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Azoospermia Factors Microdeletion and Correlation to Male Infertility: An Egyptian Study

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Abstract

Background: Infertility is a major problem that is very challenging for scientists, as numerous causes are reported as idiopathic. Genetic, viral, anatomical, immunological and environmental factors can all play a role in infertility. Male factors account for almost 50% of infertility cases, genetic abnormalities either structural or numerical account for almost 10 to 15% of the problem. While Klinefelter syndrome is considered the most common genetic cause of male infertility, microdeletions of azoospermia factors (AZF) on the long arm of the Y chromosome are the second common. AZF locus carries the genes responsible for spermatogenesis, hence any microdeletion in the subregions of the AZF locus, AZFa, AZFb or AZFc will result in severe oligospermia or azoospermia, consequently infertility. The role of geographical and ethnic variations in the frequency of AZF microdeletions is still debatable.

Aim of Study: To evaluate the frequency of Y chromosome microdeletions in AZF loci in Egyptian men. Thirteen markers in AZF regions were tested; AZFa (sY86, sY87, sY615), AZFb (sY127, sY134, sY142), AZFc (sY197, sY254, sY255, sY1291, sY1125, sY1206, sY242) and analyzed for its clinical significance in infertile Egyptian men.

Patients and Methods: This case-control study was conducted in the Andrology and Clinical Pathology Departments; Faculty of Medicine, Cairo University. In this research, fifty infertile men (19-50 years) who are unable to have children in spite of having frequent non protective sexual intercourse for more than 2 years, were included as cases, while 50 age-matched males as controls. Each subject was tested for thirteen markers in AZF region to determine their association and role, if any, in infertility. Genes in each of the AZFa, AZFb, AZFc subregions were tested and analyzed by Real Time polymerase (PCR) according to established protocols.

Results: Among the 50 infertile men screened for microdeletion, twenty subjects are found to have microdeletions (40%) which is statistically significant (p-value <0.001), seven of which show at least one microdeletion, the rest range from two to ten microdeletions. The frequency of AZFa microdeletion is not significant (p-value = 0.495), however AZFb and AZFc microdeletions are significantly present (p-value = 0.006 and <0.001, respectively). The overall frequency of AZFc microdeletions is the most prevalent (38%). The highest frequency of microdeletion is observed in genes Y1291 on the AZFc locus (26%) which is considered statistically significant with p-value <0.001. Subjects with combined AZFa microdeletion with either AZFb or AZFc are not statistically significant. Nevertheless, combined AZFc and AZFb microdeletion are statistically significant with p-value <0.001. AZF microdeletions are not observed in any of the control subjects.

Conclusion: Our results suggest that the frequency of Y chromosome AZF microdeletions, especially AZFc microdeletions, is elevated in Egyptian males with severe spermatogenic failure and hence a high risk of infertility.

Key Words: *AZF – Y-chromosome – Microdeletion – Azoospermia – Egyptian male infertility – AZFa – AZFb – AZFc.*

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Introduction

INFERTILITY is one of the most challenging problems for scientists. Anatomical, viral, genetic and environmental causes can all play a role in infertility. Male is considered the major reason for this in around half of the cases **[1]**. Genetic abnormalities either structural or numerical accounts for almost 10-15% of the problem, Klinefelter syndrome being the most common **[2,3]**. The majority of genes responsible for the process of spermatogenesis are located in the azoospermia factor (AZF) locus of the long arm of the Y chromosome (Yq) **[4,5]**. Therefore, any microdeletion, deletion or polymorphism on the long arm of the Y chromosome can affect spermatogenesis consequently, severe oligospermia (2-5%) or azoospermia (5-10%) results **[6,7]**. AZF regions, mainly AZFa, AZFb and AZFc, are the most common structural chromosomal anomaly, hence any microdeletion will lead to failure or defective spermatogenesis consequently, infertility **[3,8-10]**. For instance, AZFa microdeletion may cause azoospermia and Sertoli cell-only syndrome **[11,12]**. AZFb microdeletion may result in defective spermatogenesis maturation

and also Sertoli cell-only syndrome [13]. Finally AZFc microdeletions, which are the most prevalent mutation, may result in mild affection in sperm count to azoospermia [11,14]. Deletions are however too small to be studied by karyotyping, advanced molecular techniques made it quite easier to identify deletions and microdeletions by polymerase chain reaction, for instance [15]. Studying different markers on the AZF subregions will help in better understanding the different types of microdeletions and its associations with different clinical presentations, hence better and earlier diagnosis of infertility cases consequently timely and appropriate management [16,17]. It is of note, that the advancement in reproductive therapy and the early diagnosis helped in successful therapy with the aid of reproductive techniques such as intracytoplasmic sperm injection and other ways that are more effective in young age [18].

