bands per haploid genome.

Data Analysis

Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare the prevalence of karyotypes. Statistical significance was interpreted as $P < 0.050$.

Results

Sample Size

Three hundred and sixty-eight karyotypes were extracted from 479 medical files. The reason why in some patients karyotype analysis was not performed is not always clear, and may be related to external referrals or individual doctors and patient's preference for not performing this test. Two hundred and fifty-one karyotypes in male-to-female transsexual persons and 117 karyotypes in female-to-male transsexual individuals were determined.

One person presented as female-to-male transsexual, however with a background of complete androgen insensitivity syndrome. This patient was reported previously by our group and is not included in further analysis [9]. We are aware of one patient with a 47,XYY karyotype who was referred to our center for sex reassignment surgery, but who had a diagnostic work-up elsewhere.

The ratio of male-to-female vs. female-to-male in our patient group was close to 2:1. This confirms the existence of an important socio-cultural influence on this ratio across the world, which remains unexplained yet [5,10].

Karyotypes

In 97.55% we found normal karyotypes, in accordance with the clinical findings. There were 243 male-to-female persons with 46,XY karyotype, and 116 female-to-male individuals with 46XX karyotype.

Table 1 displays the nine abnormal karyotypes detected. Two persons (Patient 1 and 2) were confirmed with Klinefelter syndrome before presentation at our gender clinic, whereas 1 (Patient 9) was diagnosed during baseline examination here because of hypogonadism. Two karyotypes included a robertsonian translocation: one between chromosomes 14 and 21, and one between chromosomes 14 and 22. One karyotype displayed an apparently balanced translocation between chromosomes 5 and 14. Two mosaicisms were also found: some cells from one patient had an extra marker chromosome identified as deriving from chromosome 2, and the majority of another patient cells presented an apparently balanced translocation between chromosome 1 and chromosome 8.

Karyotype Aberrations Prevalence

In this group of transsexual individuals 2.45% karyotype aberrations were found. The prevalence was 3.19% among male-to-female, and 0.85% among female-to-male transsexual persons.

Discussion

We present the largest reported group of transsexual persons with karyotyping results. A frequency of 2.45% of karyotype abnormalities was found in the transsexual group. The frequency of chromosomal aberrations reported in the general population is lower; Maeda et al. found 93 karyotype aberrations (52 in males, 41 in females) corresponding to a prevalence of 0.63% in a series of 14 835 liveborn infants [11]. This frequency is 0.53% ($P < 0.001$) if infants with an abnormal karyotype whom did not survive more than 8 months are excluded (six males and nine females). Interestingly, the prevalence that was found in the current study appears to be quite similar to the previously reported ones [5–8]. Vujovic et al. reported the absence of karyotype abnormalities in 71 male-to-female and 76 female-to-male transsexual persons. Kevan et al. found one abnormal karyotype (47XXY/46,XY) in 46 male-to-female and 6 female-to-male (i.e., 1.92%) transsexual persons, whereas Hengstschläger et al. observed one balanced translocation (1.64%) in a male-to-female transsexual in a group of 30 male-to-females and 31 female-to-males. Bearman reported on 2.5% of variant karyoptypes in "about 400" transsexual persons [8]. In our study, three male-to-female individuals were diagnosed with Klinefelter syndrome, corresponding to a prevalence of 1.20% among male-to-female persons, possibly a spurious finding, but representing a figure significantly higher than expected based on population data ($P = 0.004$). Maeda et al. reported eight diagnoses of Klinefelter syndrome (7[47XXY] and 1[47XXY/46,XY]) corresponding to a frequency of 0.12% [11]. Men with Klinefelter syndrome usually report a male gender identity, but this has not systematically been studied and it is possible that not all karyotype variations have been reported by other gender teams, specifically in relation with the finding of Klinefelter syndrome.

The percentage of abnormal karyotypes found in female-to-male persons (0.85%) seemed lower than in the male-to-female population (3.19%), but the difference was not significant ($P = 0.282$). No karyotype abnormalities were reported in larger cohorts of female-to-male transsexuals [5–8].

Patient 6 (see Table 1) presented a mosaicism with an extra marker chromosome 2 composed of euchromatic material derived from centromere-near sequence 2p11.2 to sequence 2q13. Clinical consequences of this very rare aberration (a dozen of cases have been reported) are described as inconsistent, but Mrasek et al. previously observed an association between the presence of sequence 2p11.2 and clinical abnormalities [12]. Indeed this patient presented behavior problems and learning troubles associated with an attention-deficit hyperactivity disorder. However, no other case of transsexualism associated with a supernumerary marker chromosome 2 has previously been published. One person (Patient 8) showed a duplication of material derived from sequence 3q25.31 to sequence 3q26.31 of chromosome 3. This male-to-female transsexual person was also diagnosed with strabismus, autism, hearing impairment, and cryptorchidism. There was no associated disease in any of the other patients with chromosomal variations, except for hypogonadism in the patients with Klinefelter syndrome.

Conclusions

Karyotyping has been part of baseline testing before entering the hormonal phase of the transition process in several multidisciplinary gender teams, as ICD-10 states that GID must not be a symptom of a chromosomal abnormality [2]. No karyotype aberration has ever been linked to transsexualism. Moreover as karyotyping has a cost, this study challenges its systematic testing in transsexualism. Prevalence of chromosomal abnormalities in the transsexual population appears to be slightly higher than in the general population, particularly in male-to-female transsexual persons; a statement that holds if the patients with Klinefelter syndrome would be excluded. Some could argue that testing is mandatory to exclude DSD, but other clinical signs, or hormonal test results are typically observed in DSD patients [3]. In conclusion, in the absence of specific clinical signs associated with DSD, karyoptyping is only of very limited information in the transsexual population.

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