

Y-chromosome Microdeletion and Male Infertility: a Systematic Review

REVIEW

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Abstract

Objective: Evaluate the current evidence regarding different aspects (Epidemiological, histological, physiological and genetic) of male infertility caused by Y-chromosome microdeletion.

Material and Methods: A systematic review of articles from January 1st, 1996 and February 28th, 2014 present in two databases: MEDLINE and SciELO. The search was performed with the MeSH descriptors "Y Chromosome", "Infertility" and Keyword "microdeletion".

Results: The literature indicates that deletion of AZF, especially AZFc, is related to azoospermia, oligozoospermia or even infertility. The absence of other loci is also underlined by the evidence: AZFa, AZFb and AZFd, even though the prevalence rates are not equidistant. Surveys also show changes in the male hormone physiology varying the levels of testosterone/LH/FSH as well as modifying the gonadal morphology in individuals affected by Y-chromosome microdeletion.

Conclusion: More research is needed focusing on possible deletions that the Y-chromosome may suffer, giving emphasis on their clinical outcomes and correlations with infertility.

Introduction

Infertility affects 10-15% of couples of reproductive age [1-4]. The contribution of factors related to male is between 30-50% [5]. Failures in spermatogenesis are among the main reasons with 50% of

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Keywords

Y-Chromosome, Infertility, Microdeletion, Male Infertility.

cases [6, 7]. However, more than 60% of these cases the origin of reduction in testicular function is unknown [7, 8]. Chromosomal abnormalities are confirmed as one of the common causes of male infertility, the incidence of around 20% is observed in men with azoospermia [9, 10].

Y-chromosome microdeletion has played a causal role in male infertility [7, 11]. Some studies show [5, 12] that the main genetic factors involved in male infertility are chromosomal abnormalities and Y-chromosome microdeletions. The microdeletion of azoospermia factor (AZF) on the Y-chromosome was discovered as a frequent genetic cause associated with male infertility [10]. Several researchers [1, 14-16] suggest that after the Klinefelter syndrome, the Y-chromosome microdeletions is among the most frequent genetic cause of male infertility.

In this sense, the present study was based on the following guiding question: what practical contributions to the scientific literature produced in the period of 1996-2014, has to offer feedback about the impact of the Y-chromosome microdeletion in male infertility? This review highlights male infertility as a major factor responsible for human infertility as well as the Y-chromosome microdeletion as a major etiological factor of the pathogenesis of this comorbidity. Thus, our objective was to evaluate the current evidence concerning to different perspectives (Epidemiological, histological, physiological and genetic) of male infertility caused by Y-chromosome microdeletion, formulating a systematic review of published studies on the subject. Our hypothesis is that, despite the growing interest on the subject, the correlation among deletions of certain genes located on the Y-chromosome and some phenotypes of infertility are not still adequately solid, thus meriting greater theoretical contributions subsidized by multicenter studies as well as research of recognized statistical support as meta-analysis.

Material and Methods

Systematic qualitative review whose selection of the studies was performed broadly through the Virtual Health Library (VHL), which hosts the recognized data bases. Initially, the following descriptors were used:

- # 1 "Y-Chromosome" (Medical Subject Headings [MeSH]);
- # 2 "Infertility" [MeSH];
- # 3 "microdeletion" [Keyword];

Complementing search using the keyword "microdeletion" is justified because this term, though not cataloged in MeSH, is often used to characterize studies dealing with the issue the subject of this review. The results obtained led the research at the online database: Medical Literature Analysis and Retrieval System Online (MEDLINE). A similar search strategy was performed on the basis of SciELO (Scientific Electronic Library Online), using previously mentioned descriptors and equivalent in portuguese language. The period of time raised in the literature was January 1st, 1996 and February 28th, 2014. A reason to delimit the search for the period 1996-2014, was the lack of studies that focused on the Y-chromosome microdeletion and its correlation with male infertility.

The data compilation took place during the months of March and April 2014. The selection of manuscripts occurred primarily through the analysis of titles and abstracts/summaries. The analysis of the articles followed the predetermined eligibility criteria for the inclusion criteria: (1) articles that had in the title at least a combination of the terms outlined in the search strategy; (2) articles written in English, Portuguese or Spanish; (3) Articles that addressed Y-chromosome microdeletion and infertility; (4) Original studies with full text accessible via Portal of Journals of the CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), a virtual library created by the Brazilian Ministry of Health and that has restricted content to authorized users. The elements excluded: (1) non-original

studies such as Letters to the Editor, Prefaces, brief communication, Corrections/Erratum, Reviews, Editorials and Monographs. Manuscripts repeated in more than one database were counted only once.

Then, each sample item was read in its entirety, and the information was entered into a spreadsheet that included authors, year of publication, sample description of the study and main findings (**Table 1**). Some of the articles found were contemplating the theme of the male infertility correlated to other casuistics that it is not the Y-chromosome microdeletion, considering that this study focuses on male infertility as resulting from Y-chromosome microdeletion, correlated data to other elements were not analyzed. The search strategy was performed by two independent researchers, with disagreements decided in consensus with a third researcher senior.

Regarding the search strategy, this occurred in three phases. The first phase occurred in VHL, which we were taken to MEDLINE. In this first stage we use the following strategy: #1 AND #2 AND #3, yielding 190 articles of which 29 were selected. The second and third stages occurred in Scielo. The second stage used descriptors #1 AND #2 AND #3, yielding three articles of which one was selected. In the third phase the descriptors used #1 AND #2, yielding 10 items of which two were selected. In order to enhance the data analysis, the next stage involved the group, for heuristic reasons, of the results on three themes: "Epidemiological aspects of Y-chromosome microdeletion"; "Y-chromosome Microdeletion: Some histological and physiological characterizations" and "Microdeletion of Y chromosome: major sub-regions affected."