Patients and Methods

Patients and controls:

The study was conducted at andrology outpatient clinic, El Kasr El Aini, Cairo University from January 2019 to August 2021. A group of 50 male subjects (aged from 19 to 45 years) were enrolled at the outpatient clinic and chosen for this study. All male cases were infertile, failing to conceive after two years of non-protective sexual intercourse. All subjects were subjected to physical examination.

This case-control study was conducted in the Andrology and Clinical Pathology Departments; Faculty of Medicine, Cairo University. For every patient included in the study, an informed consent was obtained before data collection and after explanation of the study objectives. In this research, fifty infertile men age (19-50 years) who are unable to have children in spite of having frequent, unprotected sexual intercourse were included as cases. All cases were medically fit, free form any congenital disorder, with normal sexual life and diagnosed with infertility while 50 age-matched males as controls. They were screened for Y chromosome microdeletions AZFa (sY86, sY87, sY615), AZFb (sY127, sY134, sY142), AZFc (sY197, sY254, sY255, sY1291, sY1125, sY1206, sY242) to determine their role if any in infertility. The thirteen genes on the AZF subregions were analyzed by Real Time Polymerase (PCR) according to established protocols.

Controls are those with at least one live-born children. Those excluded are the hypertensive, diabetic or with anatomical obstruction. Data were collected directly by the researcher for each participant with regard to age, occupancy, medication and chronic illness.

Laboratory evaluation:

Two to four ml blood was withdrawn from patients in a vacuette tube with an anticoagulant either EDTA (2.0mg/ml concentration) or sodium citrate anticoagulant. The Real Time PCR genotyping kit (DNA technology) is planned to extract and amplify DNA from the Y chromosome from peripheral blood sample and detect any microdeletion (sY84, sY86, sY127, sY134, sY142, sY242, sY254, sY255, sY615, sY1125, sY1197, sY1206, sY1291). It also includes a sex-determining region Y protein (SRY gene) to ensure the sample withdrawn is from a male, it also encloses an additional genomic target to make sure that serving as sample intake control (SIC). The PCR mix includes three fluorescent dyes (Fam, Hex and Rox) and quencher molecules. The intensity of the fluorescence is directly proportion to the presence of microdeletion in the sample which is measured automatically by a software.

Statistical analysis:

Data was coded and statistically analyzed using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using frequencies (number of cases) and relative frequencies (percentages). For comparing categorical data, Chi square (χ^2) test was utilized. Exact test was used instead when the expected frequency is less than 5 [19]. p-values less than 0.05 were considered as statistically significant.

Results

In our research 40% (20/50) of the infertile men had a minimum of one microdeletion in one or more loci of the AZF, hence statistically significant with a p-value <0.001 (Table 1). Thirteen genes on the three AZF subregions (AZFa, AZFb and AZFc) were studied from the DNA extracted from blood using real time PCR for any microdeletion.

AZFa microdeletions revealed the least frequency only 4% (2 patients) with one patient showing microdeletions in all the three genes in the AZFa region (Fig. 2). Men, having microdeletions in AZFa locus, did not show any microdeletions in the rest of the loci studied. In this research. p-value for AZFa locus is 0.495 which is not statistically significant, as per Table (1).

Table (1): Frequency of microdeletion in thirteen genes on AZF loci.

