

***STUDY OF CYSTIC FIBROSIS  
TRANSMEMBRANE  
CONDUCTANCE REGULATOR (CFTR)  
GENE IN AZOOSPERMIC PATIENTS***

**THESIS SUBMITTED FOR PARTIAL  
FULLFILMENT OF MASTER DEGREE IN  
DERMATOLOGY AND VENEROLOGY**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

اللَّهُ مَا فِي السَّمَوَاتِ وَالْأَرْضِ  
يَخْلُقُ مَا يَشَاءُ يَهْدِي لِمَنْ يَشَاءُ  
إِن شَاءَ وَيَهْدِي لِمَنْ يَشَاءُ الذُّكُورَ \*  
أَوْ يَزْوِجُهُمْ ذُكْرَانًا وَإِنثَاءً  
وَيَجْعَلُ مَنْ يَشَاءُ مَقِيمًا إِنَّ  
عَلِيمٌ قَدِيرٌ \*

صَدَقَ اللَّهُ الْمَظْلَمِ

الايتين 49 ، 50

من سورة الشورى

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*Amal Mohamed*

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## ***LIST OF ABBREVIATIONS***

<b>µg</b>	Microgram
<b>µl</b>	Microlitre
<b>AD</b>	Autosomal Dominant
<b>Ad</b>	Dark Type A Spermatogonia
<b>Ap</b>	Pale Type A Spermatogonia
<b>AR</b>	Androgen Receptor
<b>AVD</b>	Absent Vas deferens
<b>AZF</b>	Azoospermic Factor
<b>B</b>	Type B spermatogonia
<b>bp</b>	Base pair
<b>cAMP</b>	Cyclic Adenosine monophosphate
<b>CBAVD</b>	Congenital Bilateral Absent Vas deferens
<b>CF</b>	Cystic Fibrosis
<b>CFTR</b>	Cystic Fibrosis Transmembrane Conductance Regulator
<b>CUAVD</b>	Congenital Unilateral Absent Vas deferens
<b>DAZ</b>	Deleted in azoospermia
<b>FSH</b>	Follicular Stimulating Hormone

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<b>g/l</b>	gram per litre
<b>GnRH</b>	Gonadotrophine Releasing Hormone
<b>ICSI</b>	Intracytoplasmic Sperm Injection
<b>IVF</b>	In Vitro Fertilization
<b>L</b>	Leptotene primary spermatocyte
<b>ml</b>	Millilitre
<b>n mol</b>	Nano mole
<b>NOAZ</b>	Non Obstructive Azoospermia
<b>OAZ</b>	Obstructive Azoospermia
<b>P</b>	Pachytene primary spermatocyte
<b>P.aeruginosa</b>	Pseudomonas Aeruginosa
<b>P mol</b>	Pico mole
<b>R</b>	Preleptotene primary spermatocyte
<b>R domain</b>	Regulatory Domain
<b>SCO</b>	Sertoli Cell only syndrome
<b>Taq</b>	Taq polymerase
<b>TRUS</b>	Transrectal Ultrasonography
<b>URA</b>	Unilateral Renal Agenesis
<b>WHO</b>	World Health Organization
<b>Z</b>	Zygotene primary spermatocyte

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## ***Introduction***

Infertility has been reported in 97 % to 98 % of male adults with cystic fibrosis. This condition is associated with azoospermia and defects in the anatomic transport of sperm cells, due mainly to congenital bilateral absence of vas deferens (*Gaillard et al., 1997*).

Congenital bilateral absence of the vas deferens (CBAVD) is a rare cause of male infertility. The condition was found in 2 % of patients with obstructive azoospermia in the Edinburgh infertility clinic and obstructive azoospermia accounts for 0.9 % of male infertility worldwide (*Donat et al., 1997*).

The cloning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and the cooperative research activity in mutation analysis have led to the establishment of genotype and phenotype correlations. The  $\Delta F 508 + / +$  mutation was shown to be the most common genotype and usually associated with severe cystic fibrosis diseases, with lung and pancreatic failure and male infertility (*Tsui, 1992*).

A strong association between CBAVD and mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been identified recently (*Donat et al., 1997*).

Microdeletions affecting various parts of the long arm of the Y chromosome in approximately 10% of men with non obstructive azoospermia and severe oligozoospermia but not in a

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fertile comparison population have been reported (*Hargreave et al., 1996*).

In the majority of cases, CBAVD can now be considered as a genital form of cystic fibrosis, presenting without the other clinical features of cystic fibrosis. Nevertheless, in about 20% of patients, CBAVD is associated with urinary tract malformations and in these cases the etiology of CBAVD is not related to defects in the CFTR gene (*Augarten et al., 1994, Dumur et al., 1995, Casals et al., 1995, Mercier et al., 1995, Rave-Har et al., 1995*).

Similarly, *McCallum T and colleagues* postulated that unilateral renal agenesis (URA) and CBAVD may have a non-CF mutation-mediated genetic basis that leads to abnormal development of the entire mesonephric duct at a very early stage in embryo development ( $< \text{ or } = 7 \text{ weeks}$ ) (*McCallum, et al., 2001*).

## ***Aim of Work***

This work aims to investigate the cystic fibrosis transmembrane conductance regulator (CFTR) gene in patients with azoospermia. Radiological imaging will check associated anomalies in urinary tract.