This was a literature review therefore no involving recruitment of patients. In this sense, ethical approval was not necessary. This revision is using the PRISMA protocol (<http://www.prisma-statement.org/>).

Results

According to the strategy adopted initially 203 manuscripts were found. Articles repeated in the course of the search strategy were computed only once. After reviewing the titles, abstracts and manuscripts entirely cited, the total of 32 articles were obtained and selected according to the eligibility criteria, being therefore excluded 171. The 32 studies were divided into three predetermined categories: "epidemiological aspects of Y-chromosome microdeletion"; "Y-chromosome Microdeletion: Some histological and physiological characterizations" and "Y-chromosome Microdeletion: major sub-regions affected." (**Figure 1**).

Given the importance of the category "Y-chromosome microdeletion: major sub-regions affected" and aiming at making the approach of the clear data, made to **Table 2**, which included authors, year of publication, patients with Y-chromosome microdeletion, percentage of carrier microdeletion sample in the following areas respectively - AZFa, AZFb, AZFc and other areas. Of the 32 selected studies 14 are from descriptive [1, 2, 4, 13, 24, 27-29, 31, 32, 34-37], 08 are cross-sectional [3, 5, 17, 18, 21, 25, 26, 33], 05 are experimental [7, 12, 19, 20, 38], 03 are case reports [22, 30, 39] and 02 are case-control studies [10, 23]. Studies have good methodological accuracy. The sample universe is quite heterogeneous, given the very design of the studies (22 case reports with 02 individuals up to 33 cross-sectional studies with 4, 441 individuals), age differences between individuals in the samples ranging from 17 years [10] to 66 years [21], as well as the origin of the patients who were: India [2, 23, 25, 35], Brazil [3, 31, 34, 36], China [4, 10, 17, 18], Iran [1, 7, 19, 21] Turkey [5, 26, 27], Italy [12, 29], Germany [13], Chile [40], Korea [20], Denmark [37], USA [22], England [38], Mexico [30], Serbia [28] and Venezuela [32]. Because of this situation, the data becomes divergent and the comparative analysis becomes troublesome.

Table 1. Y-chromosome microdeletion and male infertility: a systematic review. Main Findings.

Author (Year)	Journal	Sample	Main Findings
Fadlalla et. al. (2014) [17]	Iran J Reprod Med	2034 infertile men including 691 patients with abnormal sperm parameters were investigated retrospectively	As the same as chromosomal abnormalities group, the volumes of testes ($p=0.000$ and 0.000 , respectively) and the levels of testosterone (T) ($p = 0.000$), and testosterone/ luteinizing hormone (T/LH) ($p = 0.000$) of patients with Y-chromosome microdeletions were significantly lower than those of fertile group. In addition, the levels of follicle-stimulating hormone (FSH) ($p = 0.000$), and luteinizing hormone (LH) ($p = 0.000$) were significantly higher in patients with Y-chromosome micro deletions than those in the fertile group.
Choi et. al. (2012) [18]	PLoS One	377 patients with azoo-/oligozoospermia and 217controls were analyzed using multiplex polymerase chain reaction (PCR), analysis of DAZ-CDY1 sequence family variants (SFVs), and quantitative fluorescent (QF)-PCR.	Of the 377 men with impaired spermatogenesis, 59 cases (15.6%) had partial AZFc deletions, including 32 gr/gr (8.5%), 22 b2/b3 (5.8%), four b1/b3 (1.1%) and one b3/b4 (0.3%) deletion. In comparison, 14 of 217 normozoospermic controls (6.5%) had partial AZFc deletions, including five gr/gr (2.3%) and nine b2/b3 (4.1%) deletions. The frequency of gr/gr deletions was significantly higher in the azoo-/oligozoospermic group than in the normozoospermic control group ($p = 0.003$; OR = 3.933; 95% CI = 1.509–10.250).
Fu et. al. (2012) [10]	J Assist Reprod Genet	Karyotyping using G-banding and screening for Y-chromosome microdeletion by multiplex polymerase chain reaction(PCR)were performed in 200 controls and 1,333 infertile men, including 945 patients with non-obstructive azoospermia and 388 patients with severe oligozoospermia.	One hundred forty four of 1,333 (10.80%) patients presented Y-chromosome microdeletions. Deletion of AZFc was the most common and deletions in AZFa or AZFab or AZFabc were found in azoospermic men. In addition, 34 patients had chromosomal abnormalities among the 144 patients with Y-chromosome microdeletions.
Moghbeli-Nejad et. al. (2012) [19]	J Assist Reprod Genet	Karyotyping using G-banding and screening for Y-chromosome microdeletion by multiplex polymerase chain reaction(PCR)were performed in 200 controls and 1,333 infertile men, including 945 patients with non-obstructive azoospermia and 388 patients with severe oligozoospermia.	One hundred forty four of 1,333 (10.80%) patients presented Y-chromosome microdeletions. Deletion of AZFc was the most common and deletions in AZFa or AZFab or AZFabc were found in azoospermic men. In addition, 34 patients had chromosomal abnormalities among the 144 patients with Y-chromosome microdeletions.
Mozdarani Ghoraieian (2012) [7]	J Assist Reprod Genet	Each family is only and presents different dynamic of organization front to cancer experience, however the challenge of the health professional is to articulate these differences and insert them in the care, easing the daily hospitalization.	Each family is only and presents different dynamic of organization front to cancer experience, however the challenge of the health professional is to articulate these differences and insert them in the care, easing the daily hospitalization.