AZF Region	Gene		Cases		Control		*p*-value
			Count	%	Count	%	
AZFa	sY86	Deletion	1	2.0	0	0.0	1
		Normal	49	98.0	50	100.0	
	sY84	Deletion	1	2.0	0	0.0	1
		Normal	49	98.0	50	100.0	
	sY615	Deletion	2	4.0	0	0.0	0.495
		Normal	48	96.0	50	100.0	
AZFb	sY 127	Deletion	5	10.0	0	0.0	0.056
		Normal	45	90.0	50	100.0	
	sY134	Deletion	5	10.0	0	0.0	0.056
		Normal	45	90.0	50	100.0	
	sY 142	Deletion	7	14.0	0	0.0	0.012
		Normal	43	86.0	50	100.0	
AZFc	sY1197	Deletion	7	14.0	0	0.0	0.012
		Normal	43	86.0	50	100.0	
	sY254	Deletion	7	14.0	0	0.0	0.012
		Normal	43	86.0	50	100.0	
	sY255	Deletion	6	12.0	0	0.0	0.027
		Normal	44	88.0	50	100.0	
	sY 1291	Deletion	13	26.0	0	0.0	<0.001
		Normal	37	74.0	50	100.0	
	sY1125	Deletion	3	6.0	0	0.0	0.242
		Normal	47	94.0	50	100.0	
	sY 1206	Deletion	7	14.0	0	0.0	0.012
		Normal	43	86.0	50	100.0	
	sY242	Deletion	7	14.0	0	0.0	0.012
		Normal	43	86.0	50	100.0	
	Deletion in any	Deletion	20	40.0	0	0.0	<0.001
		Normal	30	60.0	50	100.0	

Moreover, the majority of microdeletions are detected in the AZFc, as per Fig. (2), with the highest frequency revealed in the sY1291 (22 %) and the least frequency was found in the sY1125 (6%) (Table 1). The frequency of microdeletions for the genes studied in the AZFc region is 38% which is statistically significant with *p*-value <0.001 (Table 2). No microdeletion is revealed in the control group.

AZFb microdeletions did not show any statistical significance for each of the three genes studied except for sY142 microdeletion where frequency of occurrence in our subjects reached 14% (*p*-value = 0.0 12), as per Table (1). Nevertheless, the frequency of AZFb microdeletions for three genes studied in this subregion (16%) was statistically significant with *p*-value equal to 0.006.

Table (2) and Fig. (2). Microdeletions detected in the AZFb loci were also found in AZFc loci, except two cases that were not found in SY1125. Four cases (8%) showed microdeletions in the three AZFb loci, where these cases also showed microdeletions in the seven loci of AZFc, as per Fig. (1).

Thirteen genes on the AZF locus were studied in the DNA extracted from the patients, as per Table (1). The frequency that any case has at least one microdeletion in any of the genes of the AZF loci studied in this research is 40% which is statistically significant (*p*-value <0.001). The frequency of AZFa microdeletion as well as either AZFb or AZFc is 50% (Tables 3,4).

On the other hand, the frequency that cases have AZFb microdeletion is associated with AZFc

microdeletion is 100%, hence statistically significant with p-value <0.001) (Table 5). In other words, AZFb microdeletions are always associated with at least one microdeletion in AZFc. Screening for the SYR gene revealed no abnormalities in the fertile control group.

Table (6) shows the number of cases that have the microdeletions in each subregion. For example, in AZFc there are seven genes studied in this study, where there are three patients who have microdeletions in all subregions studied (6%). From this table we can conclude that 14% of all the 50 cases have at least one microdeletion of the AZF locus.

Table (2): Frequency of microdeletion in the overall (AZFa, AZFb and AZFc) loci.

	Cases		Control		p-value
	Count	%	Count	%	
AZFa locus:					
Deletion	2	4	0	0	0.495
Normal	48	96	50	100	
AZFb locus:					
Deletion	8	16	0	0	0.006
Normal	42	84	50	100	
AZFc locus:					
Deletion	19	38	0	0	<0.001
Normal	31	62	50	100	

Table (3): Frequency of AZFa microdeletion and AZFb microdeletion.

	AZFa locus				p-value
	Deletion		Normal		
	Count	%	Count	%	
AZFb locus:					
Deletion	1	50.0	7	14.6	0.297
Normal	1	50.0	41	85.4	

Table (4): Frequency of AZFa and AZFc microdeletions.

