Journal of Molecular and Genetic Medicine

Zhao et al., J Mol Genet Med 2018, 12:2
DOI: 10.4172/1747-0862.1000352

Research Article Open Access

Frequency of Chromosomal Abnormalities in Subpopulations of Infertile Males among Chinese Hakka Population

Zhao P[1,2,3,4,5*#], Gu X[1,2,3,4,5#], Wang H[1-5] and Yang M[6]

[1]*Clinical Core Laboratory, Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Meizhou, P.R. China*
[2]*Center for Precision Medicine, Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Meizhou, P.R. China*
[3]*Meizhou Municipal Engineering and Technology, Research Center for Molecular Diagnostics of Major Genetic Disorders, Meizhou, P. R. China*
[4]*Guangdong Provincial Engineering and Technology, Research Center for Molecular Diagnostics of Cardiovascular Diseases, Meizhou, P. R. China*
[5]*Meizhou Municipal Engineering and Technology Research Center for Molecular Diagnostics of Cardiovascular Diseases, Meizhou, P. R. China*
[6]*Center for Reproductive Medicine, Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Meizhou, P.R. China*
[#] *These authors have contributed equally*

Abstract

The frequency of chromosomal abnormalities is supposed to be elevated in infertile males as well as shown negative correlation of sperm concentration. Cytogenetic analysis, recommended by guidelines in infertile men, is expensive. Hence, it may be good for recognize riskiest men with chromosomal abnormalities, potentially by analyzing sperm concentration outside of the parameters. Aim to evaluate the frequency of chromosomal abnormalities in different subpopulations among Hakka population, we assessed several clinical parameters in infertile men. A total of 1291 azoospermic men and men apply for *in-vitro* fertilization (IVF) treatment, were analyzed for semen parameters, hormone levels, Y chromosome microdeletions and medical history, related to chromosomal abnormalities. Chromosomal abnormalities were detected 46 of 1291 men (3.6%) in our study. Correlation was no shown between chromosomal abnormalities and sperm parameters except for sperm volume (OR 0.76, P=0.029). Significantly, azoospermia was related to an increased frequency of chromosomal abnormalities (OR 32.24, P<0.001). Elevated gonadotropic hormone levels, meaningfully, was related to the risk of carrying a chromosome abnormality (OR 4.38, P<0.001). Lower rate of chromosomal abnormalities was observed in infertile males with positive andrologic history (OR 0.21, P=0.003). Previous miscarriages, related to an increased frequency of chromosomal abnormalities, were discovered in non-azoospermic men (OR 4.78, P=0.003). The results indicated that azoospermic men with hypergonadotrophic as well as an eventless andrologic history have frequently risk of chromosomal abnormalities.

Keywords: Chromosomal abnormalities; Infertile male; Azoospermia; *In-vitro* fertilization

Introduction

Infertility, as a public health problem, affecting approximately 15% of families are incapable of pregnancy [1]. As early as 1979, Chandley et al. reported that in men with barren semen quality, the frequency chromosomal abnormalities is supposed to be higher than in the common population [2]. Klinefelter's syndrome and Robertsonian translocations, are regarded as important causes of cytogenetic in male infertility [3]. Chromosomal abnormalities may increase the potential risks of infertility being transmitted from infertile men to their offspring that lead to a miscarriage or a child with congenital abnormalities [4]. According to the guidelines, cytogenetic analysis are considered as an essential examination before IVF treatment in patients with severe infertile problem [5,6].

Previous researches have reported frequency of chromosomal abnormalities in men with infertility varies from 3 to 19% in different population [3]. In some researches, cytogenetic analysis was done in all infertile men, but some researches did karyotype for men with exceedingly poor semen quality merely because karyotyping is expensive and take time. And therefore, it may be good for determine riskiest men with chromosomal abnormalities. Up to now, few researches have in consideration of semen parameters and clinical characteristics of infertile men as potential risk factors of chromosomal abnormalities.

In some researches on parameters of semen, it confirmed that sperm concentration demonstrates close association with the chance of carrying chromosomal aberrations [7-9]. These studies found that the frequency of chromosomal abnormalities increasing with sperm concentration reduced, and abnormalities observed in azoospermia at most [10-12]. However, similar association could not be proved in subgroups of infertile men in other studies [10,13]. Differences in the study populations (e.g. whether infertile men or couples) and in classes of sperm concentrations seem to cause such inconsistent results.

