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Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutations in Males with CBAVD versus Nonobstructive Azoospermia: A Review

Elshahat Toson[*1], Husseini Seddiq[1], Hassan Fayed[2] and Rizk Elbaz[3]

[1]Chemistry Department, Faculty of Science, Damietta University.
[2]Dermatology and Venereology, Faculty of Medicine, Mansoura University.
[3]Genetics Unit Children Hospital, Faculty of Medicine, Mansoura University.

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[*] Corresponding author's E-mail: eatoson@yahoo.com

Abstract

Congenital bilateral absence of the vas deferens (CBAVD) accounts for 2-6 percent of male infertility and up to 25 percent of incidences of obstructive azoospermia (OA). Men having azoospermia, teratozoospermia, and oligo asthenospermia had nonobstructive azoospermia (NOA). The relationship between cystic fibrosis transmembrane conductance regulator (CFTR) mutations and poor sperm quality remains to be controversial. In this review, the structure and function of CFTR gene mutations, their classes, their role in spermatogenesis, growth of vas deference, and their relation with CBAVD as well as with non-obstructive azoospermia will be included. Also, techniques for assisted reproductive technology (ART) will be simplified. Finally, the frequency of CFTR mutations in infertile males. Among them, German, Iranian, Chinese, Saudi Arabia, and Egyptian studies will be included. A discussion of their results will be done. The correlations of the results of these studies with the Egyptian ones will be summarized. Therefore, after intracytoplasmic sperm injection (ICSI) therapy, one can expect a higher frequency of CFTR mutations. The latter may increase the prevalence of cystic fibrosis (CF) in the patient's offspring. All patients with CBAVD should urgently undergo CFTR mutations screening, especially during pre-ICSI genetic counseling.

Keywords: CFTR mutations, CBAVD, non-obstructive azoospermia, male infertility.

Introduction

CBAVD as a genital type of cystic fibrosis is responsible for 2–6% of male infertility (**Radpour *et al.*, 2008)**. The clinical signs and symptoms of CBAVD, include slightly smaller or normal testicle size, atrophy in these testicles, or even lack of either the seminal vesicle or cauda epididymis or both. At the same time, a simultaneous follicle-stimulation was observed **(Li *et al.*, 2010)**. Azoospermia, a reduction in seminal volume (<1 ml), seminal fructose concentration, diminished spermatozoa production in the testicles and a slightly acidic or neutral pH value (≤7.0) are all characteristics of CBAVD **(Ferlin *et al.*, 2020)**. CFTR gene

mutations are considered the commonest cause factor of CF, which has the incidence of CF was found to be 1:2,500 **(Gallego *et al.*, 2019)**. Since that obstructive azoospermia caused by isolated CBAVD renders nearly 97% of male CF patients to be sterile, it is possible to speculate that CF and its isolated CBAVD share a genetic basis **(Diao *et al.*, 2013)**. It is generally known that either CFTR mutations or their polymorphisms cause male infertility due to CBAVD **(Cuppens and Cassiman, 2004)**. In this regard, **Yu *et al.* (2012)** added that CBAVD causes most male CF sufferers to be infertile. Unfortunately, the precise biochemical process by which a damaged CFTR causes male infertility is still mostly unclear. Testes from both humans and rodents, germ cells, and Sertoli cells have been found to express the CFTR gene, indicating a potential role in spermatogenesis **(Boock *et al.*, 1998; Gong *et al.*, 2001 and Hihnala *et al.*, 2006)**. The CBAVD-related morphological anomalies appear during embryonic development. Also, CFTR is one of the essential factors of both sperm quality and its fertilizing capacity as was previously reported by **Li *et al.* (2010)**. In 2013 **Diao *et al.*** added that the decrease in the expression of CFTR impairs sperm quality in an age-related manner.