	AZFa locus				p-value
	Deletion		Normal		
	Count	%	Count	%	
AZFc locus:					
Deletion	1	50.0	18	37.5	1
Normal	1	50.0	30	62.5	

Table (5): Frequency of AZFb and AZFc microdeletions.

	AZFb locus				p-value
	Deletion		Normal		
	Count	%	Count	%	
AZFc locus:					
Deletion	8	100.0	11	26.2	<0.001
Normal	0	0.0	31	73.8	

Table (6): Total number of microdeletions in each patient.

	Microdeletions in subregions	Number of cases	%
AZFa locus number of deletion	3	1	2.0
	1	1	2.0
	0	48	96.0
	3	4	8.0
	2	1	2.0
AZFb locus number of deletion	1	3	6.0
	0	42	84.0
	7	3	6.0
	6	2	4.0
	5	1	2.0
AZFc locus number of deletion	3	2	4.0
	2	3	6.0
	1	8	16.0
	0	31	62.0
Total number of deletions in each patient	10	2	4.0
	9	2	4.0
	8	1	2.0
	5	2	4.0
	3	4	8.0
	2	2	4.0
	1	7	14.0
	0	30	60.0

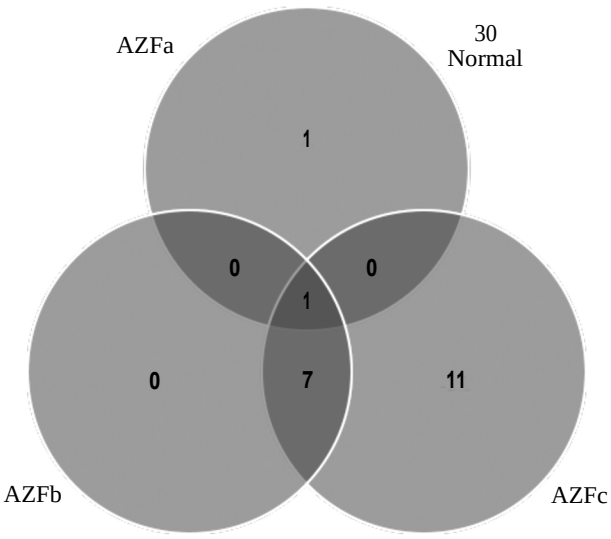

Fig. (1): Diagram manifests the count of normal and total AZFa, AZFb and AZFc microdeletions and their combinations.

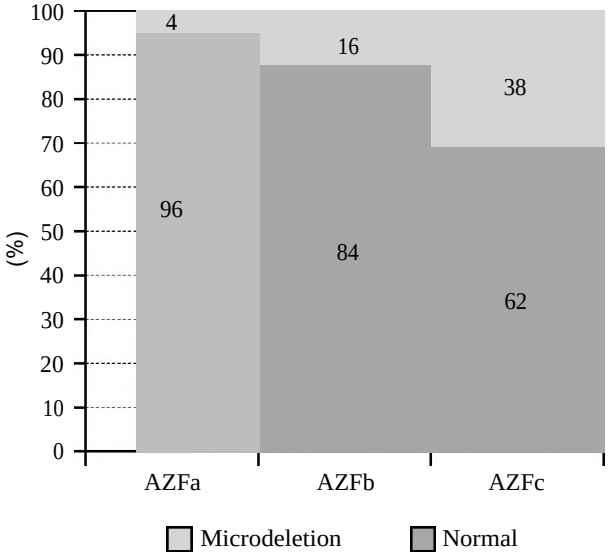

Fig. (2): Microdeletion Frequency in AZFa, AZFb and AZFc in 50 infertile men.

Discussion

Chromosomal abnormalities are considered a very high-risk factor for infertility, as microdeletion in AZF will directly affect spermatogenesis, consequently infertility [20]. As Klinefelter syndrome accounts for almost 64.7% and considered the commonest genetic cause of infertility in men, microdeletion comes second [21]. In the presented research, the total prevalence of AZF microdeletion for the thirteen genes studied was 40%. This is rather comparable to a Sudanese research with a frequency of 37.5% AZF microdeletions [22]. On the other hand, it is in disagreement with a Chinese study where AZF microdeletion is rather low (12.87%). Yet, this low prevalence is still considered more than the national Chinese average [23]. Nevertheless, all these frequencies are in agreement with the reported percentages of AZF deletions which range from 1 to 55% [23,24]. This wide range (1-55%) and discrepancy in frequencies may be a attributed to the geographical and ethnic variation.

