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Genetic Counseling and Testing Prior to Assisted Reproduction

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Genetic Counseling and Testing Prior to Assisted Reproduction

S. Markus¹, U. Hehr²

Chromosomal aberrations and monogenic conditions contribute to the heterogeneous etiology of male as well as female sub- or infertility and result in an overall increased risk for congenital malformations, developmental problems or monogenic disorders in the offspring after assisted reproduction when compared to the general population. Therefore, genetic counseling and testing has been implemented in the routine workup prior to assisted reproduction and should be individually assigned based on provided medical and anamnestic data of the couple and their close relatives. Here we provide an overview on the current clinical and genetic data regarding chromosomal as well as monogenic conditions most frequently observed in couples with sub- or infertility as well as practical considerations and recommendations to implement appropriate genetic workup in the routine diagnostic procedures prior to assisted reproduction and during subsequent pregnancies. **J Reproduktionsmed Endokrinol 2009; 6 (1): 6–10.**

Key words: assisted reproduction, genetic counseling, chromosomal aberrations, AZF, CFTR

■ Introduction

Couples with fertility problems carry a significantly increased risk for congenital malformations or developmental problems in their offspring when compared to the general population [1]. Furthermore, chromosomal abnormalities as well as single gene defects and/or monogenic or multifactorial syndromes and disorders may directly interfere with fertility [2]. Therefore, genetic counseling has been established as part of the routine workup of couples planning to undergo assisted reproduction (see current guidelines of the Richtlinie der Bundesärztekammer zur Durchführung der assistierten Reproduktion [3]). According to those German guidelines a genetic counseling should be offered to all couples with known chromosomal aberrations and/or potentially genetic disorders, mental or physical impairment or malformation syndromes in one of the partners and/or their relatives ([3]; s. paragraph 3.2.1)

Independent of the family history particular clinical findings, e.g. azoospermia, a suspected classic or late onset form of adrenal hyperplasia or premature hypergonadotropic ovarian failure as well as recurrent pregnancy loss should prompt an offer for further genetic workup in a genetic counseling session [2, 4].

During a genetic counseling session relevant medical data of both partners and

their close relatives are collected and a pedigree over three generations is drawn. Specific as well as general risks are discussed and all relevant data summarized in a medical report for the referring physician and the couple. Based on the collected data specific genetic testing is offered, which may include all or some of the following tests.

■ Karyotyping

Regardless of the cause of infertility several studies have consistently shown an increased frequency of chromosomal aberrations in both partners (reviewed in [2]). Observed chromosomal aberrations include balanced translocations, numerical aberrations involving the sex chromosomes as well as marker chromosomes or microscopically visible Y chromosome deletions. Overall, chromosomal abnormalities are about 10 to 15 fold more frequently observed in subfertile males when compared to the general population, with an inverse correlation between sperm count and observed frequency of chromosomal aberrations. However, an increased rate of chromosomal aberrations was even observed in the presence of sperm concentrations above 20 Mio/ccm, hence these data do not support a particular sperm count as cut off level. The frequency of chromosomal abnormalities in female partners of subfertile/infertile couples is likewise increased and was reported between 3.3–9.8 %. These current data warrant a chromosome analysis of both

partners regardless of sperm count and planned technique of assistant reproduction; prior informed consent is required and should be documented.

Of particular interest is the **Ullrich-Turner syndrome (UTS)** resulting from a karyotype 45,X in all cells (classical UTS) or a subset of cells (mosaic) as pure gonosomal aneuploidy or as part of complex rearrangements involving segments of the X chromosome e.g. as ring chromosome, p- or q-arm deletions or of other chromosomes, in particular the Y chromosome.

UTS is observed with a frequency of 1:2,500 female newborns, but usually only recognized due to growth retardation in the early school years ultimately resulting in short stature. Many females however are only recognized during workup of a primary amenorrhea and/or infertility, where patients with the classic UTS phenotype present with the combination of short stature, hypergonadotropic hypogonadism and streak gonads. The habitus may be compact with broad chest and widely spaced nipples, webbed neck, renal and cardiac anomalies are associated features.

