Prevalence of chromosomal abnormalities and Y chromosome microdeletion among men with severe semen abnormalities and its correlation with successful sperm retrieval

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Abstract

AIM:

To estimate the prevalence of chromosomal abnormalities and Y chromosome microdeletion among men with azoospermia and severe oligozoospermia and its correlation with successful surgical sperm retrieval.

SETTING AND DESIGN:

A prospective study in a tertiary level infertility unit.

MATERIALS AND METHODS:

In a prospective observation study, men with azoospermia and severe oligozoospermia (concentration <5 million/ml) attending the infertility center underwent genetic screening. Peripheral blood karyotype was done by Giemsa banding. Y chromosome microdeletion study was performed by a multiplex polymerase chain reaction.

RESULTS:

The study group consisted of 220 men, 133 of whom had azoospermia and 87 had severe oligozoospermia. Overall, 21/220 (9.5%) men had chromosomal abnormalities and 13/220 (5.9%) men had Y chromosome microdeletions. Chromosomal abnormalities were seen in 14.3% (19/133) of azoospermic men and Y chromosome microdeletions in 8.3% (11/133). Of the 87 men with severe oligozoospermia, chromosomal abnormalities and Y chromosome microdeletions were each seen in 2.3% (2/87). Testicular sperm aspiration was done in 13 men and was successful in only one, who had a deletion of azoospermia factor c.

CONCLUSIONS:

Our study found a fairly high prevalence of genetic abnormality in men with severe semen abnormalities and a correlation of genetic abnormalities with surgical sperm retrieval outcomes. These findings support the need for genetic screening of these men prior to embarking on surgical sperm retrieval and assisted reproductive technology intracytoplasmic sperm injection.

KEY WORDS: Azoospermia, karyotype, Y microdeletion

INTRODUCTION

Infertility is defined as the failure to conceive after 12 months of unprotected intercourse.[1] Infertility is a significant health burden and according to recent reports approximately 48.5 million couples are affected worldwide.[2] Male factor is considered to account for up to half of these cases.[3] The initial screening evaluation for the male partner includes a reproductive history and a semen analysis. When severe semen abnormality is detected, there is a need for additional tests and procedures including genetic evaluation.

Genetic abnormalities implicated in male infertility include numerical and structural chromosomal abnormalities, Y chromosome microdeletions, congenital absence of vas deferens associated with cystic fibrosis, and the ciliary dyskinesia syndromes/Kartagener syndrome.[4,5,6,7] Among these, Klinefelter syndrome (KS) due to gain of an X chromosome (47,XXY) is the leading cause followed by Y chromosome microdeletions.[8]

In nonobstructive azoospermia, the chances of successful sperm retrieval depend on various factors such as serum levels of follicle-stimulating hormone (FSH), testicular volume, and the presence of genetic abnormalities. In patients with KS and microdeletions of the azoospermia factor a (AZFa) and AZFb loci on the Y chromosome, the rates of successful retrieval are very low. Prior identification of such men can help in clinical decision making and counseling before embarking on invasive procedures.

There is universal agreement on the need for chromosome analysis (karyotyping) in the workup of male infertility, especially in those with azoospermia and severe oligozoospermia (sperm count <5 million/ml). However, there is still a lack of consensus regarding the role of Y chromosome microdeletion studies, with the American Society of Reproductive Medicine (ASRM) recommending the use of both karyotyping and Y chromosome microdeletion studies prior to performing intracytoplasmic sperm injection (ICSI) with their own sperms while the National Institute for Health and Care Excellence recommends only karyotyping for this group of patients.[9,10,11,12]

In view of the conflicting recommendations, we undertook this study to estimate the prevalence and the need for performing karyotype and Y chromosome microdeletion studies in men with severe oligozoospermia or azoospermia. We also decided to explore the relation between genetic

abnormalities and surgical sperm retrieval outcomes in men with nonobstructive azoospermia.