Taking it together, one can conclude that CFTR may be involved in various procedures which were found to be crucial for male fertility. In fact, the role of CFTR gene in the pathophysiology of male reproduction is yet unknown. Therefore, this review will emphasize the advancements in understanding the importance of the CFTR gene in modulating the signaling mechanisms in male infertility and will describe current findings relating CFTR to male fertility and some of the recent research connecting CFTR gene mutations to CBAVD **(Chen *et al.*, 2012)**. How genetic counseling and assisted reproductive technologies (ART) can precisely diagnose and give such patients treatment options will be included. [H1]

CFTR gene structure and function.

The CFTR gene was initially discovered by **Riordan et al** in 1989. It is containing 27 exons, 230 kb, and is found on chromosome 7q31.2 in humans. **(Tsui *et al.*, 2013)**. The protein of such a gene contains 1480 residues of amino acids with a molecular weight of 168.13 kDa **(Guillot *et al.*, 2014)**. CFTR protein is an ATP-bound glycosylated transmembrane structure found on exocrine epithelial cells **(Linsdell *et al.*, 2014).** It consists of two membrane-spanning domains (MSD- 1 and 2). These domains combine to form the selective chloride channel. This channel contains nucleotide-binding domains (NBD- 1 and 2) as well as the regulatory one (R domain). The first two were found to consist of 6 helically transmembrane patterns **(Poroca *et al.*, 2020).** Both NBD-1 and MSD-2 are interconnectedly with the R domain **(Jarosz *et al.*, 2020)**. The selective channel of chloride is formed by both MSD domains, and its gating is controlled by the two NBD ones. Finally, the channel activity will be regulated by the R domain phosphorylation **(Jaworska *et al.*, 2020)**. A highly conserved cyclic AMP-dependent kinase called protein kinase A has several phosphorylation sites in the R domain**.** This enzyme is responsible for RD phosphorylation **(Chen *et al.*, 2020).** This structure was graphically abstracted as shown in Figure 1.

Chemicals and fluids secretions as well as maintenance of electrolytes balance and lumen homeostasis including chloride are facilitated by CFTR. Generally, it is expressed in epithelial tissues of numerous tissue and organs; including vas different, pancreatic cells, gut, and sweat glands **(Nandy et al., 2020)**. Anions or other negatively charged molecules in the regulatory R domain block the chloride channel in the steady state. For such channel action, the R domain must be firstly phosphorylated **(Laselva et al., 2020)**. Generally, the channel will be opened if the protein kinase A (PKA) containing structure becomes activated. Such activation protein increases the amount of intracellular chloride ions **(Mc et al., 2020).** In addition, the extracellular presence of chloride ions can also regulate such channel gating. Further, the increment in the extracellular chloride concentrations was found to promote the opening of the channels. For these reasons, one can suggest that CFTR protein can facilitates the two-way chloride ions permeability across-membrane as was previously reported by **Froux et al. (2020).** Recent research has revealed that CFTR controls a number of ion transporters, including sodium and water channels [H2] **(Cui *et al.*, 2020)**. It also controls chloride ion transportation across the epithelial cells **(Choi et al., 2000; Van et al., 2020).** Consequently, maintaining pH and

ion homeostasis depends critically on physiological processes that are CFTR-dependent.

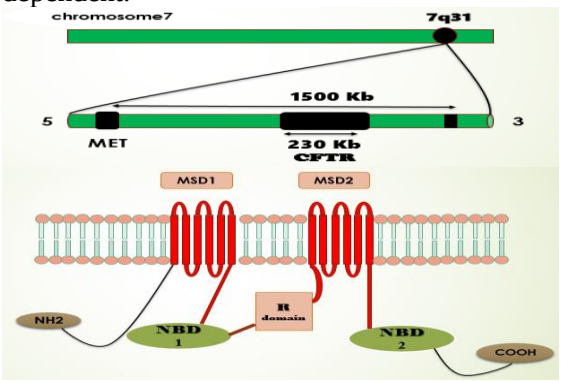

Figure 1: Structural representation of CFTR Protein**.** Membrane-spanning domain **(MSD)**, kilobase **(Kb)**; Nucleotide-binding domain **(NBD)**; methionine (**Met)**; Regulatory domain **(RD)**; **C**-terminus **(COOH)**; **N**-terminus (**H2N)**; Cystic fibrosis transmembrane conductance regulator (**CFTR**[H3]**).**

Classes of CFTR mutations.