With respect to literature, AZFc is the most prevalent deletion in male infertility followed by AZFb then AZFa which is rather rare [25]. This is in concordance with our research, where AZFc microdeletions are 38%, AZFb are 16% and AZFa microdeletions are 4%. In a Syrian research by Al-Achkar et al., the frequency of AZFc microdeletion was 34.8% and AZFb was 15.2% which is comparable to our results [26]. Similarly, in a Serbian study by Ristanovic et al., it was reported that AZFc microdeletion frequency was the highest when compared to the other AZF microdeletions, besides it is being considered the most common genetic cause of idiopathic infertility in Serbian men [27]. In disagreement with our results, a Moroccan study by Imken et al., reported very low frequency for AZFc microdeletions (3.15%) [28] and a Sudanese study by El Said et al., revealed the highest frequency is AZFa microdeletion [22]. A possible explanation for this discrepancy could be due to ethnic or geographical factors, yet it is still debatable if they have a consequential role in infertility [29].

The three regions microdeletions can lead to five microdeletion patterns [11,30], as presented in Fig. (1). Combined microdeletions revealed some thought-provoking results as they may have an impact on prognosis and management. To start with, Al-Achkhar et al., reported combined microdeletions for the three AZF subregions in one case only, which is in concordance with our research results [26]. Similarly, a Moroccan study by Imken et al., reported infertile men with AZFb microdeletion have AZFc microdeletion as well [28]. Our research revealed the same finding, as per Fig. (1).

AZF is located on the long arm of the Y chromosome and subregions of the AZF locus are responsible for different steps in spermatogenesis, hence reflects different patients' manifestations. For instance, AZFa is responsible for the early stages of spermatogenesis and survival of germ cells, thus these patients will suffer from azoospermia [6,15,31,32]. Therefore, intracytoplasmic sperm injection (ICSI) for these patients might be ineffective. In our research, AZFa microdeletions were not statistically significant, where only 2 patients were not normal (4%), one of which showed deletions for all the AZFa markers tested. AZFa showed the least frequency in comparison to the other two loci. This is in agreement with literature [25].

AZFb, on the other hand, is responsible for the maturation of spermatozoa. Therefore, microdeletions in this region cause absence of spermatozoa and hence these patients are good candidates for ICSI [6,33]. According to literature and in agreement with our results, frequency of the AZFb microdeletion is the second common after AZFc.

AZFc, however, is responsible for the final steps in spermatogenesis, hence any microdeletion in this region will result in defect in the quantity and quality of sperm [23,34]. Therefore, semen cryopreservation in early adulthood will be relatively effective for infertile men with AZFc microdeletion [16]. In our research, this microdeletion

was the most frequent, hence eligible for treatment especially those who are young and had AZFc microdeletion solely.

Conclusion:

In summary, the frequencies of AZF microdeletions and chromosomal abnormalities in infertile men from Egypt were comparable with those of infertile men from other countries and regions in the world. Thus, it is advised to conduct molecular testing for Y chromosome microdeletions as an imperative step in diagnosis, management and genetic counseling of infertile Egyptian men. The early detection of Y chromosome microdeletions in infertile men not only identifies the etiology of oligospermia and azoospermia, but also helps for the clinical management of both infertile male and his future male offspring.

Conflict of Interest:

Authors declare no conflict of interest.