MATERIALS AND METHODS

This was a prospective observational study carried out in a tertiary care hospital from January 2010 to December 2014. Semen analysis was done for all male partners undergoing infertility evaluation and those with either azoospermia or severe oligozoospermia was recruited after obtaining informed consent. Azoospermia was diagnosed by the absence of sperm in the ejaculate from both the fresh and the centrifuged samples.[13] Nonobstructive azoospermia was diagnosed based on serum FSH levels, testicular volume, and by exclusion of an obstructive cause. Anonymized data were collected and ethical guidelines were followed.

Patients with the following conditions were excluded from the study: Obstructive azoospermia as diagnosed by normal testicular volume with a distended epididymis or absent vas and a normal serum FSH and obvious cause of testicular dysfunction such as gonadotoxic drug exposure and pituitary and hypothalamic causes. For severe oligozoospermia, sperm count of <5 million/ml was taken as the cutoff to initiate genetic testing as per the ASRM guidelines.[11,14]

The sample size required to estimate the prevalence of a chromosomal abnormality was calculated to be 140 for a 5% precision based on an estimated prevalence of chromosomal abnormalities and Y chromosome microdeletion of 10% and 8%, respectively, among men with severe semen abnormalities.[14]

Peripheral blood karyotyping was done using standard protocols. G-banded karyotypes were reported according to the International System for Human Cytogenetics Nomenclature.[15,16] Y chromosome microdeletion analysis was done by polymerase chain reaction in accordance with the guidelines of the European Academy of Andrology and the European Molecular Genetics Quality Network[8] using the following sequence tagged sites loci: AZFa (sY84, sY86), AZFb (sY127, sY134), and AZFc (sY254, sY255) with ZFY and SRY as controls.

RESULTS

The study group consisted of 220 men with severe oligozoospermia/nonobstructive azoospermia. Severe oligozoospermia was seen in 87/220 participants (39.5%) and azoospermia in the remaining 133 (60.5%). The majority (201/220, 91%) presented with primary infertility. All 19 men who presented with secondary infertility had severe oligozoospermia.

Chromosomal abnormalities

Chromosomal abnormalities were seen in 21/220 men (9.5%). These abnormalities were seen in 19/133 azoospermic men (14.3%) and 2/87 men (2.3%) with severe oligozoospermia. The most commonly seen abnormality (14/21) was KS. Three KS had additional abnormalities as follows: One, a pericentric inversion of the Y chromosome which is a normal variation, one mosaic KS, and one with AZFc deletion. Structural abnormalities of the Y chromosome were seen in four men. These were due to a pseudodicentric Y chromosome, an isodicentric Y chromosome with coexistent AZFb and c microdeletions, and an insertion (Y;7) in one patient each. The fourth was a 45, X male who had an unbalanced t(Y;1) with deletion of entire AZF region (AZFa, AZFb, and AZFc). Mosaic karyotypes were seen in two patients: One mosaic KS and one 46, XY/46, XX.

Y chromosome microdeletions

Y chromosome microdeletions were seen in 13/220 men (5.9%), with deletions of AZFb and AZFc in five each, AZFb + AZFc in two, and AZFa + AZFb + AZFc in one. Among these 13 men, azoospermia was seen in 11 (8.3%) and oligospermia in 2 (2.3%), both of whom had AZFc deletion. Ten had normal chromosomes with azoospermia in eight. Three men had chromosomal abnormalities, as well as Y chromosome microdeletions [Tables 1 and 2].

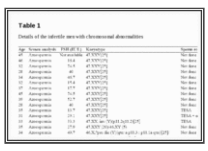

Table 1

Details of the infertile men with chromosomal abnormalities

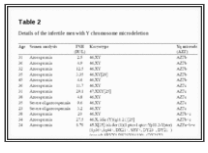

Table 2

Details of the infertile men with Y chromosome microdeletion

Surgical sperm retrieval outcomes

All these men underwent genetic counseling regarding implications for fertility, the possibility of aneuploid gametes and the risk of genetic abnormalities in the offspring. The 14 couples with KS were also counseled regarding the higher risk of aneuploidy in the offspring resulting from assisted conception after which 11 elected to forgo further assisted conception with self-gametes.