The mutations in CFTR can not only reduce protein expression, and therefore its function, and stability, but also a combination of them **(Amaral and Farinha, 2013; Veit *et al.*, 2016).** The CFTR gene alterations consist of 11.4% splicing, 15.6% frameshift, 39.6% missense, and 8.3% nonsense mutations; 2.6% large and 2.0% in-frame deletions or insertions; 0.7% promoter mutations; and 15.0% presumed non-pathological variants **(Amaral *et al.*, 2015)** .Sex classes of mutations are reported for this gene. The first class which lacks protein synthesis; is formed as a result of the occurrence of nonsense and frameshift mutations, including G542X, W1282X, and frameshift mutations. All of these result in the formation of premature stop codons. Class II; is abnormal intracellular trafficking that causes either a lack of plasma membrane protein or its decrement. The mutations in this class are characterized by amino acid residue deletion, e.g. (ΔF508 and I507del). ΔF508 is the most effective. It can also be considered as a golden standard cause of the disease. In Class III; the protein is located at the membrane. It was found that such protein had a defect response to cAMP stimulation. Mutations in this class are mainly of the missense type (G551D). Class IV; decreased in the mediate the conductance. In this regard, the abnormality in anion conductance mainly results in the impairment of function in the protein (R117H). Class V; a reduction in protein synthesis occurs. This group of mutations includes those that cause both aberrant and normal CFTR to coexist (3849-10kbCT). The last Class is characterized by a reduction in plasma membrane protein stability. This finally renders CFTR to fold, move, and function (nearly) normally, but with a shorter lifetime of the membrane (120del123) **(Ramalho *et al.*, 2009**) .

CFTR and spermatogenesis.

Spermatogenesis is defined as a complicated process. In this process, the primitive stem cell is divided for its re-newel to generate its daughter cells. The latter develops into sperms synthesizing cells via meiosis. In this regards, many functional and morphological differentiations are included. All of them are hormonal-dependent. Among these follicles stimulating hormone (FSH[H4]), luteinizing hormone (LH[H5]), and testosterone are included. These events take place at the Sertoli cells that support the seminiferous tubules. Male infertility can be brought on by spermatogenic defects such as azoospermia, oligospermia, and teratozoospermia **(Chen *et al.*, 2012).** In 1991 the gene expression of the CFTR from each testis was established (**Trezise and Buchwald, 1991)**. Therefore, it has been hotly debated for a very long time whether or not CFTR plays a role in spermatogenesis. Early research attempted to address this question by histopathological examining the tissues of male's testis having CF with or without CBAVD. These investigations produced conflicting results, ranging from normal spermatogenesis up to severely decreased spermatozoa number and morphology **(Tuerlings *et al.*, 1998; Larriba *et al.*, 1998)**.

Role of CFTR gene in the growth of the vas deferens.

Primary infertility affects most male CF and CBAVD patients **(Van *et al.*, 2020),** indicating that the CFTR protein is important to the development of the male reproductive system **(De *et al.*, 2020)**. Male genital epithelial cells produce highly viscous mucus because mutations in the CFTR gene inhibit the chloride channel's function. As a result, the passage of chloride ions as well as water across the cellular membrane was impaired **(Morris *et al.*, 2020)**. As a result, the vas deferens, which are blocked