In the presence of a constitutional karyotype 45,X ovarian failures usually excludes offspring from own germ cells. However, successful pregnancies have been reported after egg donation and it has been suggested, that cryopreservation of primary follicles after surgical

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resection of the ovaries at an early age may perhaps preserve the option of genetical parenthood in some patients [5, 6].

Patients with mosaic karyotypes display a wide spectrum of milder phenotypes up to phenotypically normal women with regular period, ovulation and spontaneous conception are possible. However, menopause may occur prematurely due to premature ovarian failure [7].

Whether or not women with constitutional or mosaic 45,X karyotypes carry an increased risk for gonosomal aberrations in their offspring, is still under debate. However, when discussing the option of a prenatal diagnosis in this context the ethical issue of the potential consequences in case of a fetus with 45,X or 47,XXX or 47,XXY warrant caution.

Structural aberrations of the X chromosome (e.g. deletions) warrant special attention, because e.g. in combination with a Y chromosome from the father a partial monosomy X with severe impact on intrauterine development and adverse outcome may result [7].

In the presence of Y chromosome segments female patients need to be counseled about an increased risk for gonadoblastoma and early gonadectomy is recommended with thorough histologic examination to exclude microcarcinoma [8].

In contrast, in a relevant subgroup of women without UTS phenotype and with normal reproductive findings gonosomal aberrations, e.g. cells with 45,X and/or 47,XXX are observed and need to be distinguished from those women with classic or mosaic UTS phenotype.

It is known, that such numerical aberrations involving the sex chromosomes (both X and Y) increase over time. However, chromosome analysis of short time lymphocyte cultures are purely descriptive and allow not to distinguish, whether this observation represents mosaicism solely present in blood cells, a true mosaicism also affecting other tissues or finally may be artificially generated during the process of cell division in the tissue culture medium. It has been suggested, that the observation of up to

10 % of such cells in "normal" women may most likely be without clinical relevance for the women itself as well as for her offspring [7].

Whether the observed increase of such low grade gonosomal mosaicism in cohorts of female partners of sub- or infertile couples may only result from the increased age of this population when compared to control samples or perhaps reflect low grade true mosaicism at least in some of these patients, remains unresolved.

But based on current knowledge those results should be transferred to the respective patients very cautiously, as they may create anxiety without obvious evidence for any clinical relevance for the patients itself or their offspring.

The **Triple-X syndrome** with the karyotype 47,XXX has an estimated incidence of one in 800 to 1,000. Two thirds of the affected girls and women are without any clinical features. Learning problems and psychotic disturbances are more common in the latter third [9]. Fertility may be reduced in case of premature ovarian failure. There is no significantly increased risk for chromosomal imbalance in the offspring [7].

Klinefelter syndrome with the karyotype 47,XXY is the most frequent numerical gonosomal aberration in males with an incidence of 1 in 500. In childhood learning difficulties and passive behaviour are well known problems. Many patients are only recognized during the clinical and genetic workup of infertility. Affected males typically show a hypergonadotropic hypogonadism and azoospermia. After puberty testes remain small and a tall stature with female fat distribution and gynecomastia are frequently observed. There is an increased risk for osteoporosis and breast cancer, testosterone substitution should be offered [9]. Beside the 47,XXY karyotype other variants of mosaic karyotypes, e.g. 46,XY/47,XXY are documented. Those patients with mosaic karyotypes may have some residual spermatogenesis, presenting e.g. as oligozoospermia. Quite a few patients underwent testicular sperm extraction (TESE), for some of them sperm cells could be retrieved and intracytoplasmatic sperm injection (ICSI) was per-

formed. Up to now most of the offspring showed normal chromosomes, but a slightly increased risk for gonosomal aberrations has to be discussed. Tachdjian et al. 2003 published a study of 38 pregnancies. In 36 cases there was a normal karyotype, while in two offspring a karyotype 47,XXY reported [7, 10, 11].