Both of sperm motility and morphology were studied the correlation of chromosomal abnormalities. No significant results in these parameters were implied between males with or without chromosomal abnormalities [9]. But some researches did observe a meaningful difference in oligozoospermia that men with a low total motile sperm count (TMSC) present higher prevalence of chromosomal aberrations [14,15].

These results of researches on sperm motility and morphology are obviously conflicting and greatly influenced by sperm concentration. Few researches have concentrated on effect of infertile men characteristics on chromosomal abnormalities. Few studies have been

***Corresponding author:** Dr. Pingsen Zhao, PhD, Head and Associate Professor of Clinical Core Laboratory, Center for Precision Medicine, Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, No 63 Huangtang Road, Meijiang District, Meizhou 514031, P.R. China, Tel: +753-213 1-591, Fax: +753-2131-592; E-mail: zhaopingsen01@163.com or zhaopingsen@hotmail.com

Received April 11, 2018; **Accepted** April 28, 2018; **Published** May 02, 2018

Citation: Zhao P, Gu X, Wang H, Yang M (2018) Frequency of Chromosomal Abnormalities in Subpopulations of Infertile Males among Chinese Hakka Population. J Mol Genet Med 12: 352 doi:10.4172/1747-0862.1000352

focused on whether previous miscarriages and positive andrological history is a prophet for chromosomal abnormalities in men with infertility. When increasing frequency of chromosomal abnormalities in men with subgroups of Y chromosome microdeletions, levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were significantly higher [16]. Men with these features were eliminated by some researches, or no association were found in gonadotrophin levels between men with normal or abnormal karyotypes [17].

Most studies excluding men with a history of genital infection, testicular biopsy, varicocele, children with congenital anomalies, enorchia and urethral fissure. Although these characteristics from a medical history of a man may not directly associate with infertility, it is likely that the characteristics and infertility have a coincident genetic beginning. A correlation between cryptorchidism, barren semen quality and genetic abnormalities has been advised in the testicular dysplasia [18]. Whether relation between these patient characteristics and chromosomal abnormalities is independence was not verified.

Until now, relation between Y chromosomal microdeletions and chromosomal abnormalities in infertile men had been studied in different population [1,19,20]. The most regularly studied parameter related to the frequency of chromosomal abnormalities was sperm concentration in infertile men, but few systematic studies on relation with other sperm parameters, hormone levels, Y chromosome microdeletions and patients characteristic. The aim of our cohort study is to assess accessional sperm parameters and patient characteristics in males with azoospermic and non-azoospermic, to evaluate the frequency of chromosomal abnormalities in different subpopulations of infertile men among Hakka population.

Materials and Methods

Subjects

A total of 1,291 infertile men with azoospermia who were applying for IVF treatment were recruited from Hakka population in Meizhou of Guangdong Province in China. These patients visited Center for Reproductive Medicine of Meizhou *People's Hospital (Huangtang Hospital), Meizhou* Hospital Affiliated to Sun Yat-sen University, from January 2015 to December 2017. Couples applied for IVF due to male factor infertility is defined by the total number of spermatozoa < 20 million, or sperm concentration < 10 million/ml, or TMSC < 4 million, or when more than twice failure in artificial insemination procedure. All men took in a general questionnaire before treatment, including period of infertility, previous miscarriages and andrological history.

Patients whose cytogenetic and sperm analysis results were valid were included in the study. Our study was approved by the Ethics Committee of the Meizhou People's Hospital *(Huangtang Hospital), Meizhou* Hospital Affiliated to Sun Yat-sen University. All participants for the study signed a written informed consent forms.

Cytogenetic analysis

Cytogenetic analysis was examined the cultured peripheral blood lymphocytes. Five GTG-banded metaphases with 440 banding resolution at least were analyzed for each patient and pictures were collected by karyotyping system (ZEISS, Hensoldt Wetzlar, Germany). If chromosome numerical mosaics were present, 100 metaphases were screened by microscope. In the case of complex chromosomal structure aberration, array comparative genome hybridization would be carried out on sample. Chromosomal heteromorphisms, as definition was mentioned in the International System for Human Cytogenetic Nomenclature 2009, were excluded from chromosome abnormality [21].

Sperm analysis

Sperm analysis was measured based on the criteria of 2010 World Health Organization [22]. Specimens were sent at indoor temperature to andrology laboratory within 1 hour of ejaculation and analyzed by semen analyzer (SQA-V GOLD, Los Angeles, USA). When the sperm density was lower than 5 million per ml, microscopic examination would be performed strictly. Sperm volume, sperm concentration and positive motility, and TMSC were collected. In statistical analyses, data was used only from first examination due to semen analysis of patients up to a maximum of seven included in our study.