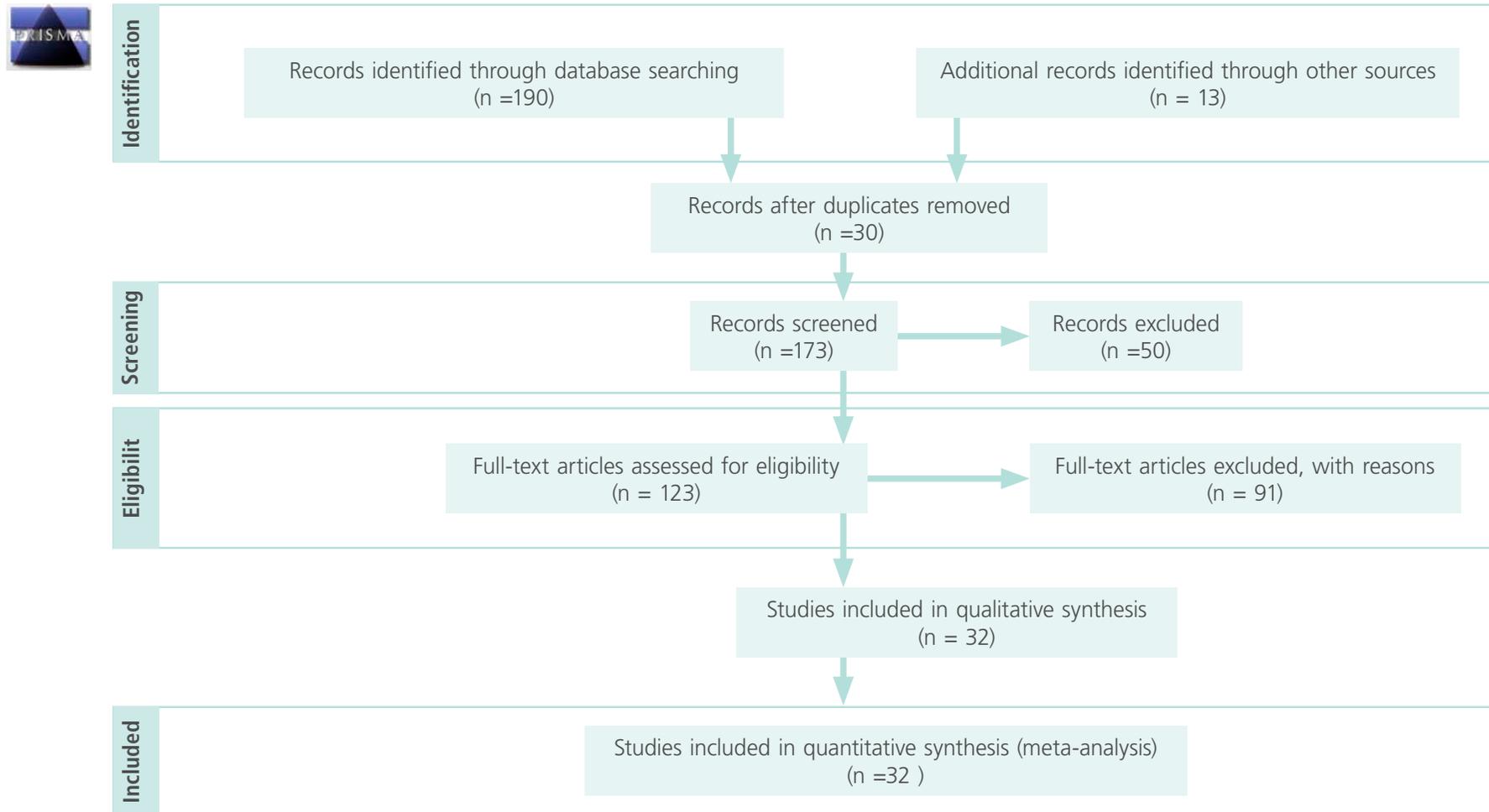
Author (Year)	Journal	Sample	Main Findings
Salimi-nejad et. al. (2012) [1]	Genet Test Mol Biomarkers	94 azoospermic and 21 severe oligozoospermic patients were screened for the presence of Y-chromosome microdeletions. One hundred and five fertile men were included as a control group, as well.	No microdeletions were detected in the men with severe oligozoospermia. In the azoospermic group 2/94 (2.13%) patients showed Y-chromosome microdeletions.
Seung-Hun et. al. (2012) [20]	Gene	37 patients with severe male factor infertility, defined as severe nonobstructive type oligozoospermia ($\leq 5 \times 10^6/ml$) or azoospermia, and 10 controls.	CGH results showed no specific gains or losses related to impaired spermatogenesis other than Yq microdeletions, and there were no novel candidate genetic abnormalities in the patients with severe male infertility.
Totonchi et. al. (2012) [21]	J Assist Reprod Genet.	A total of 3654 infertile men were included in this study.	Out of the 3654 patients who were analyzed, AZF region microdeletions were detected in 185 cases (5.06 %). One hundred and forty-seven cases with Yq microdeletions suffered from azoospermia and 38 from severe oligozoospermia. Our data show that the most frequent microdeletions were in the AZFc region, followed by the AZFb + c + d, AZFb + c, AZFb, AZFa, and AZF a + c regions.
Akin et. al. (2011) [5]	J Assist Reprod Genet	87 infertile men in Turkey.	In remaining 178 subjects, 7 subjects (3.93%) were detected to have Y-chromosome microdeletions. The AZFc region was the most frequently involved region in microdeletion process in affected subjects. All subjects having microdeletion were azoospermic.
Chen et. al. (2011) [22]	J Androl	2 cases of rare genetic anomalies that resulted in hypogonadism.	A Y-chromosome microdeletion assay showed a deletion in the azoospermia factor a region. The second patient presented with infertility and nonobstructive azoospermia.
Mafra et. al. (2011) [3]	Int. braz j urol.	143 infertile men with severe oligozoospermia or non-obstructive azoospermia from the Andrology Outpatient Clinic of the Human Reproduction Service at the ABC School of Medicine.	Chromosomal abnormalities were found in 6.2% of the patients, being more prevalent in the azoospermia group (11.6%) than in the oligozoospermia group (4%). Chromosomal variants were found in 8.3%, and Y-chromosome microdeletions in 4.2% of patients.
Sachdeva et. al. (2011) [2]	Genet Test Mol Biomarkers	200 infertile males in India.	The STS markers prescribed by EAA detected deletions in only 6 (3%) of 200 infertile males. Y-chromosome microdeletions were observed in 21 (10.5%) of 200 patients. Of these, 13 were cases of azoospermia and 8 were cases of severe oligozoospermia.
Gatta et. al. (2010) [12]	BMC Genomics	16 patients carrying an AZFc microdeletion or affected by idiopathic infertility.	An intriguing and unexpected finding is that all the samples showing the AZFc deletion cluster together irrespectively of their testicular phenotypes. The four idiopathic patients present in the cluster showed no testicular expression of DAZ despite the absence of AZFc deletion in the peripheral blood.