Deletions of the Y-chromosome appear cytogenetically as a partial loss of chromosomal material or may result from submicroscopic deletions/rearrangements, which are only detected by molecular genetic evaluation [2]. Depending on the deleted chromosomal region there can be infertility despite a normal male phenotype [7].

Balanced autosomal rearrangements are more frequently observed in subfertile couples. These include reciprocal translocations with exchange of chromosomal material between two non homologous chromosomes without microscopically visible loss or gain of chromosomal material (Fig. 1). Balanced Robertsonian translocations result from fusion of two acrocentric chromosomes within their p arms (Fig. 2). Both, Robertsonian or reciprocal balanced autosomal translocations are usually without clinical relevance for the proband itself – despite possible effects on their fertility and their offspring resulting from unbalanced translocations passed on with the gametes – chromosomal imbalances may also occasionally be observed and usually result in particular clinical features. The resulting derivative chromosomes may be passed on over several generations as balanced translocations without any impact on development or health of their carriers [7].

However, during meiosis with exchange of chromosomal material between homologous chromosomes, gametes with an unbalanced translocation may result and subsequently affect intrauterine and postnatal development. The increased frequency of such balanced translocations in both partners of subfertile couples implies a direct impact at least of some translocations on gamete function, which may present as decreased rate of fertilized egg cells during assisted reproduction and/or disturbed early embryonal development with subsequent pregnancy loss.

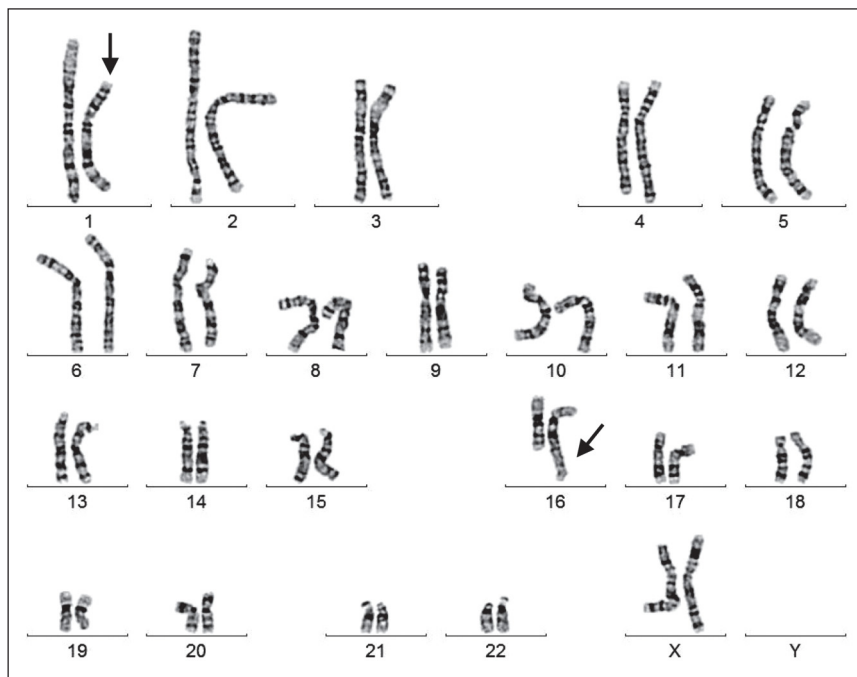


Figure 1: Female karyotype showing a reciprocal balanced translocation between the short arm of chromosome 1 and the long arm of chromosome 16 (arrows indicate derivative chromosomes).