Hormone analysis

Hormone analysis, including serum FSH, LH and testosterone were measured by electrochemiluminescence immunoassays (ECLIA) on the Automatic immune analyzer (Roche, Basel, Switzerland). According to our laboratory reference interval and cut-off levels referred to researches on hormone levels and Y chromosome microdeletions before, cut-off levels were selected [19].

Y-chromosome microdeletions

Genomic DNA was separated from peripheral blood by the DNA extraction kit (Qiagen, Germany). The sequencing of Y chromosome microdeletions was performed by multiplex PCR, using Y chromosome microdeletions kit (Microread, Beijing, China) which including several sequence-tagged sites (STSs): sY84, sY86, sY127, sY134, CDY2, SCMY, sY157, sY254, sY255, sY1191, DAZ, CDY1, as well as internal controls consist of SRY and ZFX/ZFY genes. Finally, PCR products were detected by capillary electrophoresis (Applied Biosystems, USA).

Statistical analysis

Statistical analysis was carried out using SPSS version 20.0 software (Chicago, IL, USA). Data were performed in percentages and absolute counts. Associations were evaluated by a multivariate binary logistic regression analysis with method of entering and univariate binary logistic regression. Odds ratios (ORs), 95% confidence interval (CI) and *P*-values are shown in the results. Results were recognized statistically significant as $P < 0.05$.

Results

The study contained 1291 men with available results of chromosomal analysis and semen analysis. The median age of the patients was 31.0 years (range 22-59). Chromosomal abnormalities were detected in 46 of the 1291 men (3.6%). Among these abnormalities, there were 31 men had gonosomal abnormalities: twenty seven 47,XXY, one 46,XX, one 46,XY/47,XXY mosaics, one 46,X,del (Y) (q11.23) and one 46,X,psudic (X;Y) (p11.1,p11.1). These aberrations also consisted of 15 men autosomal abnormalities: nine reciprocal translocations, four inversions, one Robertsonian translocations and one individual had four translocations as well as an inversion.

In our cohort of 1291 patients, at least one semen analysis was valid. 886 men (68.5%) had at least two, 423 men (32.7%) had three or more sperm analyses were recorded. The consequence of first semen parameters using multivariate binary logistic regression analysis is performed in Table 1. Of the semen parameters, median volume was 2.7 ml (range 0.1-11.2), median density was 34.1 million/ml (0-196.7), median positive motility was 26.0% (0-63) and median TMSC was 26.6 million (0-399.8). Research showed that only sperm volume statistically significant lower the risk of carrying a chromosomal

aberration (OR 0.76) while concentration, positive motility and TMSC were not associated with chromosomal abnormality. Compared to non-azoospermic men, azoospermia had an increased risk of a chromosomal abnormality (OR 32.24). All 31 men with gonosomal abnormal karyotype were found in azoospermia and 15 men with autosomal abnormalities were detected in non-azoospermia either.

Results of univariate regression analysis of patient characteristics were also provided in Table 1. FSH, LH and testosterone were examined in all the azoospermic men and only 12.7% of non-azoospermic men. Data showed that men with FSH > 10 IU/l or LH > 12 IU/l had a statistically significant correlation of the risk of a chromosomal abnormality, respectively (OR 4.38 and OR 7.96). Inversely, testosterone had a decrease risk of a chromosomal abnormality (OR 0.64).

Y chromosome microdeletions were carried out in 410/1291 men (31.8%) and 188/1291 men (14.6%) had previous miscarriages, neither of these two factors demonstrated an association with chromosomal abnormalities. Patient with a positive andrological history including genital infection, testicular biopsy, varicocele, children with congenital anomalies, cryptorchism and hypospadia lowered the risk of an abnormal karyotype (OR 0.21).

Significantly, the prevalence of chromosomal abnormalities between azoospremia and non-azoospermia were different, and a univariate regression analysis for several variables was carried out in both groups. Results of 106 azoospermia were performed in Table 2, positive associations with chromosomal abnormalities were found in azoospermia with FSH > 10 IU/l or LH > 12 IU/l in our cohort (OR 26.1 and OR 20.8, respectively). On the contrary, testosterone and positive andrological history had a reduce risk of chromosomal abnormalities, respectively (OR 0.463 and OR 0.074). Unfortunately, Y chromosome microdeletions did not show meaningfully relation with chromosomal abnormalities.