Thirteen men elected to undergo testicular sperm aspiration (TESA). Six had normal karyotypes and AZF deletions (four AZFb, one with AZFc, and one combined AZFb + AZFc), three had KS, and four had chromosomal abnormalities other than KS. We followed up the results of surgical sperm retrieval and identification of mature sperms during the procedure was considered as a successful outcome.

TESA was successful only in 1 of the 13 patients who had AZFc deletion and a normal karyotype. Only spermatogonia could be obtained from one KS. Another patient who had KS, as well as AZFc microdeletion, underwent testicular sperm extraction (TESE) under ×25 magnification (micro-TESE) after the failure of TESA. Micro-TESE yielded mature spermatozoa which were cryopreserved for assisted reproductive technology (ART) [Tables 1 and 2].

DISCUSSION

In our study of men with severe semen abnormalities, the overall prevalence of chromosomal abnormalities and Y chromosome microdeletions was 9.5% and 5.9%, respectively. Among azoospermic men, chromosomal abnormalities were seen in 14.3% and Y chromosome microdeletions in 8.3%. Chromosomal abnormalities and Y chromosome microdeletions were each seen in 2.3% of severe oligospermic men.

Chromosomal abnormalities account for most of the genetic causes of male infertility. The frequency of chromosomal abnormalities varies from 1% in the general population to 5% among severely oligozoospermic men and 10–15% among azoospermic men.[4,17] In a study evaluating genetic abnormalities in men with severe oligozoospermia, the prevalence of chromosomal abnormalities and Y microdeletions was 5.6% and 6%, respectively, which is in agreement with our results among severe oligospermic subgroup.[17]

KS accounts for two-thirds of the karyotypic abnormalities in infertile men and is the single leading genetic cause of male infertility.[18,19] KS is reported to be present in approximately 5% of severely oligozoospermic men and 10% of azoospermic men.[20] However, a recent systematic review has reported that surgical sperm retrieval has been successful in up to half of patients with KS.[21] This is possibly due to the presence of euploid (46, XY) germ cells in spermatogenetic foci in the testes of KS patients.[22] The review has therefore concluded that all men with KS need not be considered to be obligatorily infertile.[21] In our study, sperms were obtained successfully from one of the three men with KS who opted for surgical retrieval.

The frequency of autosomal and sex chromosomal aneuploidy is possibly increased in spermatozoa from KS patients in comparison with controls.[23] According to the literature, 101 babies have been to born to KS fathers.[21] There have been two reported cases of fetuses diagnosed with 47,XXY prenatally.[24,25] Despite a large case series of 65 KS fathers who conceived 17 chromosomally normal children through ICSI using testicular sperms, concerns regarding the long-term health of such children still remain.[26] Due to limited data, whether preimplantation genetic diagnosis is routinely required in KS is still an open question.

Structural chromosomal abnormalities such as inversions and translocations are also higher among infertile men compared to fertile men. The formation of bivalents during meiosis is impaired in men with structural chromosomal abnormalities, leading to impaired meiosis and spermatogenetic arrest.[27,28,29] In our study, two men had balanced translocations between autosomes.

Y chromosome microdeletion is the second most common genetic cause of male infertility.[8] Initial studies estimated that the prevalence of Y chromosome microdeletions increases from approximately 2% in fertile men to 16% in men with azoospermia or severe oligozoospermia.[30] However, the prevalence appears to be significantly higher in azoospermic men (10–15%) when compared to oligozoospermic men (5–10%).[20,31]

The male-specific region of the Y chromosome (MSY) is unique to the male sex and bears the three AZF regions AZFa, AZFb, and AZFc. Deletions of these specific regions are thought to be due to nonallelic homologous recombination[8] because the MSY does not participate in X-Y crossing over.[32] AZFc deletion is the most common, accounting for more than two-thirds of the total Y microdeletions, followed by AZFb deletion.[31]

AZFa deletion results in Sertoli cell-only syndrome and there have been no reported cases of successful surgical sperm retrieval in this subgroup.[33,34,35,36,37] AZFb deletion is also associated with spermatogenic arrest and unsuccessful surgical sperm retrieval in most cases.[34,36,38] However, there are a few case reports suggesting that AZFb deletions may rarely be associated with some residual spermatogenesis in the form of spermatid arrest, cryptozoospermia, and oligozoospermia.[39,40] In our study, all the men who had isolated AZFb deletion and those with combined microdeletion underwent unsuccessful surgical retrievals (a + b + c or b + c).