Author (Year)	Journal	Sample	Main Findings
Kan, Ganesan e Kumar (2010) [23]	Chemosphere	50 fertile and 50 infertile males.	Out of 100 males studied, we found 10 patients with Yq deletion in AZFa and AZFc regions. Subdivision of infertile group revealed a deletion incidence of 61.5% in azoospermic patients, 11.1% in oligospermic patients and 16.6% in oligo-asthenospermic patients. The presence of Yq deletion in azoospermic patients with a significant mean difference of beta-HCH and total HCH in relation to reduced semen quality seem to corroborate with the mutagenic activity of HCH.
Pandey et. al. (2010) [24]	Genetics and Molecular Research	64 clinically diagnosed infertile male patients.	We found a 3% frequency of microdeletion of the AZFc region; hormone profiles (FSH, LH and testosterone) showed significantly ($P<0.001$) elevated levels compared to controls. No mutations were observed in the AZFa and AZFb regions.
Abid et. al. (2008) [25]	J. Clin. Lab. Anal.	200 men were recruited for clinical examinations, spermograms, hormonal profiles, and cytogenetic and Yq microdeletion profiles.	3.0% had Yq microdeletions, which is very low as compared to other populations. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were significantly increased in men with nonobstructive azoospermia (NOA) as compared to severe oligoasthenozoospermia ($P<0.0001$), whereas testosterone levels were significantly decreased in men with microdeletions as compared to men with no microdeletions ($P<0.0083$).
Balkan, Tekes e Gedik (2008) [26]	J Assist Reprodut Genet	80 infertile males (52 were azoospermic, 25 oligospermic and 3 asthenospermic).	The deletions of Y-chromosome were seen in one patient (1.3%) with features of normal karyotype and azoospermia. Microdeletions were seen in the AZFc and AZFd regions. Neither AZFa nor AZFb microdeletions were detected.
Çinar et. al. (2008) [27]	Genet Test	Sixty-three infertile males [44 nonobstructive azoospermic, 8 severe oligozoospermic, and 11 oligoasthenoteratozoospermic].	Microdeletion and sex chromosome aneuploidy (47,XXY) rates in somatic cells were found to be approximately 3.2% and 4.7%, respectively
Zhu et. al. (2008) [4]	Asian J Androl	178 infertile patients with azoospermia (non-obstructed), 134 infertile patients with oligozoospermia as well as 40 fertile man	The microdeletion frequency was 14% (25/178) in the azoospermia group and 8.2% (11/134) in the oligozoospermia group. Among 36 patients with microdeletions, 19 had deletions in the AZFc region, seven had deletions in AZFa and six had deletions in AZFb. In addition, four patients had both AZFb and AZFc deletions. No deletion in the AZF region was found in the 40 fertile controls.

Author (Year)	Journal	Sample	Main Findings
Ristanovic et. al. (2007) [28]	Genetika	90 patients with normal cytogenetic findings with azoospermia and severe oligozoospermia	Deletions on Y-chromosome were detected in 14 of 90 cases (15.6%), 9 with azoospermia and 5 with severe oligozoospermia. Of total number of 17 deletions, 11 (64.7%) were detected in AZFc region, 3 (17.6%) in AZFa region and 3 (17.6%) in AZFb region. Microdeletions in AZF region of Y chromosome, especially AZFc microdeletions, represent common genetic cause of idiopathic azoospermia and severe oligozoospermia in Serbian infertile men.
Ferlin et. al. (2007) [29]	J Clin Endocrinol Metab	3073 consecutive infertile men, of which 625 were affected by nonobstructive azoospermia and 1372 were affected by severe oligozoospermia. And ninety-nine patients with microdeletions.	Only 2 of 99 deletions were found in men with more than 2 million sperm/ml. Most deletions are of the AZFc-b2/b4 subtype and are associated with variable spermatogenic phenotype, with sperm present in 72% of the cases. Complete AZFa and AZFb (P5/Proximal P1) deletions are associated with Sertoli cell-only syndrome and alterations in spermatocyte maturation, respectively, whereas partial deletions in these regions are associated with milder phenotype and frequent presence of sperm. Men with AZFc-b2/b4 deletions produce a higher percentage of sperm with nullisomy for the sex chromosomes and XY-disomy.
Meza-Vázquez et. al. (2007) [30]	Acta Urol Esp	Man, 24 years old with infertility	It is suggested that in patients with primary infertility more severe oligozoospermia (or azoospermia), require the detection of Y-chromosome microdeletions in as part of the initial study of infertility, irrespective of concomitant disorders that may be present.
Pina-Neto et. al. (2006) [31]	Braz J Med Biol Res	165 infertile men whose infertility was attributable to testicular problems (60 were azoospermic, 100 were oligospermic and 5 were asthenospermic).	Karyotyping revealed somatic anomalies in 16 subjects (16/165 = 9.6%). Of these 16, 12 were in the azoospermic group (12/60 = 20%) and 4 were in the oligospermic group (4/100 = 4%). Microdeletions of AZF genes were detected in 12 subjects (12/160 = 7.5%).
Fernández-Salgado et. al. (2006) [32]	Invest. clín	29 Venezuelan males with idiopathic azoospermia or oligospermia.	One of 29 patients (3.4%) had Yq microdeletions on AZFc. The frequency of AZF microdeletions in Venezuelan patients was similar to other populations with different ethnical or geographical origin.
Nathanson et. al. (2005) [33]	Am J Hum Genet	large series of TGCT cases with and without a family history of TGCT	Presence of the gr/gr deletion was associated with a twofold increased risk of TGCT (adjusted odds ratio [aOR] 2.1; 95% confidence interval [CI] 1.3–3.6; $P = .005$) and a threefold increased risk of TGCT among patients with a positive family history (aOR 3.2; 95% CI 1.5–6.7; $P = .0027$). The gr/gr deletion was more strongly associated with seminoma (aOR 3.0; 95% CI 1.6–5.4; $P = .0004$) than with nonseminoma TGCT (aOR 1.5; 95% CI 0.72–3.0; $P = .29$).