Results of 1185 non-azoospermia were given in Table 3, negative association was found between chromosomal abnormalities and hormone levels, Y chromosomal microdeletions and positive andrological history. However, in this subgroup, positive association was discovered between previous miscarriage and chromosomal abnormalities (OR 4.78).

Characteristics	n	Abnormal karyotype (47)	Normal karyotype (1245)	Univariate analysis		
				OR	95%CI	P-value
Azoospermia	106	29.00%	70.10%	32.24	16.677-62.327	<0.001
Non-azoospermia	1185	1.30%	94.70%	1		
Sperm volume per ml	1291	2.4 (0.1- 6.9)	2.8 (0- 11.2)	0.76	0.594- 0.972	0.029
Sperm concentration per million/ml	1185	0 (0- 102.6)	35.10 (0- 196.7)	0.97	0.957- 0.991	0.003
Sperm motility per %	1185	0 (0- 58.0)	27.00 (0- 63.5)	0.95	0.932- 0.986	<0.001
TMSC per million	1291	0 (0- 343.4)	0 (0- 399.76)	1.01	1.009- 1.028	0.291
FSH per IU/l	252	31.45 (5.29- 107.9)	6.27 (0.58- 80.24)	1.06	1.040- 1.081	<0.001
FSH > 10 IU/l	252	67.40%	5.30%	4.38	2.216- 8.674	<0.001
LH per IU/l	252	20.28 (3.71- 55.88)	5.50 (0.26- 37.84)	1.14	1.092- 1.186	<0.001
LH > 12 IU/l	252	60.90%	2.80%	7.96	3.974- 15.927	<0.001
Increased gonadotrophins[a]	252	67.40%	5.30%	4.38	2.216- 8.674	<0.001
Testoterone per nmol/l	252	2.43 (0.38-6.58)	4.24 (0.21- 13.73)	0.64	0.516- 0.781	<0.001
Y chromosome microdeletions	410	8.70%	4.40%	0.78	0.264- 2.296	0.65
Previous miscarriage (s)	1291	15.20%	14.50%	1.06	0.465-2.395	0.898
Postitive andrological history[b]	1236	8.70%	30.40%	0.21	0.073-0.575	0.003

Note: Data are frequency or median (range).
n Number of cases that data were valid for analysis.
[a]Increased gonadotrophins: FSH >10 IU/l or LH >12 IU/l.
[b]Positive andrologic history: genital infection (328), testicular biopsy (30), varicocele (12), children with congenital anomalies (6), enorchia (2), urethral fissure (1). Note: one case may contain several events.

Table 1: Sperm parameters and clinical characteristics in 1291 men with azoospermia or men applying for IVF in association with chromosomal abnormalities.

Characteristics	n	Abnormal karyotype (31)	Normal karyotype (75)	Univariate analysis		
				OR	95%CI	P-value
Sperm volume per ml	106	2.3 (0.1- 6.4)	2.1 (0.1- 5.2)	0.963	0.688- 1.348	0.827
FSH per IU/l	101	43.18 (9.21- 107.9)	6.85 (1.63- 80.24)	1.08	1.049- 1.1116	<0.001
FSH > 10 IU/l	101	93.5%	33.3%	26.1	5.743-118.62	<0.001
LH per IU/l	101	23.38 (3.85- 55.88)	5.87 (2.19- 29.92)	1.238	1.140- 1.345	<0.001
LH > 12 IU/l	101	83.9%	18.7%	20.8	6.773-63.881	<0.001
Increased gonadotrophins[a]	101	93.5%	33.3%	26.1	5.743-118.62	<0.001
Testoterone per nmol/l	101	2.35 (0.38- 5.45)	4.40 (0.34- 11.53)	0.463	0.325- 0.659	<0.001
Y chromosome microdeletions	106	9.7%	6.7%	1.48	0.331-6.608	0.609
Postitive andrological history[b]	106	3.2%	44.0%	0.074	0.016- 0.330	0.001

Note: Data are frequency or median (range).
n Number of cases that data were valid for analysis.
[a] Increased gonadotrophins: FSH >10 IU/l or LH >12 IU/l.
[b]Positive andrologic history: genital infection (328), testicular biopsy (30), varicocele (12), children with congenital anomalies (6), enorchia (2), urethral fissure (1). Note: one case may contain several events.

Table 2: Sperm parameters and patient characteristics in 79 azoospermic men in association with chromosomal abnormalities.