by this mucus throughout embryonic development will be denatured or deteriorated as a result in 12-18-week-old **(Galillard *et al.*, 1997)**. Additionally, **Gaillard *et al.* (1997)** found that human embryos with mutations in CFTR had low levels of CFTR expression in their epididymal epithelium; especially at the 10-33 weeks of gestation. Such decrements lead to a generation of highly viscous mucus from the epithelial cells of the male genital tract. The absence of CFTR mutations in CBAVD cases with renal insufficiency which was reported by **Gaillard *et al.* (1997)** leads one to conclude that, mesonephric not only mediates the formation of the vas deferens but also plays a significant role in their context**.** Also, it has been established that fluid secretion is important for the mesonephric duct to normally mature **(Morris *et al.*, 2020).** Normal development is inhibited by abnormal fluid secretion, these results in early embryonic degeneration and mesonephric duct hypoplasia. Thus, CFTR may be crucial for the formation of the vas deferens, and therefore, CFTR mutations may contribute to the development of CBAVD **(Gaillard *et al.*, 1997; Morris et al., 2020).**

Causes of azoospermia.

This cause included obstructive and non-obstructive ones. CBAVD exemplifies one of the obstructive causes.

Congenital Bilateral Absence of the Vas Deferens (CBAVD).

One to two percent of infertility in males is due to CBAVD **Hussein *et al.* (2011),** reported that male infertility is the predominant symptom of this condition. Lack of bilateral vas deferens is a characteristic. This criterion prevents sperm from leaving the tests after passing through the epididymis **(Bieth *et al.*, 2021)**. As a result, CBAVD is frequently discovered through infertility which is caused by a lack of sperm. CF-related CBAVD is a human autosomal recessive condition. This condition affects more than 95% of CF cases. These might have CBAVD as one of its symptoms as was previously reported by **Chillón *et al.* (1995)**. If CBAVD is not linked to CF; in this case, the disorder is termed as isolated CBAVD **(Bieth *et al.*, 2021).** Other congenital urogenital disorders; primarily dysplasia which is characterized by the lack of kidneys as well as seminal vesicles can coexist with CBAVD in addition to symptoms of CF **(Casals *et al.*, 2000; Akinsal *et al.*, 2018)**. By using ART and sperm extraction surgery, patients with CBAVD can conceive children **(Llabador *et al.*, 2015)**. In 2018 **de Souza *et al.*** showed that genetic mutations that have a certain inheritance in the offspring of patients having CBAVD are widely acknowledged to be the pathogenesis for CFTR. Therefore, males' patients having CBAVD together with their female's partner's must be forced for genetic counseling if they are thinking to have a child. The reason is to prevent or minimize their offspring to have a risk of CF and consequently CBAVD**.**

Non-obstructive Causes

In married couples with azoospermia in the male partner, the use of advanced ART is considered to improve the incidence of pregnancy. Since the distinction between OA and non-obstructive one (NOA) is crucial, it is necessary at first to distinguish. OA has good results for conception and is a reasonably benign disorder. Surgery can sometimes be used to successfully reconstruct it **(Miyaoka *et al.*, 2018)**. Whereas NOA is difficult to treat and typically necessitates not only highly advanced Microdissection Testicular Sperm Extraction (microTESE) but also additional Intracytoplasmic Sperm Injection (ICSI), it results in generally mediocre outcomes **(Dohle *et al.*, 2004; Esteves *et al.*, 2014)**. The distinction between OA and NOA is therefore crucial in patient counseling to set realistic expectations.

NOA is seen more frequently than OA. Despite a thorough diagnostic investigation, its etiology can still be unknown. Contrarily, due to its congenital or acquired character, OA typically has a distinct etiology. To differentiate between OA and NOA, at least in part on the lab level, the levels of serum hormones, and the findings of genetic testing are used **(Gamidov *et al.*, 2021).**

Techniques used for assisted reproduction.