Deletion of the AZFc region is associated with a wide spectrum of findings ranging from severe oligozoospermia to complete absence of spermatogenesis. There have been reports of spontaneous conception[41,42] leading to the transmission of the AZFc deletion to the male offspring. With AZFc deletions, the likelihood of successful surgical sperm retrieval appears to be close to 50%, thus paving the way for the use of assisted conception in these patients.[8] The success of surgical sperm retrieval appears to be partly dependent on the method used, with higher success rates reported with micro-TESE.[36] We retrieved sperms in both our azoospermic men who had isolated AZFc abnormality.

In our study, there was one patient who had a combination of KS with a Y chromosome microdeletion (AZFc). The association of KS with Y chromosome microdeletion is controversial, with some studies[43,44,45,46] supporting such an association and other studies[47,48,49] refuting it. The recent guidelines on Y chromosome microdeletion[8] state that this discrepancy could be a result of methodological disparities. However, another author[45] has speculated that this could be a result of ethnicity and genetic drift due to the consistent associations of Y chromosome microdeletion and karyotyping reported among Asian populations and the discrepant results reported among Caucasians. Hence, this needs to be explored in future larger studies.

The Y chromosome carrying the microdeletion is likely to be passed on to the sons of the affected fathers during ICSI.[50] There is a concern among several authors that this would cause the infertility phenotype to be passed on to the next generation with the sons being likely to become infertile adults.[51,52] However, since most of the children conceived following ICSI are still in their teens, the definite extent of the risk is still unknown.

There is also some concern that Y chromosome microdeletions may be associated with Y chromosomal instability leading to aneuploid (45,X) cell lines in the offspring. There have been two studies in which preimplantation genetic diagnosis was performed on embryos obtained after ICSI with sperms of Y chromosome microdeletion. The results of these studies have been conflicting. One study showed no significant increase in aneuploidies,[53] whereas the other study showed a significant increase in 45,X cell lines in these embryos.[54]

The clinical implication of detection of Y chromosome microdeletion is to decide on the feasibility of surgical sperm retrieval. Patients with AZFc deletion can be advised to undergo surgical sperm retrieval in view of good success rates. AZFa and AZFb microdeletion carriers need to be counseled about the very low probability of surgical sperm retrieval which is an invasive procedure. In our study, we did not find mature sperms in men with isolated AZFb or in combined AZFa, b, or c deletion which is agreement with the previous studies. Karyotyping and Y chromosome microdeletions studies play a major role in counseling patients regarding the implications of these findings with regard to their impact on fertility, chances of successful surgical retrieval, and the possible risk of transmission of genetic abnormalities to the offspring following ART.[11]

CONCLUSIONS

The findings of our study support the current guidelines regarding the need for offering genetic screening for men with severe semen abnormalities before undergoing ART-ICSI due to the fairly high prevalence of genetic abnormalities in this group. The abnormal genetic findings play an important role in prognostication and counseling of these couples prior to undertaking ART. However, there is a need for more research into the long-term impact on children conceived to fathers with genetic abnormalities.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: A committee opinion. Fertil Steril. 2013;99:63. [PubMed] [Google Scholar]

2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. PLoS Med. 2012;9:e1001356. [PMC free article] [PubMed] [Google Scholar]

3. Attia AM, Abou-Setta AM, Al-Inany HG. Gonadotrophins for idiopathic male factor subfertility. Cochrane Database Syst Rev. 2013;8:CD005071. [PubMed] [Google Scholar]

4. Van Assche E, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, et al. Cytogenetics of infertile men. Hum Reprod. 1996;11(Suppl 4):1–24. [PubMed] [Google Scholar]

5. Suganthi R, Vijesh VV, Vandana N, Fathima Ali Benazir J. Y choromosomal microdeletion screening in the workup of male infertility and its current status in India. Int J Fertil Steril. 2014;7:253–66. [PMC free article] [PubMed] [Google Scholar]