Characteristics	n	Abnormal karyotype (15)	Normal karyotype (1170)	Univariate analysis		
				OR	95%CI	P-value
Sperm volume per ml	1185	2.8 (1.6- 6.9)	2.8 (0.2- 11.2)	0.934	0.614- 1.421	0.749
Sperm concentration per million/ml	1185	43.00 (7.3- 102.6)	36.7 (1- 196.7)	0.988	0.981- 1.015	0.818
Sperm motility per %	1185	31.70 (8.1- 58.0)	28 (0.1- 63)	1.042	0.992- 1.094	0.102
TMSC per million	1185	38.76 (1.9-343.5)	31.53 (0.16- 399.8)	1.003	0.992- 1.015	0.578
FSH per IU/l	151	6.63 (5.29-25.87)	5.97 (0.58- 76.96)	0.976	0.912- 1.045	0.484
LH per IU/l	151	6.35 (2.77- 14.21)	5.42 (0.26- 37.84)	0.992	0.901- 1.093	0.878
Increased gonadotrophins[a]	151	3.71 (1.34- 6.58)	4.17 (0.21- 13.73)	0.92	0.703- 1.204	0.544
Testoterone per nmol/l	151	13.3%	3.5%	0.356	0.077- 1.651	0.187
Y chromosome microdeletions	301	6.7%	25.9%	2.52	0.224- 28.327	0.454
Previous miscarriage (s)	1185	46.7%	15.3%	4.78	1.713- 13.348	0.003
Postitive andrological history[b]	1130	20.0%	29.2%	0.558	0.156- 1.990	0.368

Note: Data are frequency or median (range).
n Number of cases that data were valid for analysis.
[a]Increased gonadotrophins: FSH >10 IU/l or LH >12 IU/l.
[b]Positive andrological history: genital infection (328), testicular biopsy (30), varicocele (12), children with congenital anomalies (6), enorchia (2), urethral fissure (1). Note: one case may contain several events.

Table 3: Sperm parameters and patient characteristics in 1159 non-azoospermic men in association with chromosomal abnormalities.

Discussion

Our study observed that azoospermia and high hormone levels were increased the frequency of chromosomal abnormalities, while sperm volume, testoterone and positive andrologic history were decreased the risk of carrying a chromosomal abnormality.

The frequency of chromosomal abnormalities 3.6% in infertile men from Hakka population, which is lower than previous researches shown frequency between 3% and 19% [18]. The result may casued by the extensive range in semen quality in our study as well as males with azoospermic and non-azoospermic were included, and therefore, we can compare different subgroups of men with varies sperm qualities associated with chromosomal abnormalities.

Chromosomal abnormalities in our cohort are in agreement with those reported in other researches in male with infertility: gonosomal abnormalities, are most commonly examined in azoospermia, while autosomal abnormalities, in particular reciprocal translocations, are most commonly examined in non-azoospermia [11,23]. Klinefelter's syndrome, is known with a phenotype of small and firm testis caused by primary testicular failure, with correlation of gonosomal abnormalities [24]. In men with autosomal aberrations, normozoospermia or oligozoospermia are almost inevitably present, rarely result in azoospermia [18].

Statistical analysis performed base on the first sperm analysis collected in our center. Numerous researches in constant sperm analysis [25,26] and therefore, guidelines on infertile male suggest performing more than one sperm analysis [27]. In present study, 3/1291 (0.2%) men transform from severe oligozoospermia to azoospermia in later sperm analysis, which hardly influenced the frequency of chromosomal aberrations in subpopulations of our cohort, we determine to analysis only results from first sperm analysis. Azoospermia shown a significant relation to chromosomal abnormalities, but no association was found in non-azoospermia between semen density, TMSC or sperm motility and chromosomal abnormalities.

Hormone levels had been detected in only 12.7% cases due to hormone levels were not the basic examination in non-azoospermic patients before IVF in the situation of China. We observed that FSH > 10 IU/l or LH > 12 IU/l were related to chromosomal abnormalities. High levels of gonadotrophins results from testicular dysplasia and increased FSH make a contribution to the diagnosis of non-obstructive azoospermia [28,29]. Compared to males with normal gonadotrophin levels, males with high gonadotrophin levels had an increased frequency of chromosomal abnormalities. Although no statistical significance cut-off level of FSH could be worked because of the small size of patients in this group, FSH was positively correlated to chromosomal abnormalities. Moreover, we found that testosterone decreased the frequency of chromosomal abnormalities in azoospermia. Whether the correlation between gonadotrophin levels or testosterone and chromosomal aberrations in azoospermia as a common test to distinguish the risk of carrying a chromosomal abnormality should be confirm in the future studies. No correlation was shown between FSH, LH or testosterone and chromosomal aberrations in non-azoospermia group.