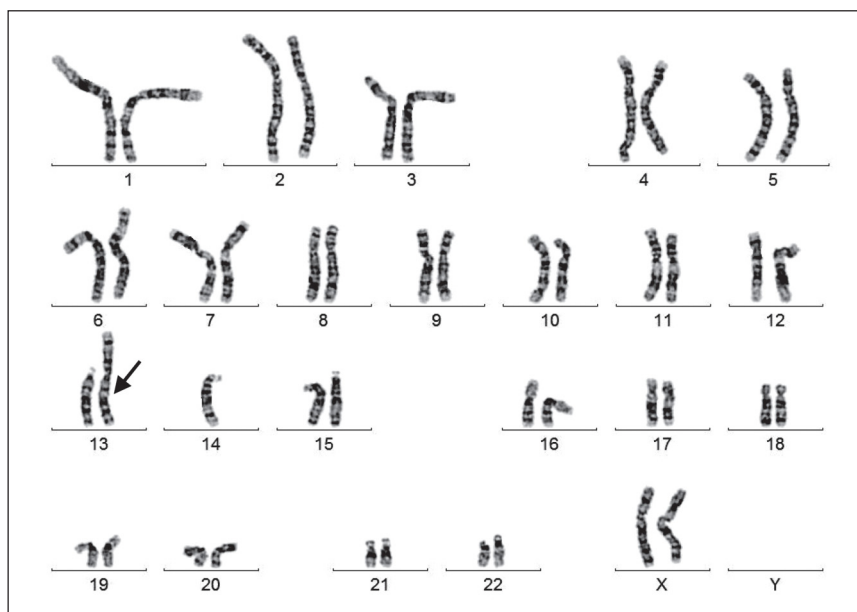


Figure 2: Female karyotype showing a Robertsonian translocation between chromosomes 13 and 14 (arrow indicates derivative chromosome resulting from Robertsonian translocation).

Dependent upon the size of the chromosomal fragments distal to the break-points and most likely their gene content, resulting imbalances may also be compatible with live birth and result in severe and complex malformation syndromes and/or mental disability [7]. This increased risk should be discussed with the couple in the setting of a genetic counseling session and a prenatal chromosome analysis should be offered in all subsequent pregnancies.

In most cases of a balanced autosomal translocation the couple can be assured, that healthy offspring can be conceived. There is only one exception: the gametes of the carrier of a constitutional Robertsonian translocation between two homologous chromosomes (e.g. two chromosomes 21) will always be aneuploid: disomy of the affected chromosome in combination with a normal haploid gamete of the partner invariably results in an aneuploid fetus with a trisomy for the respective chromosome.

Molecular Genetic Testing

Based on the observation of recurrent microscopically visible and submicroscopic deletions within the long arm of the Y chromosome (Yq11.21-23) in patients with non-obstructive azoospermia and/or oligozoospermia the three regions AZFa, AZFb and AZFc were defined [12]. The reported frequency of AZF deletions varies widely from 0.6–1 % in non-selected male patient cohorts with infertility problems, to 7–10 % in males with severe oligozoospermia to 15–20 % in patients with non-obstructive azoospermia [2] (Fig. 3). AZFa deletions usually result in azoospermia with Sertoli-cell-only syndrome (SCOS) with complete absence of germ cells on testicular biopsy. AZFb deletions have been described to result in maturation arrest at the spermatocyte stage, while the most frequent AZFc deletions may present with a wide phenotypic spectrum ranging from SCOS to severe oligozoospermia with all germ cell types present [12]. In particular the presence of an AZFa deletion as an unfavourable prognostic factor for a planned testicular sperm extraction (TESE) may support the decision process of the couple. Furthermore, patients with any AZF deletion need to be informed about the higher risk of fertility problems in their male offspring [2]. Based on current data molecular genetic testing for AZF deletions should be offered as a reasonable complement of genetic workup for patients with azoospermia or a sperm count below 1 mio/ml (find the Guidelines of the American Academy of Andrology online: http://www.uni-leipzig.de/~caa/Guidelines_2004.pdf).

Another important genetic factor for male fertility problems are mutations within the CFTR gene. Homozygous or compound heterozygous CFTR mutations result in the characteristic phenotype of cystic fibrosis (CF), with a frequency of 1:2,000–1:2,500 in many European populations one of the most common autosomal recessive inherited metabolic disorders. 1 in 20–25 individuals is heterozygous mutation carrier (Fig. 4). Classic CF usually manifests in early infancy with recurrent pulmonary and/or gastrointestinal symptoms with failure to thrive [9]. Today milder, non classical forms are known, which may only be recognized during adulthood.