6. van der Ven K, Messer L, van der Ven H, Jeyendran RS, Ober C. Cystic fibrosis mutation screening in healthy men with reduced sperm quality. Hum Reprod. 1996;11:513–7. [PubMed] [Google Scholar]

7. Sha YW, Ding L, Li P. Management of primary ciliary dyskinesia/Kartagener's syndrome in infertile male patients and current progress in defining the underlying genetic mechanism. Asian J Androl. 2014;16:101–6. [PMC free article] [PubMed] [Google Scholar]

8. Krausz C, Hoefsloot L, Simoni M, Tüttelmann F. European Academy of Andrology; European Molecular Genetics Quality Network. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: State-of-the-art 2013. Andrology. 2014;2:5–19. [PMC free article] [PubMed] [Google Scholar]

9. Tüttelmann F, Rajpert-De Meyts E, Nieschlag E, Simoni M. Gene polymorphisms and male infertility - A meta-analysis and literature review. Reprod Biomed Online. 2007;15:643–58. [PubMed] [Google Scholar]

10. Stouffs K, Lissens W, Tournaye H, Haentjens P. What about gr/gr deletions and male infertility? Systematic review and meta-analysis. Hum Reprod Update. 2011;17:197–209. [PubMed] [Google Scholar]

11. Practice Committee of American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: A committee opinion. Fertil Steril. 2012;98:294–301. [PubMed] [Google Scholar]

12. O'Flynn N. Assessment and treatment for people with fertility problems: NICE guideline. Br J Gen Pract. 2014;64:50–1. [PMC free article] [PubMed] [Google Scholar]

13. Practice Committee of American Society for Reproductive Medicine in Collaboration with Society for Male Reproduction and Urology. Evaluation of the azoospermic male. Fertil Steril. 2008;90(5 Suppl):S74–7. [PubMed] [Google Scholar]

14. Coppola MA, Klotz KL, Kim KA, Cho HY, Kang J, Shetty J, et al. SpermCheck® Fertility, an immunodiagnostic home test that detects normozoospermia and severe oligozoospermia. Hum Reprod. 2010;25:853–61. [PMC free article] [PubMed] [Google Scholar]

15. Shaffer LG, McGowan-Jordan J, Schmid M, editors. ISCN 2013: An International System for Human Cytogenetic Nomenclature (2013) Recommendations of the International Standing Committee on Human Cytogenetic Nomenclature. Basel: S Karger AG; 2013. [Google Scholar]

16. Korf BR. Overview of Clinical Cytogenetics. In: Haines JL, editor. Current Protocols in Human Genetics. Ch. 8. Unit 8.1. New York: John Wiley; 2001. [Google Scholar]

17. Ravel C, Berthaut I, Bresson JL, Siffroi JP. Genetics Commission of the French Federation of CECOS. Prevalence of chromosomal abnormalities in phenotypically normal and fertile adult males: Large-scale survey of over 10,000 sperm donor karyotypes. Hum Reprod. 2006;21:1484–9. [PubMed] [Google Scholar]

18. De Braekeleer M, Dao TN. Cytogenetic studies in male infertility: A review. Hum Reprod. 1991;6:245–50. [PubMed] [Google Scholar]

19. Foresta C, Garolla A, Bartoloni L, Bettella A, Ferlin A. Genetic abnormalities among severely oligospermic men who are candidates for intracytoplasmic sperm injection. J Clin Endocrinol Metab. 2005;90:152–6. [PubMed] [Google Scholar]

20. O'Flynn O'Brien KL, Varghese AC, Agarwal A. The genetic causes of male factor infertility: A review. Fertil Steril. 2010;93:1–12. [PubMed] [Google Scholar]

21. Fullerton G, Hamilton M, Maheshwari A. Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009? Hum Reprod. 2010;25:588–97. [PubMed] [Google Scholar]

22. Sciurano RB, Luna Hisano CV, Rahn MI, Brugo Olmedo S, Rey Valzacchi G, Coco R, et al. Focal spermatogenesis originates in euploid germ cells in classical Klinefelter patients. Hum Reprod. 2009;24:2353–60. [PubMed] [Google Scholar]