In our study, 59 of 1291 men (13.4%) were detected as having Y chromosoma microdeletions, which is consistent with the observation reported by Zhang et al. [30], but no correlation was found between males with Y chromosome microdeletions and chromosomal abnormalities. In non-azoospermic group, males with previous miscarriages history have the highest frequency of chromosomal abnormalities, and this is in agreement with the consequence found in previous study [18]. Males with autosomal abnormalities are more likely lead to miscarriage of his partner.

In azoospermic men, postive andrological history including genital infection, testicular biopsy, varicocele, children with congenital anomalies, cryptorchism and hypospadia lowered the risk of a chromosomal abnormality (OR 0.21). It indicated that azoospermia who have a reasonable explanation for azoospermia in their clinical history have a lower risk of chromosomal abnormalities than azoospermia with an eventless history. Similar result was observed in non-azoospermia, although correlation was not statistically significant.

All couples have received a questionnaire in clinical history for the first visit to our center for reproductive medicine, but not all problems were completed, which lead to loss of data. In addition, we have only a limited number of hormone results valid due to the design of the retrospective study and the situation of China. Moreover, the frequency of chromosomal abnormalities was low in the study, although a huge research group of patients were included. A multivariate regression analysis was accomplished on all factors and chromosomal abnormalities, but it was not crucial because of the small sizes of different subpopulations. Hence, we created a model

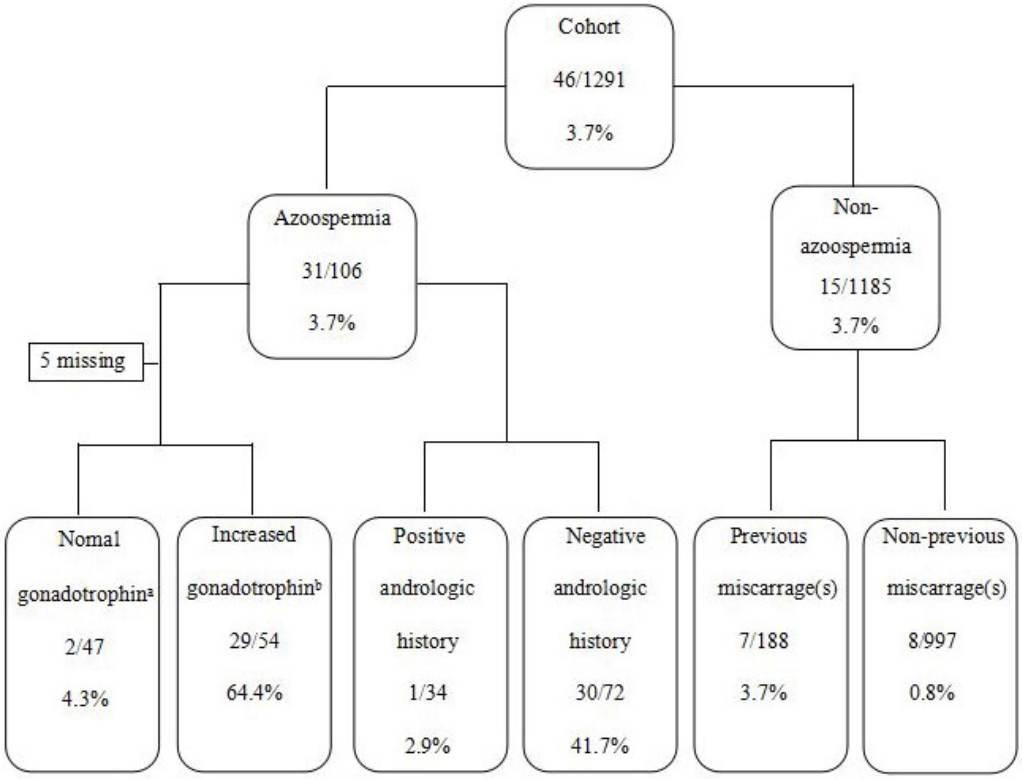

Figure 1: Frequency of chromosomal abnormalities in subpopulations of men with azoospermia or applying for IVF. [[a]FSH ≤ 10 IU/l and LH ≤ 12 IU/l, [b]FSH > 10 IU/l or LH > 12 IU/l].

based on univariate regression analysis and performed it in Figure 1. It performed that azoospermia with high gonadotrophin levels increased the risk of a chromosomal abnormality, while positive andrological history that can explain the barren sperm quality lowered the risk. Also, non-azoospermia with previous miscarriages history had the highest risk of chromosomal abnormalities. Whether these consequences are applicable to all infertile men remains to be further study.