Author (Year)	Journal	Sample	Main Findings
Carrara et. al. (2004) [34]	Genet Mol Biol	65 infertile individuals, and 56 of them were also screened for microdeletions in Yq11 (AZF region).	Three out of the 56 patients studied were carriers of microdeletions in the AZF region, one of them also presenting a chromosomal mosaicism for an extra i(22p).
Dada, Gupta e Kucheria (2004) [35]	J Biomol Tech	One hundred and seventy five males with nonobstructive oligozoospermia and azoospermia.	DNA was extracted using peripheral blood. The sequence tagged site primers tested in each case were sY84, sY86 (AZFa); sY113, sY116, sY127, sY134 (AZFb); sY254, sY255 (AZFc). Eight of the 133 cases showed deletion of at least one of the sequence tagged site markers.
SãoPedro et. al. (2003) [36]	Bras J Med Biol Research	60 brazilian nonobstructive azoospermic and severely oligozoospermic men.	Four of the 60 infertile patients tested (6.7%) exhibited deletion of the Y chromosome, 2 of them being severely oligozoospermic patients (P10 and P32) and 2 azoospermic men (patients P47 and P57). Patients P10 and P32 presented deletions confined to the AZFc region, involving the DAZ locus. Male relatives of patients P10 and P32 had no Y-chromosome deletions and presented a normal karyotype, suggesting a de novo status of the deletions found.
Bor et. al. (2002) [37]	J Assist Reprod Genet	400 Intracytoplasmic sperm injection (ICSI) candidates attending the Fertility Clinic at Aarhus University Hospital, Denmark.	Chromosomal anomalies were found in 6.1% of azoospermic men and in 2.7% of oligozoospermic men. A high frequency of cytogenetic abnormalities was found in normozoospermic men with fertilization failure (7.4%)
Blanco et. al. (2000) [38]	J Med Genet	Breakpoints of an AZFa microdeletion close to two highly homologous complete human endogenous retroviral sequences (HERV), separated by 700 kb.	Recurrent double crossovers have occurred between the HERVs, resulting in the loss of a 1.5 kb insertion from one HERV, an event underlying the first ever Y chromosomal polymorphism described, the 12f2 deletion. This event produces a substantially longer segment of absolute homology and as such may result in increased predisposition to further intrachromosomal recombination. Intrachromosomal crosstalk between these two HERV sequences can thus result in either homogenising sequence conversion or a microdeletion causing male infertility.
Castro et. al. (2000) [39]	Rev Med Chile	37 year old male with severe oligozoospermia and a history of infertility for thirteen years and surgery for severe unilateral varicocele.	Multiplex PCR revealed the presence of a de novo microdeletion in the azoospermia factor (AZF) c region involving the deleted in azoospermia (DAZ) and basic protein Y-2 (BPY2) genes
Vogt et. al. (1996) [13]	Hum Mol Genet	370 men with idiopathic azoospermia or severe oligozoospermia.	In testis tissue sections, disruption of spermatogenesis was shown to be at the same phase when the microdeletion occurred in the same Yq11 subregion but at a different phase when the microdeletion occurred in a different Yq11 subregion.

Figure 1: PRISMA 2009 Flow Diagram.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

Table 2. Y-chromosome microdeletion and male infertility: a systematic review. Y-chromosome microdeletion: major sub-regions affected.