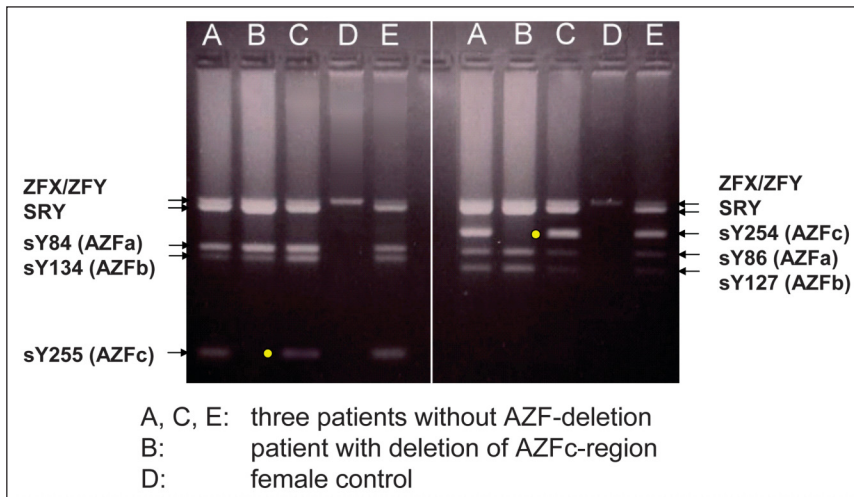


Figure 3: Molecular diagnostic of AZF deletion: after PCR the products are separated on an agarose gel showing specific bands. Absence of a band indicates a deletion (dot indicates deleted band).

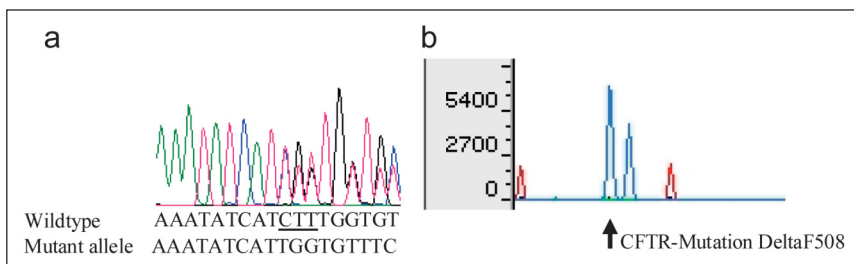


Figure 4: (a) Electrophoretic separation of a sequencing reaction of a PCR product of exon 10 of the CFTR gene from a heterozygous mutation carrier of the common CFTR mutation DeltaF508. The mutant allele has a deletion of 3 basepairs (CTT), resulting in a deletion of the amino acid phenyl alanine at position 508 of the wildtype CFTR gene product. (b) Electrophoretic separation of the PCR product with the smaller mutant CFTR allele to the left, wildtype allele to the right.

Affected males in addition present with congenital bilateral absence of the vas deferens (CBAVD), resulting in obstructive azoospermia, which may be the only clinical sign in patients with milder phenotypes. There is some correlation between the type of mutation identified and the severity of the resulting clinical features (genotype phenotype correlation). Some mutations, in particular R117H, are more prevalent in the patient cohort with isolated CBAVD without CF phenotype.

Current data on an association between sperm count and frequency of identified CFTR mutations are inconsistent. A slightly increased rate of heterozygous mutations in males with a sperm count below 1 Mio/ccm appears likely and subsequently has been proposed as clinical indication for CFTR testing to exclude the most frequent CFTR mutations [2].

Identification of mutation carriers is important, because in combination with a

female heterozygous mutation carrier offspring carry a risk of 25 % to develop classic CF. Therefore, the identification of a CFTR mutation should always be discussed with the couple in the setting of a genetic counseling session and prompt the offer of a mutation analysis for the partner.