CBAVD patients more found to be more likely to have mild CFTR gene mutations if compared with those having CF, these patients are categorized under the IV and V classes of CFTR mutated gene i.e., those having CFTR protein

dysfunction. In general, most patients with CBAVD are presented with normal spermatogenic activity. Therefore, such partners may be impregnated either via testicular tissue sperm extraction (TESE) or through intracytoplasmic sperm injection (ICSI). In each case, a single sperm is selected. The selected male sperm is then injected into the cytoplasm of the partner's mature oocyte related to its partner in order to obtain the target embryo. To the reader's knowledge, the year 1987 was the first to identify pregnancy and newborns for couples with CBAVD male **(Silber et al., 1990)**. The source of either fresh sperm or a frozen one can be used as a source of sperm. Epididymal or testicular sources of sperm were also reported by **Nicopoullos et al, (2004).** Together play no role in the percentage of ICSI success or even increment in the percentage of such success. In their meta-analysis, they added that patients with acquired aspermia had a higher rate of fertilization and a lower rate of miscarriage compared to those with CBAVD **(Nicopoullos et al., 2004).**

Thus, it's extremely important for patients with CBAVD to be subjected to genetic counseling prior to their undergoing ART. This is due to the potential inheritance of the CFTR mutation and the increment risk of CF incidence **(Rechitsky et al., 2013).**

Additionally, the bad risk of both CF and CBAVD in the progeny was uncertain; especially when uncommon mutations in males and females were found. In addition, parents must be aware that while testing for CFTR every DNA mutation cannot be identified. This is to say that, negative mutation screening may lessen but not completely remove the possibility of being a carrier for the target disease. Therefore, follow-up of children born to CBAVD-affected couples and their evaluation is extremely important. The choice of CFTR mutations may not cover the whole range of the disease. Thus, it is critical for both the patient and his family to determine whether a guy with CBAVD has CFTR mutations or not. A male embryo that is born for a male having CBAVD has a 50% probability of healthy siblings developing CF. As a result, testing for CFTR gene mutations should be done on both the patient and their partner. If CFTR mutations were not detected in the male partner, the uncertainty of the born child having CFTR mutations is acceptable **(Ferec et al., 2012).**

Mutation frequency of CFTR in males' infertility.

The genetic relationship between CFTR gene mutations and CBAVD-induced male infertility has been thoroughly investigated. In 2001 **Ravnik-Glavac *et al*** discovered that the mutations in the CFTR gene also contribute to another type of infertility apart from those having CBAVD. In this regard, the relationship between variations in sperm parameters and the CFTR gene seems to be uncertain and is mostly unclear **(Stuhrmann *et al.*, 2000)**. The current review aimed to identify the relationship between CFTR mutations and other types of infertility such as azoospermia, oligospermia, teratozoospermia, asthenospermia, and Oligoasthenoteratozospermia.

According to the Germans study by **(van der Ven et al., (1996),** 13 CFTR mutations were examined in the semen of 127 having poor sperm quality. Heterozygous CFTR mutations were found in three of 21 (14.2 percent) azoospermic patients and fourteen mutations of 80 (17.5%) were found in patients with poor sperm quality. In addition, a large German study was done by **Schulz *et al.* (2006)** who examined 597 infertile people with Oligoasthenoteratozospermia, asthenospermia, oligospermia, teratozoospermia, and cryptospermia. In their study, CFTR mutations were observed in one of 13 (7.69%) patients with oligospermia, seven of 67 (10.44%) patients with azoospermia, one of 51(1.96%) patients with cryptozoospermia, five of 39 (12.82%) patients with asthenozoospermia, seven of 138 (5.07%) patients with oligo asthenozoospermia thirteen of 282 (4.60%) patients with Oligoasthenoteratozospermia. According to the study[H6] of **Schulz *et al.* (2006)**, the sum of the mutations of the CFTR gene which were observed is 34 among the studied 597 infertile males (5.7%).