Author (Year)	Patients with Y-chromosome microdeletion (N)	AZFa (%)	AZFb (%)	AZFc (%)	Others (%)
Fadlalla et. al. (2014) [17]	38 patients with oligozoospermia, oligoasthenozoospermia, oligoasthenoteratozoospermia, and oligoteratozoospermia.	No microdeletion was identified	2.6%	97.4%	No Y-chromosome microdeletion was identified
Choi et. al. (2012) [18]	59 patients with azoo-/oligozoospermia and 14 with normozoospermia	No microdeletion was identified	No microdeletion was identified	gr/gr (50.7%); b2/b3 (42.5%); b1/b3 (5.5%); b3/b4 (1.3%).	No Y-chromosome microdeletion was identified
Fu et. al. (2012) [10]	111 patients with azoospermia and 33 with severe oligozoospermia	9.0%	10.4%	54.2%	AZFab (2.1%); AZFac (2.1%); AZFbc (18.7%); AZFabc (3.5%).
Saliminejad et. al. (2012) [1]	02 patients with azoospermia	No microdeletion was identified	No microdeletion was identified	50%	AZFbc (50%)
Seung-Hun et. al. (2012) [20]	10 patients with azoospermia or oligozoospermia	No microdeletion was identified	No microdeletion was identified	70.0%	AZFb-c (30%)
Totonchi et. al. (2012) [21]	147 patients with azoospermia and 38 with severe oligozoospermia	2.7 %	5.9%	52.9 %	AZFac (0.54%); AZFbc (19.45%); AZFcb (2.7%).
Akin et. al. (2011) [5]	07 patients with azoospermia	No microdeletion was identified	No microdeletion was identified	71.4%	AZFabc (14.3%); AZFbc (14.3%)

Author (Year)	Patients with Y-chromosome microdeletion (N)	AZFa (%)	AZFb (%)	AZFc (%)	Others (%)
Mafra et. al. (2011) [3]	03 patients with azoospermia and 03 with oligozoospermia	16.7%	No microdeletion was identified	50%	AZFb-c (33.3%)
Pandey et. al. (2010) [24]	02 infertile patients	No microdeletion was identified	No microdeletion was identified	100%	No Y-chromosome microdeletion was identified
Balkan, Tekese Gedik (2008) [26]	01 patient with azoospermia	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	AZFc-d (100%)
Zhu et. al. (2008) [4]	25 patients with azoospermia and 11 with oligozoospermia.	19.4%	16.6%	52.8%	AZFb-c (11.2%)
Ristanovic et. al. (2007) [28]	9 patients with azoospermia and 5 with severe oligozoospermia	17.6%	17.6%	64.7%	No Y-chromosome microdeletion was identified.
Pina-Neto et. al. (2006) [31]	07 patients with oligospermia, 04 with azoospermia and 01 with asthenozoospermia.	19.4%	25%	52.8%	AZFb-c (2.8%);
Fernández-Salgado et. al. (2006) [32]	01 patient with azoospermia	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	100%	No Y-chromosome microdeletion was identified
Carrara et. al. (2004) [34]	03 infertile patients	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	100%	No Y-chromosome microdeletion was identified
Dada, Gupta e Kucheria (2004) [35]	07 patient with azoospermia and 01 with oligoasthenozoospermia	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	100%	No Y-chromosome microdeletion was identified
SãoPedro et. al. (2003) [36]	02 patients with azoospermia and 02 patients with severe oligozoospermia	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	50%	AZFac (25%); AZFbc (25%)
Bor et. al. (2002) [37]	02 patients with oligozoospermia and 01 with azoospermia	No Y-chromosome microdeletion was identified	No Y-chromosome microdeletion was identified	66.7%	AZFbc (33.3%)

Discussion

Epidemiological aspects of Y-chromosome microdeletion

One hundred and forty four (10.80%) of 1, 333 infertile men showed Y-chromosome microdeletion. The frequency of microdeletions was 11.75% (111/945) in the group of azoospermic patients, significantly higher compared with 8.51% (33/388) of oligospermic patients ($P>0.05$) [10]. Yq Microdeletion (long arm of the Y chromosome) were detected in ten patients in the study by Seung Hun et. al. [20]. Bor et. al. [37] tracked three (0.75%) Y-chromosome microdeletions in a total of 400 blood samples from men undergoing ICSI (Intracytoplasmic Sperm Injection).

In the sample composed to 80 men with infertility in southeast Turkey, the deletion of the Y-chromosome was found in one patient (1.3%) with normal karyotype and azoospermia [26]. Sachdeva et. al. [2] detected by analyzing 200 infertile men in India, microdeletions in 21 (10.5%). Among them, 13 were in cases of azoospermia and eight in cases of severe oligozoospermia. In the study of São Pedro et. al. [36], four (6.7%) of 60 infertile patients tested exhibited Y-chromosome microdeletion, two of whom were patients with severe oligozoospermia (P10 and P32) and two men with azoospermia (P47 and P57).

In evaluating 143 men with severe oligozoospermia and non-obstructive azoospermia, Mafra et. al. [3] reported that the Y-chromosome microdeletions were found in 4.2% of infertile men studied. And that by doing a separate analysis, were detected 3% (3/100) microdeletions in oligozoospermic group of patients and 6.9% (3/43) in the group of azoospermic. Faldalla et. al. [17] found microdeletions in 38 (11, 62%) of 327 patients with altered semen parameters. The authors emphasize that the Y microdeletion rates in patients with oligozoospermia, oligoasthenozoospermia, oligoasthenoteratozoospermia and oligoteratozoospermia are respectively

12.07% (28/232), 10.41% (5/48) 9.52% (2/21) and 33.33% (1/3) [17].

Abid et. al. [25] by analyzing 100 men with severe oligoasthenozoospermia and 100 with nonobstructive azoospermia showed Y-chromosome microdeletions in six (3%), of which three had azoospermia and three asthenoligozoospermia. The opinion of Çinar et. al. [27] is that of the 63 patients Y-chromosome microdeletion were observed in two patients with azoospermia and normal karyotype (46, XY). In one study [37], the frequency of Y-chromosome microdeletions was higher in men with azoospermia (2%) compared with oligozoospermic men (0.6%). Zhu et. al. [4], examining 312 infertile men in Chengdu (China) of which 14% (25/178) of the Y-chromosome microdeletions were found in the azoospermic patients and 8.2% (11/134) in the group of oligozoospermic. In the study of Khan, Ganesan and Kumar [23] there was an index deletion of 61.5% in cases of azoospermia, 11.1% in oligozoospermic patients and 16.6% in oligo-asthenozoospermic patients.