23. Rives N, Joly G, Machy A, Siméon N, Leclerc P, Macé B. Assessment of sex chromosome aneuploidy in sperm nuclei from 47,XXY and 46, XY/47,XXY males: Comparison with fertile and infertile males with normal karyotype. Mol Hum Reprod. 2000;6:107–12. [PubMed] [Google Scholar]

24. Ron-El R, Strassburger D, Gelman-Kohan S, Friedler S, Raziel A, Appelman Z. A 47,XXY fetus conceived after ICSI of spermatozoa from a patient with non-mosaic Klinefelter's syndrome: Case report. Hum Reprod. 2000;15:1804–6. [PubMed] [Google Scholar]

25. Friedler S, Raziel A, Strassburger D, Schachter M, Bern O, Ron-El R. Outcome of ICSI using fresh and cryopreserved-thawed testicular spermatozoa in patients with non-mosaic Klinefelter's syndrome. Hum Reprod. 2001;16:2616–20. [PubMed] [Google Scholar]

26. Madureira C, Cunha M, Sousa M, Neto AP, Pinho MJ, Viana P, et al. Treatment by testicular sperm extraction and intracytoplasmic sperm injection of 65 azoospermic patients with non-mosaic Klinefelter syndrome with birth of 17 healthy children. Andrology. 2014;2:623–31. [PubMed] [Google Scholar]

27. Debiec-Rychter M, Jakubowski L, Truszczak B, Moruzgala T, Kaluzewski B. Two familial 9;17 translocations with variable effect on male carriers fertility. Fertil Steril. 1992;57:933–5. [PubMed] [Google Scholar]

28. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: Role of genetic background. Reprod Biomed Online. 2007;14:734–45. [PubMed] [Google Scholar]

29. Chantot-Bastaraud S, Ravel C, Siffroi JP. Underlying karyotype abnormalities in IVF/ICSI patients. Reprod Biomed Online. 2008;16:514–22. [PubMed] [Google Scholar]

30. Pryor JL, Kent-First M, Muallem A, Van Bergen AH, Nolten WE, Meisner L, et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med. 1997;336:534–9. [PubMed] [Google Scholar]

31. Massart A, Lissens W, Tournaye H, Stouffs K. Genetic causes of spermatogenic failure. Asian J Androl. 2012;14:40–8. [PMC free article] [PubMed] [Google Scholar]

32. Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. Nature. 2003;423:825–37. [PubMed] [Google Scholar]

33. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. Hum Mol Genet. 1996;5:933–43. [PubMed] [Google Scholar]

34. Krausz C, Quintana-Murci L, McElreavey K. Prognostic value of Y deletion analysis: What is the clinical prognostic value of Y chromosome microdeletion analysis? Hum Reprod. 2000;15:1431–4. [PubMed] [Google Scholar]

35. Kamp C, Huellen K, Fernandes S, Sousa M, Schlegel PN, Mielnik A, et al. High deletion frequency of the complete AZFa sequence in men with Sertoli-cell-only syndrome. Mol Hum Reprod. 2001;7:987–94. [PubMed] [Google Scholar]

36. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z, Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. Hum Reprod. 2003;18:1660–5. [PubMed] [Google Scholar]

37. Kleiman SE, Almog R, Yogev L, Hauser R, Lehavi O, Paz G, et al. Screening for partial AZFa microdeletions in the Y chromosome of infertile men: Is it of clinical relevance? Fertil Steril. 2012;98:43–7. [PubMed] [Google Scholar]

38. Kleiman SE, Yogev L, Lehavi O, Hauser R, Botchan A, Paz G, et al. The likelihood of finding mature sperm cells in men with AZFb or AZFb-c deletions: Six new cases and a review of the literature (1994-2010) Fertil Steril. 2011;95:2005–12. 2012.e1–4. [PubMed] [Google Scholar]

39. Longepied G, Saut N, Aknin-Seifer I, Levy R, Frances AM, Metzler-Guillemain C, et al. Complete deletion of the AZFb interval from the Y chromosome in an oligozoospermic man. Hum Reprod. 2010;25:2655–63. [PubMed] [Google Scholar]