Safinejad *et al.* (2011) examined five common CFTR mutations; namely G542X, R117H, W1282X, ΔF508, and N1303K in Iranians having congenital absence of the vas deferens (CAVD) with obstructive cause of azoospermia (n=53). They found heterozygous CFTR mutations in 5 of 53 (9.43%) for ΔF508 and in 4 of 53 (7.55%) for G542X**. Heidari *et al.* (2017)** examined two CFTR mutations in Iranian with NOA (n=100). ΔF508 was found in three of 100 (3%) There was no statistically

significant connection between this mutation and NOA. **Asadi *et al.* (2019)** investigated five common CFTR gene mutations (ΔF508, G542X, N1303K, G551D, and W1282X) in Iranian infertile men with NOA (n=50) and CBAVD (n=50). No mutations were found in NOA patients but in CBAVD patient's CFTR mutations were observed in 8 of 50 (16%), 4 of 50 (8%), and 4 of 50 (8%) of subjects were heterozygote for ΔF508, G542X, and N1303K, respectively. Thus, the total number of Iranian individuals having CFTR mutations will be 16 of 50 (32%) with a highly significant contribution of CFTR mutation for male infertility. In a more recent Iranian study **(Jafari *et al.*, 2022).** 200 Iranian infertile men with extremely severe oligozoospermia were studied. In this group of patients, 9 showed a ΔF508 mutation. In addition, 3 showed the G542X mutation and 2 were found to have the W1282X mutation. Further, the N1303K and R117H were found in one patient each. Thus, the sum of Iranian individuals with severe oligospermia having CFTR mutations was found to be 16 of 200, i.e., 8%.

In India, **Sharma *et al.* (2014)** examined 210 infertile males of whom 60 were with a state of NOA and 150 with failure in their spermatogenesis. They found that, the mutations in the CFTR gene were detected in 11% of patients with NOA and 7% of those with spermatogenic failure.

Almaghamsi *et al.* (2020) examined 50 infertile Saudi men with azoospermia or Oligoasthenoteratozospermia for CFTR mutations. Heterozygous CFTR mutations were observed in 7 of 50 (14%). These participants' range of CFTR gene mutations matched those reported in other studies conducted around the world.

In the Chinese study which was carried out by **Li *et al.* (2022),** 151 infertile males were tested for the presence of CFTR mutations. This study includes 61 healthy controls and 18 CAVD cases as well as 72 patients with severe oligo asthenospermia. Only 6 of the 72 patients with severe oligo asthenospermia, or 8.33%, have CFTR mutations. Additionally, high-frequency of CFTR mutations were detected in patients with CBAVD (about 66.7%).

In infertile Egyptian patients, CFTR mutations were only studied in patients having CBAVD. In **Hussein *et al.* (2011)** study, 30 infertile males with CBAVD were included. In their findings, 12 patients were found to have ΔF508 mutation (40%). Also, 14 Egyptian individuals with CBAVD were examined by **Fathy *et al.* (2016)** for the presence of the 5T variant, p.Ser1251Asn mutations, and ΔF508. Heterozygous CFTR mutations for ΔF508 and p. Ser1251Asn were found in 3/14 (21.4%) and 1/14 (7.1%), respectively. Thus, in the study [H7][H8][H9]of **Fathy *et al.* (2016)** the total number of Egyptian patients having CFTR mutations with subsequent CBAVD is 28.5%. This percentage truly matched that of the Iranian study (**Asadi *et al.*, 2019).** On the other hand, the Egyptian study which was created by **Hussein et al. (2014)** showed a higher percentage **(Table 1).**

Conclusions

CBAVD is a typical manifestation of CF. The latter is caused by mutations in the CFTR gene. This is why the mutation in CFTR leads to human male infertility. Upon reviewing the literature in the current review, it was revealed that the infertility risk of male offspring born to males with NOA is still unknown. Therefore, pre-implantation genetic diagnosis (PGD), prenatal diagnosis (PND), as well as genetic counseling, are advised for all couples who received positive results for CFTR mutations. The reason is to avoid the generation of either a child having homozygous (25%) or heterozygous (50%) CFTR mutations Mendelian "monogenic" recessive genetic disorder **(Welsh et al., 2001)**.