Conclusion

We observed that congenital frequency of chromosomal abnormalities is 3.6% in infertile men in our cohort, sperm volume can imply lower risk of chromosomal abnormalities, sperm concentration is not a good prophet for chromosomal abnormalities while the absence of sperm is. Sperm motility does not associate with chromosomal abnormalities. Frequency of chromosomal abnormalities in azoospermia is 41.3%. If gonadotrophin levels are high (FSH>10 IU/l and/or LH >12 IU/l) and testosterone are low, risk of chromosomal abnormality adds significantly. Azoospermia had a positive andrological history, low gonadotrophin levels and high testosterone levels, the risk reduced. Frequency of chromosomal abnormalities in non-azoospermia is 1.3%, and men had previous miscarriages history, the risk increased. Our finding allow a more specific risk evaluate on chromosomal abnormalities in subpopulations of infertile men among Hakka population. Whether cytogenetic analysis should be offered in men should be based on cost-benefit analysis, which the cost of unhealth events (such as miscarriages) because of chromosomal abnormalities in males should be considered. Data acquired in our study can be used in these future economic models.

Acknowledgements

The author would like to thank other colleagues whom were not listed in the authorship of Clinical Core Laboratory and Center for Precision Medicine, Meizhou *People's Hospital (Huangtang Hospital), Meizhou* Hospital Affiliated to Sun Yat-sen University for their helpful comments on the manuscript.

Contributors

Pingsen Zhao conceived and designed the experiments; Xiaodong Gu and Man Yang recruited subjects and collected clinical data. Pingsen Zhao, Xiaodong Gu and Huaxian Wang conducted the laboratory testing. Pingsen Zhao and Xiaodong Gu prepared the manuscript.

Funding

This study was supported by Medical Scientific Research Foundation of Guangdong Province, China (Grant No.: A2016306 to Dr. Pingsen Zhao), National Key Research and Development Program of China (Grant No.: 2017YFD0501705 to Dr. Pingsen Zhao), National Key Research and Development Program of China (Grant No.: 2016YFD0050405 to Dr. Pingsen Zhao), Natural Science Foundation of Guangdong Province, China (Grant No.: 2016A030307031 to Dr. Pingsen Zhao) and Key Scientific and Technological Project of Meizhou People's Hospital (Huangtang Hospital), *Meizhou* Hospital Affiliated to Sun Yat-sen University, Guangdong Province, China (Grant No.: MPHKSTP-20170102 to Dr. Pingsen Zhao).

Competing Interests

None declared.

Patient Consent

Patient consent is obtained.

Ethics Approval

The study was approved by the Ethics Committee of the Meizhou People's

Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University.