The topic of a **Steroid-21-hydroxylase deficiency** as another important monogenic cause of fertility problems in females with the frequent syndrome of polycystic ovaries (PCO) will be extensively covered by M. Bals-Pratsch in the accompanying article in this journal.

■ Genetic Counseling for Patients with Suspected Genetic Disorder

Furthermore, the reader should be aware of the wide variety of additional genetic syndromes as a rare but important cause of sub- or infertility in both males and females [13]. Depending upon the mode

of inheritance and the clinical variability offspring may carry a significantly increased risk for particular monogenic disorders incl. congenital malformations and/or developmental problems. Some of these disorders may also confer an increased risk for pregnancy complications or pregnancy loss. Special concern is always warranted in the presence of additional dysmorphic features or malformations in the proband itself. Likewise, **primary amenorrhea** or **premature ovarian failure** may be a feature of an underlying monogenic disorder like Fragile X syndrome and should prompt referral for genetic counseling and further genetic workup [14]. An insight in some of these monogenic conditions will be given by M. Hempel in the accompanying article in this journal.

Multifactorial traits may also be an important issue, like renal anomalies which may be accompanied by CBAVD in males or uterus anomalies in females due to the close neighbourhood of the muellerian and wolffian ducts and their derivatives during embryonic development. The recurrence risk is increased, therefore a detailed ultrasound examination should be offered in pregnancy [15].

■ Summary Genetic Counseling and Testing Prior to Assisted Reproduction

Couples with sub- or infertility carry a significantly increased risk for underlying genetic factors, which may be associated with an increased risk for their offspring. Prior to any form of assisted reproduction a detailed family history should be obtained and abnormalities, potentially relevant for the offspring should prompt referral to genetic counseling. Furthermore, current data support the importance of a chromosome analysis of both partners regardless of additional clinical data like sperm count or family history. In addition, further molecular genetic testing of the CFTR gene should be offered for male patients with azoospermia or oligozoospermia below 1 Mio/ccm and may be complemented by an AZF analysis, in particular for patients with azoospermia planning to undergo TESE.

Any suspicious results of genetic testing should be explained to the patients in the

setting of a genetic counseling session, which also includes discussion of the potential impact and possible risks for the offspring and available options including prenatal diagnosis or polar body diagnosis. Recommendations for genetic counseling and testing of further relatives may be conferred.

■ Prenatal Care after Assisted Reproduction

After assisted reproduction the risks for the offspring are a reduced birth weight and a slightly increased basic risk regarding malformations and developmental disorders when compared to the general population. Current data suggest that the latter may rather be due to underlying risk factors conferred by the couple than the applied techniques of assisted reproduction (ART) [16].

During pregnancy many couples are concerned, whether or not additional genetic testing of the fetus should be performed after assisted reproduction. However, if karyotyping of both parents prior to ART revealed normal chromosomes and there is no evidence of recognizable other risks resulting from the patient's medical history and the family history, and if the fetal development is unremarkable, invasive genetic testing should only be offered according to maternal age. In addition to routine prenatal care detailed ultrasound examination is recommended [17].

In conclusion, potential genetic risk factors should be identified and discussed with the couple prior to assisted reproduction and anticipated pregnancy. In the majority of cases the diagnostic outcome is unremarkable, which can assure the patient with respect to the planned fertility treatment.

For more information see also:

- Arbeitsgemeinschaft Reproduktionsgenetik der DGRM
<http://www.repromedizin.de>
- American Society of Reproductive Medicine
<http://www.asrm.org>
- Deutsche Gesellschaft für Human-genetik
<http://www.gfhev.de>
- GeneClinics
<http://www.geneclinics.org>
- Online Mendelian Inheritance in Men®
<http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>

■ Practical Aspects

- Infertility and chromosome aberrations
- Infertility and monogenic diseases
- Recommendation for genetic counseling prior to assisted reproduction

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