Table 1. Frequency of CFTR mutations in German, Iranian, Chinese, Saudi Arabian, and Egyptian studies in infertile males

Authors	Country	Number	Diagnosis	CFTR Mutations
van der Ven et al. (1996)	Germany	n=127	Normal (n=26)	Not found
			Azoospermia (n=21)	G551D (4.7%), G542X (4.7%), ΔF508 (4.7%), R117H (4.7%)
			Asthenozoospermia (n=27)	ΔF508 (14.8%), G542X (3.7%)
			Teratozoospermia (n=4)	G542X (25%)
			Oligoasthenozoospermia (n=5)	3849+10kbC->T/- (20%)
			Oligoteratozoospermia (n=7)	G542X (14.3%)

			Oligoasthenoteratozoospermia (n=16)	ΔF508 (6.25%), G542X (18.75%), 621 + 1G-+T/-(6.25%)
			Asthenoteratozoospermia (n=17)	G542X (5.9%)
			Oligozoospermia(n=4)	Not found
Schulz *et al.* (2006)	Germany	n=579	oligozoospermia (n=13)	
			asthenozoospermia (n=39)	
			Oligoasthenozoospermia (n=138)	ΔF508 (4.35%), R117H (1%), CFTRdele2,3 (0.5%)
			Oligoasthenoteratozoospermia (n=282)	
			cryptozoospermia (n=51)	
			azoospermia (n=67)	
Heidari *et al.* (2017)	Iranian	n=200	Control (n=100)	Not found
			non-obstructive azoospermia's (n=100)	ΔF508 (3%)
Safinejad *et al.* (2011)	Iranian	n=103	control (50)	Not found
			non-CAVD obstructive azoospermia (n=53)	ΔF508 (9.4%), G542X (7.5%)
Asadi *et al.* (2019)	Iranian	n=200	control (n=100)	Not found
			Non-obstructive azoospermia (n=50)	Not found
			CBAVD (n=50)	ΔF508 (16%), G542X (8%), N1303K (8%)
Jafari *et al. (*2022)	Iranian	n=400	fertile men (n=200)	Not found
			very severe oligozoospermia (n=200)	ΔF508 (4.5%), G542X (1.5%), W1282X (1%), N1303K (0.5%), R117H (0.5%)
Sharma *et al. (*2014)	India	n=310	Normal (n=100)	Not found
			non-CBAVD obstructive azoospermia (n=60)	ΔF508 (11.6%), IVS (8)-5T homozygous (6.6%), IVS (8)-5T heterozygous (18.3%), R1358I (1.6%), K1351R (1.6%)
			spermatogenic failure (n= 150)	ΔF508 (7.3%), IVS (8)-5T homozygous (4.6%), IVS (8)-5T heterozygous (8.6%)
Li *et al.* (2022)	China	n=151	controls (n=61)	Not found
			CAVD (n=18)	c.3736A>G (5.5%), c.3468G>T (5.5%), c.595C>T (5.5%), c.3587C>G (5.5%), c.1000C>T (5.5%), c.4056G>C (5.5%), c.635T>G (5.5%), c.482delA (5.5%), c.3208C>T (5.5%), c.1858C>T (5.5%), c.3659C>T (5.5%), c.926C>G (5.5%)
			severe oligoasthenospermia (n=72)	c.2042A>T (1.3%), 4056G>C (1.3%), c.3659C>T (1.3%), c.1586A>C (1.3%), c.3468G>T (1.3%), c.3659C>T (1.3%)
Almaghamsi *et al.* (2020)	Saudi Arabia	n=100	control (n=50)	Not found
			azoospermia or Oligoasthenoteratozoospermia (n=50)	10 in 7 (14%) (c.1408G>A, c.4389G>A, c.2562T>G, c.869+11C>T, c.2909-92G>A, c.3469-65C>A, c.1210-6delT, c.1210-6T>A, c.2988+1G>A, and c.1210-13GT>TG.)
Hussein *et al.* (2011)	Egypt	n=60	controls (n=30)	Not found
			CBAVD (n=30)	ΔF508 (40%), 5T (46.6%)
Fathy *et al.* (2016)	Egypt	n=14	CBAVD (n=14)	ΔF508 (21.4%), p. Ser1251Asn (7.1%)

CFTR, Cystic fibrosis transmembrane conductance regulator; CBAVD, congenital bilateral absence vas deference; n,

Number of cases.