40. Soares AR, Costa P, Silva J, Sousa M, Barros A, Fernandes S. AZFb microdeletions and oligozoospermia - Which mechanisms? Fertil Steril. 2012;97:858–63. [PubMed] [Google Scholar]

41. Kühnert B, Gromoll J, Kostova E, Tschanter P, Luetjens CM, Simoni M, et al. Case report: Natural transmission of an AZFc Y-chromosomal microdeletion from father to his sons. Hum Reprod. 2004;19:886–8. [PubMed] [Google Scholar]

42. Xia XY, Cui YX, Pan LJ, Hao LJ, Jin BF, Wu YM, et al. Analysis of an AZFc deletion family with natural transmission. Zhonghua Nan Ke Xue. 2006;12:720–2. [PubMed] [Google Scholar]

43. Mitra A, Dada R, Kumar R, Gupta NP, Kucheria K, Gupta SK. Y chromosome microdeletions in azoospermic patients with Klinefelter's syndrome. Asian J Androl. 2006;8:81–8. [PubMed] [Google Scholar]

44. Hadjkacem-Loukil L, Ghorbel M, Bahloul A, Ayadi H, Ammar-Keskes L. Genetic association between AZF region polymorphism and Klinefelter syndrome. Reprod Biomed Online. 2009;19:547–51. [PubMed] [Google Scholar]

45. Zhang HG, Zhang ZB, Wang RX, Yu Y, Yu XW, Fadlalla E, et al. Male infertility in Northeast China: Molecular detection of Y chromosome microdeletions in azoospermic patients with Klinefelter's syndrome. Genet Mol Res. 2013;12:4972–80. [PubMed] [Google Scholar]

46. Ceylan C, Ceylan GG, Serel TA. The azoospermia factor locus-c region was found to be related to Klinefelter syndrome in Turkish patients. Genet Mol Res. 2010;9:1229–33. [PubMed] [Google Scholar]

47. Choe JH, Kim JW, Lee JS, Seo JT. Routine screening for classical azoospermia factor deletions of the Y chromosome in azoospermic patients with Klinefelter syndrome. Asian J Androl. 2007;9:815–20. [PubMed] [Google Scholar]

48. Simoni M, Tüttelmann F, Gromoll J, Nieschlag E. Clinical consequences of microdeletions of the Y chromosome: The extended Münster experience. Reprod Biomed Online. 2008;16:289–303. [PubMed] [Google Scholar]

49. Rajpert-De Meyts E, Ottesen AM, Garn ID, Aksglaede L, Juul A. Deletions of the Y chromosome are associated with sex chromosome aneuploidy but not with Klinefelter syndrome. Acta Paediatr. 2011;100:900–2. [PubMed] [Google Scholar]

50. Kent-First MG, Kol S, Muallem A, Ofir R, Manor D, Blazer S, et al. The incidence and possible relevance of Y-linked microdeletions in babies born after intracytoplasmic sperm injection and their infertile fathers. Mol Hum Reprod. 1996;2:943–50. [PubMed] [Google Scholar]

51. Page DC, Silber S, Brown LG. Men with infertility caused by AZFc deletion can produce sons by intracytoplasmic sperm injection, but are likely to transmit the deletion and infertility. Hum Reprod. 1999;14:1722–6. [PubMed] [Google Scholar]

52. Komori S, Kato H, Kobayashi S, Koyama K, Isojima S. Transmission of Y chromosomal microdeletions from father to son through intracytoplasmic sperm injection. J Hum Genet. 2002;47:465–8. [PubMed] [Google Scholar]

53. Stouffs K, Lissens W, Tournaye H, Van Steirteghem A, Liebaers I. The choice and outcome of the fertility treatment of 38 couples in whom the male partner has a Yq microdeletion. Hum Reprod. 2005;20:1887–96. [PubMed] [Google Scholar]

54. Mateu E, Rodrigo L, Martínez MC, Peinado V, Milán M, Gil-Salom M, et al. Aneuploidies in embryos and spermatozoa from patients with Y chromosome microdeletions. Fertil Steril. 2010;94:2874–7. [PubMed] [Google Scholar]