Totonchi et. al. [21] have reported 147 cases with Yq microdeletion who suffered azoospermia and 38 of them severe oligozoospermia. Deletion of the Y-chromosome was found in the study of Ristanovic et. al. [28] in 14 (15.6%) cases, nine with azoospermia and five with severe oligozoospermia. The analysis of an Italian study [29] the microdeletions occurred in 3.2% of unselected infertile men, 8.3% in men with non-obstructive azoospermia and 5.5% in men with severe oligozoospermia [29].

In the work of Saliminejad et. al. [1] microdeletion was not found in men with severe oligozoospermia. And, in the group with azoospermia 2/94 (2.13%) of the patients showed Y-chromosome microdeletions. Four of 60 (6.7%) infertile patients tested in a study [36] showed Y-chromosome deletion, two of which had severe oligozoospermia (P10 and P32) and 2 had azoospermia (P47 and P57 patients).

In a survey of 2012 [10] thirty four patients had chromosomal abnormalities among 144 with Y-

chromosome microdeletion. In the control group of the previously mentioned study, chromosomal abnormalities or microdeletions in AZF region [10] were not detected. Cytogenetic study [5] revealed seven (3.93%) Y-chromosome microdeletions. In Bor et. al. [37] chromosomal abnormalities were found in 6.1% of men with azoospermia and in 2.7% of the oligozoospermic men.

Y-chromosome Microdeletion: Some histological and physiological characterization

Regarding hormonal aspects evaluated in an Indian study [25], the concentrations of FSH (Follicle Stimulating Hormone) in patients with microdeletion were significantly lower when compared to those without microdeletions ($P < 0.017$). The concentration of LH (Luteinizing Hormone) was significantly higher in patients with microdeletions when compared to those without microdeletion ($P < 0.019$). Testosterone levels in patients with microdeletion were significantly lower compared to patients who had not microdeletions ($P < 0.0083$). These evidences are in accordance with Faldalla et. al. [17] whose findings indicate that levels of testosterone, testosterone/LH of the group with microdeletions in the AZF region (azoospermia factor) was significantly lower when compared to the control group ($P = 0.000$). Moreover, the levels of FSH/LH were found significantly higher than those in the control group ($p = 0.000$).

However, Pandey et al. [24] show that hormonal levels (FSH, LH and testosterone) showed significantly higher ($P < 0.001$) in relation to controls, when evaluated 64 men with infertility, of which 3% were in AZFc microdeletion. São Pedro et. al. [36] reported that the 4 patients with Y-chromosome microdeletion in their study, all male had high concentrations of serum FSH. Levels of testosterone and LH were within normal range except for patient P57 (azoospermic) who showed elevation of the serum LH and decreased testosterone.

Studies [13, 25] showed patients with microdeletion and severe aspects in testicular histology (Syndrome of Sertoly-only cells and stop at maturity) compared to non-affected by deletion. In other study [13], two other patients with a microdeletion in proximal Yq11 (patient H49 and HD23) had very small testis volumes (6–8 ml).

Nathanson et. al. [33] demonstrated that deletion of the segment gr/gr AZF region on the Y-chromosome doubling the chance of TGTC (Testicular germ cell tumor), with a three-fold increase for those with a family history of the disease. Deletion gr/gr was more strongly associated with seminoma (aOR 3.0, 95% CI 1.6-5.4, $p = 0.0004$) compared with non-seminoma from TGCT (aOR 1.5, 95% CI 0.72-3.0, $p = .29$) [33]. In the point of view of Dada, Gupta and Kucheria [35] the patient 2 presented in cytopathology Sertoli cell-only syndrome. Patient #3 had deletions of the AZFa region and partial deletion of the AZFb region. In FNAC (Fine needle Aspiration Cytology), patient #3 showed Sertoli cell-only syndrome. The patients 6, 7 and 8 had deletions of the AZFc region of the Y-chromosome. Patients 6 and 8 showed hypospermatogenesis, and patient 7 stop of the maturation in the spermatocyt II stage.

Y-chromosome Microdeletion: Key affected subregions

In the study by Fu et. al. [10] the deletion of AZFc subregion (54.17%) was the most frequent deletion in the AZF. Fifteen infertile patients (10.42%) had a deletion in AZFb subregion (13 azoospermic and two with severe oligozoospermia) and 13 (9.03%) men with azoospermia presented deletions in AZFa subregion. The types of extensive deletions involving two or three completed AZF regions included 2.08% of subregions AZFab, 2.08% of AZFac, 18.75% of AZFbc and 3.47% of AZFabc, respectively [10]. In Totonchi et. al. [21] the most frequent microdeletion was the AZFc region followed by regions AZFb +c+d, AZFb + c, AZFb,

AZFa and AZF a + c. Ristanovic et. al. [28] showed 64.7% deletions in AZFc region, 17.6% in the AZFa region and 17.6% in the AZFb region. Microdeletions in the AZF region of the Y-chromosome, particularly microdeletion of the AZFc region, represented a common genetic cause of idiopathic azoospermia and severe oligozoospermia in infertile men in Serbia [28].

Fernandez-Salgado et. al. [32] detected microdeletions in the AZFc region of the Y-chromosome in 3.4% of the patients. Choi et. al. [18] showed 8.5% Korean men had deletions in the segment gr/gr ($P < 0.003$), 5.8% had deletions of the region b2/b3, 1.1% had deletions in the region b1/b3, 0.3% had deletions in the region B3/B4, totaling 15.6% subjects ($P < 0.001$). The authors also indicate that partial deletions of AZFc region were more often found in men with insufficient spermatogenesis when compared with the control group [18].