List of Abbreviations.

CFTR, cystic fibrosis transmembrane conductance regulator
NOA, non-obstructive azoospermia
CBAVD, Congenital bilateral absence of the vas deferens
CAVD, congenital absence of the vas deferens
ICSI, intracytoplasmic sperm injection
MSD, membrane-spanning domains
PKA, protein kinase A
NBD, nucleotide-binding domains
FSH[H10], follicles stimulating hormone
LH[H11], luteinizing hormone
microTESE, Microdissection Testicular Sperm Extraction
TESE, testicular tissue sperm extraction
ART, assisted reproductive technology
PGD, pre-implantation genetic diagnosis
PND, prenatal diagnosis

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الملخص العربي

عنوان البحث: الطفرات الجينية لجين التليف الكيسي المنظم للتوصيل عبر الغشاء في الذكور المصابين بالعقم بسبب الانسداد في الوعائين الناقلين والغير مصابين بهذا الانسداد

الشحات طوسون*[١]، حسيني صديق[١]، حسن فايد[٢]، رزق الباز[٣]

[١] قسم الكيمياء - كلية العلوم – جامعة دمياط -دمياط الجديدة – مصر
[٢] قسم الجلدية والتناسلية – كلية الطب – جامعة المنصورة – مصر
[٣] مستشفى الاطفال – كلية الطب – جامعة المنصورة – مصر

يمثل الانسداد في الوعائين الناقلين للحيوانات المنوية أو ما يسمي (CBAVD) نسبة تتراوح من ٢-٦٪ من حالات العقم عند الذكور ومما يصل الى ٢٥٪ من حالات الانسداد بشكل عام. وعند عمل مسح للدراسات السابقة في هذا الصدد وجد انه لاتزال العلاقة بين الطفرات الجينية للجين المنظم للتوصيل عبر الغشاء في النليف الكيسي (CFTR) غير واضحة حتى الان وذلك في الاشخاص الذين ليس لديهم حيوانات منوية في سوائلهم المنوية (Azoospermia)؛ والاشخاص الذين يعانون من وجود تشوهات في الحيوانات المنوية (Teratozoospermia)؛ وأيضا في الرجال الذين يعانون من قصور في سرعة وعدد الحيوانات المنوية (Oligo asthenozoospermia). وفي هذا البحث المرجعي تم شرح وتوضيح تركيب ووظيفة الجين المنظم للتوصيل عبر الغشاء وأهمية دوره في عملية تكوين الحيوانات المنوية، وكذلك دوره في تكوين الوعائين الناقلين لها؛ وعلاقة وجود طفرات في ذلك الجين بوجود انسدادات في الوعائين الناقلين أوفي ظل عدم الاصابة بهذا الانسداد. أضف الى ذلك؛ فقد تم عمل حصر لمعدل انتشار طفرات هذا الجين في بعض دول العالم للذكور العقيمة. وعلى سبيل الحصر فقد شمل هذا البحث المرجعي على بعض الدراسات الالمانية؛ الايرانية؛ الصينية؛ السعودية وكذلك المصرية. وفي نهاية هذا البحث المرجعي تم دراسة ما إذا كان هناك ارتباط بين نتائج الدراسات في الدول المذكورة ومثيلتها في مصر من عدمه. والخلاصة المستنتجة من نتائج هذه الدراسات تشير الى انه يجب اخضاع الأشخاص الذين يعانون من العقم بسب وجود انسدادات في الوعائين الناقلين للفحص الجيني للتليف الكيسي قبل اللجوء لعملية الحقن المجهري أو ما يسمى بأطفال الانابيب وذلك لتجنب إنجاب المزيد من الأطفال المصابين بهذا التليف.