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فقد النطاف عوامل الحذف الدقيق والارتباط بالعقم عند الذكور: دراسة مصرية

الخلفية: العقم مشكلة رئيسية تمثل تحدياً كبيراً للعلماء، حيث تم الإبلاغ عن العديد من الأسباب على أنها مجهولة السبب. يمكن أن تلعب العوامل الورائية والفيروسية والتشريحية والمناعية والبيئية دوراً فى العقم. تمثل العوامل الذكورية ما يقرب من ٥٠٪ من حالات العقم أما التشوهات الجينية سواء الهيكلية أو العددية فهى مسؤولة عن ما يقرب من ١٠ إلى ١٥٪ من المشكلة. بينما تعتبر متلازمة كلا ينفيلتر السبب الجينى الأكثر شيوعاً لعقم الذكور، فإن الحذف الصغير لعوامل فقد النطاف (AZF) على الذراع الطويلة لكروموسوم Y هو السبب الثانى الشائع. يحمل موقع AZF الجينات المسؤولة عن تكوين الحيوانات المنوية، وبالتالى فإن أى حذف مجهرى فى المناطق الفرعية من موقع AZF أو AZFa أو AZFb أو AZFc سيؤدى إلى قلة النطاف الشديدة أو فقد النطاف، وبالتالى العقم. لا يزال دور الاختلافات الجغرافية والعرقية فى تكرار عمليات الحذف الصغيرة لمؤسسة AZF محل نقاش.

هدف الدراسة: تقييم وتيرة الحذف الصغير لكروموسو م Y فى مواقع AZF فى الرجال المصريين. تم اختبار ثلاثة عشر علامة فى مناطق: sY1206, sY242) (sY86, sY87, sY615), AZFb (sY127, sY134, sY142), AZFc (sY197, sY254, sY255, sY1291), AZFa sY1125,) وتحليلها لأهميتها السريرية فى الرجال المصريين المصابين بالعقم.

المرضى والطرق: أجريت دراسة الحالات والشواهد هذه فى أقسام أمراض الذكورة والأمراض السريرية، كلية الطب جامعة القاهرة. فى هذا البحث، تم إدراج خمسين رجلاً مصاباً بالعقم (١٩–٥٠ عاماً) غير قادرين على إنجاب الأطفال على الرغم من ممارسة الاتصال الجنسى غير الوقائى المتكرر لأكثر من عامين كحالات بينما تم تضمين ٥٠ ذكرا متطابقاً فى العمر كعناصر تحكم. تم اختبار كل موضوع لثلاثة عشر علامة فى منطقة AZF لتحديد ارتباطهم ودورهم، إن وجد، فى العقم. تم اختبار وتحليل الجينات فى كل من المناطق الفرعية AZFa و AZFb و AZFc بواسطة لوليميراز الوقت الحقيقى (PCR) وفقاً للبروتوكولات المعمول بها.

النتائج: من بين ٥٠ رجلاً يعانون من العقم تم فحصهم من أجل الحذف الصغير، وجد أن عشرين شخصاً لديهم حذف دقيق (٤٠٪) وهو أمر مهم إحصائياً (قيمة $p<0.001$) ، سبعة منهم أظهروا حذفاً صغيراً واحداً على الأ قل، أما البقية فتتراوح من اثنين إلى عشر عمليات حذف دقيقة. تواتر الحذف الصغير AZFa ليس مهماً (قيمة $p=0.495$)، ولكن الحذف الصغير AZFb و AZFc موجود بشكل كبير (قيمة $p=0.006$ و <0.001 على التوالى). معدل تكرار الحذف الصغير AZFc هو الأكثر انتشاراً (٣٨٪) لوحظ أعلى معدل تكرار للحذف الصغير فى الجينات Y1291 فى موضع (٢٦٪ AZFc) والذى يعتبر ذا دلالة إحصائية مع قيمة $p<0.001$. الموضوعات ذات الحذف الصغير AZFa المدمج مع AZFb أو AZFc ليست ذات دلالة إحصائية. ومع ذلك، فإن الحذف الصغير AZFc و AZFb المدمج لهما دلالة إحصائية مع قيمة $p<0.001$. لم تتم ملاحظة عمليات الحذف الصغيرة من AZF فى أى من الأشخاص الخاضعين للمراقبة.

الاستنتاج: تشير نتائجنا إلى أن تواتر الحذف الصغير لكرو موسوم AZF، وخاصة الحذف الصغير AZFv مرتفع فى الذكور المصريين الذين يعانون من قصور شديد فى تكوين الحيوانات المنوية، وبالتالى ارتفاع خطر الإصابة بالعقم