Akin et. al. [5] reported that the AZFc region was the most frequently involved in the processes of microdeletion in affected subjects. And that one of the subject (patient 6) had microdeletion in 3 regions (AZFa, AZFb, AZFc) and another individual (patient 2) had microdeletions in AZFb and AZFc regions. All study subjects who had Y-chromosome microdeletion were azoospermic [5]. Gatta et. al. [12] observed that all the samples had a set of deletions in AZFc region (loci sY152 and sY158) regardless of their testicular phenotypes. About the AZFc region, an interesting finding in the study was Moghbeli-Nejad et. al. [19], in which variations in the number of copies of the studied markers in region AZFc of lymphocyte of infertile men (microdeletion and duplication) in all samples after exposure to increased radiation dose dependent. The frequency instability was significantly higher in samples from infertile men compared with fertile ($p < 0.001$) [19].

Patients 1 and 2 from a study [37] presented the Y-chromosome contiguous microdeletion in

the AZFc region, while patient 3 who had azoospermia, had deletions of noncontiguous in the AZFb and AZFc regions. No microdeletions were detected in AZFa region [37]. In Seung Hun et. al. [20] three patients showed deletion in the region AZFb-c and other seven had deletions in AZFc region. No involved new regions were found specifically with male infertility [20]. Saliminejad et. al. [1] detected a patient completed deletion of the AZFc region and another showed completed deletion of both AZFb and AZFc regions. Microdeletion was not found in the AZFa region. Balkan, Tekes and Gedik [26] founded microdeletions in AZFc and AZFd regions, but no microdeletion in AZFa region or AZFb. In Pandey et. al. [24] there was the frequency of 3% of the AZFc microdeletion region, and no mutations were observed in AZFa and AZFb regions, maybe due to selective use of sequences of markers.

Khan, Ganesan and Kumar [23] found ten patients with Yq deletion in AZFa and AZFc regions. In São Pedro et. al. [36], patients with azoospermia showed large deletions. Deletions located in the AZFa and AZFc regions were found in patient P47, while deletions in AZFb and AZFc regions were found in patient P57. Patients with severe oligozoospermia, P10 and P32, showed microdeletions that could not be detected by classical cytogenetic analysis methods, both showed normal morphology for chromosome Y. Patients P47 and P57, on the other hand, showed a chromosomal constitution 46, XY, del(Y)(q11) [36].

In the search of Ferlin et. al. [29] the most deletions are AZFc-b2/b4 subtype and they were associated with variable spermatogenetic phenotype, with present sperm in 72% of the cases. Complete deletions in AZFa and AZFb (P5/Proximal P1) are associated only with the Sertoli cells syndrome and changes in maturation of the spermatocyte, while partial deletions in these regions are associated with milder phenotypes and the frequent presence of sperm. Men with deletions AZFc-b2/b4 produce

a higher percentage of spermatozoa with nulissomia of the sex chromosomes and dissomy of the XY [29].

Carrara et. al. [34] highlight the following chromosomal mosaicism for patient # I-9, 47, XY, +i(22p) [10]/46, XY [90]. In this sample [34], three patients had Y-chromosome microdeletion. Mozdarani and Ghoraeian [7] simultaneously detected the *DAZ* gene (Deleted in azoospermia) in centromeres of X and Y chromosomes, and aneuploidies. About *DAZ*, the PCR multiplex revealed the linked presence of the *DAZ* to AZFc and the presence of genes of basic protein Y-2 (*BPY2*) in one study [39]. In the study by Gatta et. al. [12] four patients showed no expression of *DAZ* in the testis despite the absence of AZFc deletion in the peripheral blood.

Kan, Ganesan and Kumar [23] highlight the presence of Yq deletion in cases of azoospermia with a significant mean difference of β -HCH (hexachlorocyclohexane) and total HCH in relation to reduced semen quality, suggesting corroboration with mutagenic activity of HCH. Recurrent double crossovers have occurred between the HERVs (human endogenous retroviral sequences), in Blanco et al [38] resulting in the loss of a 1.5 kb insertion from one HERV, an event underlying the first ever Y chromosomal polymorphism described, the 12f2 deletion. This event produces a substantially longer segment of absolute homology and as such may result in increased predisposition to further intrachromosomal recombination. Intrachromosomal crosstalk between these two HERV sequences can thus result in either homogenizing sequence conversion or a microdeletion causing male infertility. Finally, the AZFc microdeletions may be associated with characteristics ranging from normal fertility [7], mild oligozoospermia, infertility, characterized by severe oligozoospermia or azoospermia.

Final Considerations

Despite major advances in molecular techniques and cellular biology, infertility is a worldwide public health problem. Its etiopathogenesis is not well understood, however, it's known the importance of the role of microdeletion of subregions of the Y-chromosome in the casuistry. The literature indicates that deletion of AZF, especially AZFc [12, 19, 32], is related to azoospermia [1, 5, 10, 18, 21, 26, 31, 35], oligozoospermia [10, 18, 21, 31, 36], infertility [4, 24] or even normal fertility [7]. The absence of other loci is also underlined by the evidence: AZFa, AZFb, AZFd [10, 20, 21, 23, 25, 29] and although the prevalence rates are not equidistant.

Surveys also show changes in the male hormone physiology varying the levels of testosterone/LH/FSH [17, 25] as well as modifying the gonadal morphology in individuals affected by the microdeletion of Y-chromosome [24, 35].

Therefore, more research is needed focusing on possible deletions that the Y-chromosome may suffer, giving emphasis on its clinical outcomes and correlations with infertility, so that you can draw effective affirmative action policies, and methods of early detection of male infertility.

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