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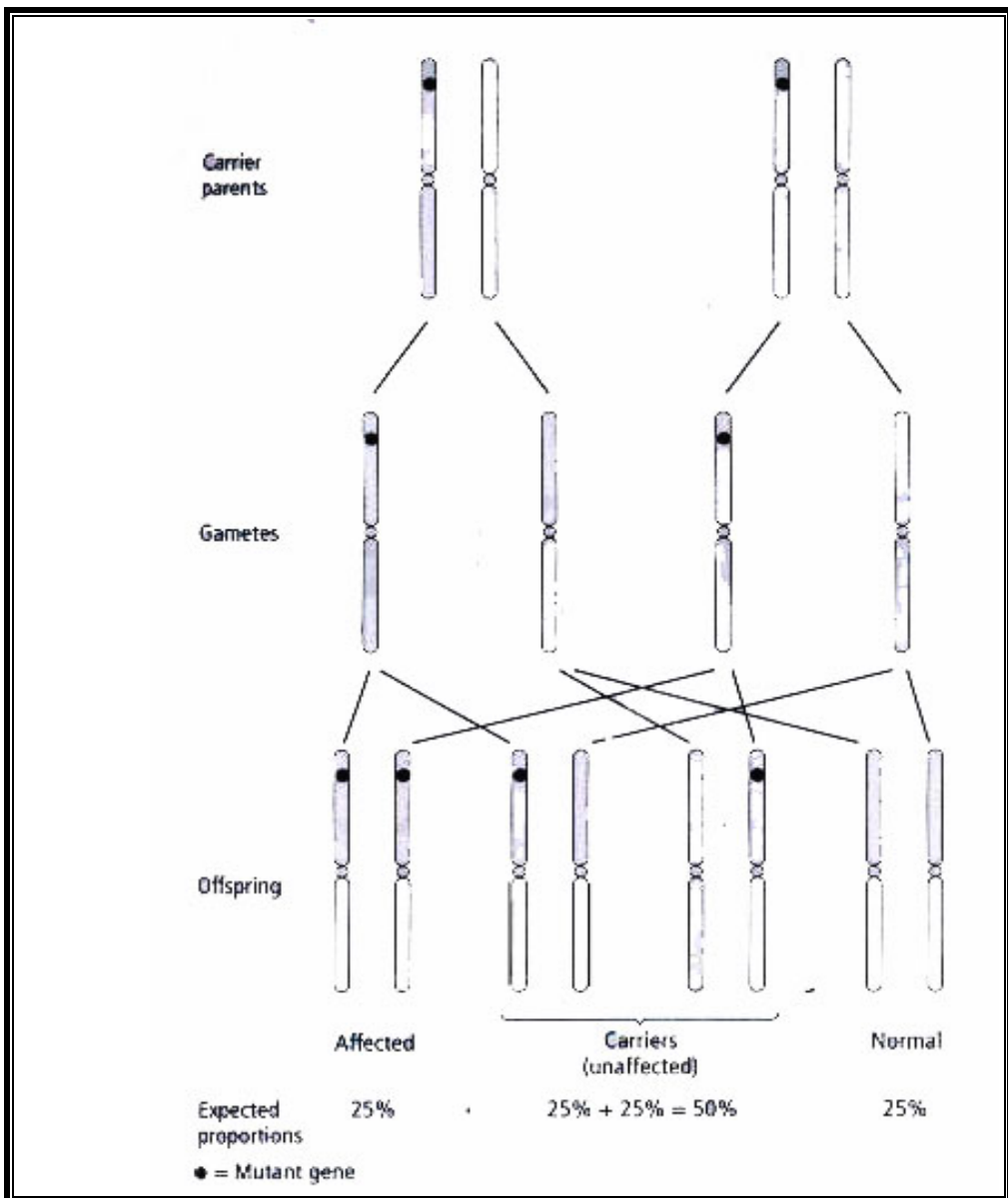
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## ***Autosomal Recessive Disorders***

Of all the recognized single gene traits, more than half are inherited in an autosomal dominant pattern, one third are inherited in an autosomal recessive pattern, and the remainder are x-linked (*Thompson et al. ,1991*).

Autosomal recessive inheritance is the single largest category of mendelian disorders. Because autosomal recessive disorders result only when both alleles at a given loci are mutants, such disorders are characterized by the following features: -

- 1) The trait does not usually affect the parents, but siblings may show the disease.
  - 2) Siblings have one chance in four of being affected (i.e., the recurrence risk is 25% for each birth).Fig. (1).
  - 3) If the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the proband is the product of a consanguineous marriage (*Cotran, 1999*).
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**Fig. (1)** Diagram of autosomal recessive inheritance (*Connor, 1997*).

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In autosomal recessive conditions, both unaffected parents are carriers and each has one mutant copy and one normal copy of the gene. When both parents are carriers, they have a 25% chance with each pregnancy of having an affected child who inherits both copies of the mutant gene (***Roche and Kuller, 1996***).

In contrast to those of autosomal dominant diseases, the following features generally apply to most autosomal recessive disorders: -

- 1) The expression of the defect tends to be more uniform than in autosomal dominant disorders.
  - 2) Complete penetrance is common.
  - 3) Onset is frequently early in life.
  - 4) Although new mutations for recessive disorders do occur, they are rarely detected clinically. Since the individual with a new mutation is an asymptomatic heterozygote, several generations may pass before the descendants of such a person mate with other heterozygotes and produce affected offspring.
  - 5) In many cases, enzyme proteins are affected by a loss of function. In heterozygotes, equal amounts of normal and defective enzyme are synthesized. Usually the natural "margin of the safety" ensures that cells with half their usual complement of the enzyme will function normally (***Cotran, 1999***).
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