References

1. Naasse Y, Charoute H, Houate BE, Elbekkay C, Razoki L, et al. (2015) Chromosomal abnormalities and Y chromosome microdeletions in infertile men from Morocco. Bmc Urology 15: 1.
2. Chandley AC (1979) The chromosomal basis of human infertility. Br Med Bull 35: 181-186.
3. Martin R (2008) Cytogenetic determinants of male fertility. Hum Reprod Update 14: 379-390.
4. Kim MJ, Choi HW, Park SY, Song IO, Seo JT, et al. (2012) Molecular and cytogenetic studies of 101 infertile men with microdeletions of Y chromosome in 1,306 infertile Korean men. J Assist Reprod Genet 29: 539-546.
5. PlumX Metrics (2004) Report on optimal evaluation of the infertile male ☆. Fertil Steril 82 Suppl: 123-130.
6. National Collaborating Centre for Women's and Children's Health (2013) Fertility: Assessment and treatment for people with fertility problems. RCOG Press, London, UK. 1: 21-28.
7. Clementini E, Palka C, Iezzi I, Stuppia L, Guancialifranchi P, et al. (2005) Prevalence of chromosomal abnormalities in 2078 infertile couples referred for assisted reproductive techniques. Hum Reprod 20: 437-442.
8. Stegen Ç, Rumste MMEV, Mol BWJ, Koks CAM (2012) The value of chromosomal analysis in oligozoospermic men. Fertil Steril 98: 1438-1442.
9. Gekas J, Thepot F, Turleau C, Siffroi JP, Dadoune JP, et al. (2001) Chromosomal factors of infertility in candidate couples for ICSI: an equal risk of constitutional aberrations in women and men. Hum Reprod 16: 82-90.
10. Dul EC, Ravenswaaijarts CMAV, Groen H, Echtenarends JV, Land JA (2010) Who should be screened for chromosomal abnormalities before ICSI treatment? Hum Reprod 25: 2673-2677.
11. Pylyp LY, Spinenko LO, Verhoglyad NV, Zukin VD (2013) Chromosomal abnormalities in patients with oligozoospermia and non-obstructive azoospermia. J Assist Reprod Genet 30: 729-732.
12. Salahshourifar I, Gilani MAS, Masoudi NS, Gourabi H (2007) Chromosomal Abnormalities in Iranian infertile males who are candidates for assisted reproductive techniques. Int J Fertil Steril 1: 75-79.
13. Riccaboni A, Lalatta F, Caliari I, Bonetti S, Somigliana E, et al. (2008) Genetic screening in 2,710 infertile candidate couples for assisted reproductive techniques: results of application of Italian guidelines for the appropriate use of genetic tests. Fertil Steril 89: 800-808.
14. Yoshida A, Miura K, Shirai M (1998) Cytogenetic survey of 1,007 infertile males. Urol Int 58: 166-176.
15. Van A E, Bonduelle M, Tournaye H, Joris H, Verheyen G, et al. (1996) Cytogenetics of infertile men. Hum Reprod 11 Suppl 4: 1-26.
16. Kim SY, Kim HJ, Lee BY, Park SY, Lee HS, et al. (2017) Y chromosome microdeletions in infertile men with non-obstructive azoospermia and severe oligozoospermia. J Reprod Fertil 18: 307-315.
17. Haidl G, Peschka B, Schwanitz G, Montag M, Vand VK, et al. (2000) Cytogenetic and andrological status and ICSI-results in couples with severe male factor infertility. Asian J Androl 2: 293-296.
18. Dul E C, Groen H, Van Ravenswaaij CM, Dijkhuizen T, Van EAJ, et al. (2012) The prevalence of chromosomal abnormalities in subgroups of infertile men. Hum Reprod 27: 36-43.
19. Wang RX, Fu C, Yang YP, Han RR, Dong Y, et al. (2010) Male infertility in China: Laboratory finding for AZF microdeletions and chromosomal abnormalities in infertile men from Northeastern China. J Assist Reprod Genet 27: 391-396.
20. Mascarenhas M, Thomas S, Kamath MS, Ramalingam R, Kongari AM, et al. (2016) Prevalence of chromosomal abnormalities and Y chromosome microdeletion among men with severe semen abnormalities and its correlation with successful sperm retrieval. J Hum Reprod Sci 9: 187-193.
21. Willatt L, Morgan SM, Shaffer LG, Slovak ML, Campbell LJ (2009): ISCN 2009 an international system for human cytogenetic nomenclature. Hum Genet 126: 603-604.
22. World (2010) WHO laboratory manual for the examination and processing of human semen (Non-serial publications). Asian J Androl 30: 9-9.
23. O'Brien KLOF, Varghese AC, Agarwal A (2010) The genetic causes of male factor infertility: A review. Fertil Steril 93: 1-12.
24. Kanakis GA, Nieschlag E (2018) Klinefelter syndrome: More than hypogonadism. Metab Clin Exp 2: 1.
25. Gentiluomo M, Crifasi L, Luddi A, Locci D, Barale R, et al. (2017) Taste receptor polymorphisms and male infertility. Hum Reprod 32: 2324-2331.
26. Leushuis E, Jawd VDS, Steures P, Repping S, Bossuyt PM, et al. (2010) Reproducibility and reliability of repeated semen analyses in male partners of subfertile couples. Fertil Steril 94: 2631-2635.
27. Cocuzza M (2015) RE: Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination. International Braz J Urol Official Journal of the Brazilian Society of Urology 41: 181-184.
28. Bernie AM, Ramasamy R, Schlegel PN (2013) Predictive factors of successful microdissection testicular sperm extraction. Basic Clin Androl 23: 1-5.
29. Pa K, Ozçelik NAK (2010) Cytogenetic abnormalities detected in patients with non-obstructive azoospermia and severe oligozoospermia. J Assist Reprod Genet 27: 17-21.
30. Zhang ZB, Jiang YT, Yun X, Yang X, Wang RX, et al. (2011) Male infertility in Northeast China: A cytogenetic study of 135 patients with non-obstructive azoospermia and severe oligozoospermia. J Assist Reprod Genet 29: 83-87.