Dystrophin gene detection

E S S A Y

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Submitted for Partial Fulfillment of the Masters Degree in Neuro-Psychiatry

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2010

بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية (٣٢)

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Acknowledgment

I would like to express my sincere gratitude to ***Prof. Dr.* Sherif Hamdy** Professor of Neurology, Faculty of Medicine, Cairo University for his excellent guidance, valuable advises and fatherly concern.

I’m greatly indebted to ***Dr. Faisal Abd El-Wahab*** Assistant Professor of Neurology for his meticulous supervision.

I’m also extremely grateful to ***Dr. Sherien Abd El-Fatah*** Assistant Professor of Neurology, Faculty of Medicine, Cairo University, who kindly provided me with a lot of time and effort during the preparation of this essay.

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Abstract

The Dystrophin gene is the largest gene described during the research of the Human Genome project, it is responsible for the formation of the Dystrophin protein in skeletal muscles Disturbances in formation or absence of Dystrophin gene and the protein lead to a group of diseases called: Dystrophinopathies the most severe of which is the Duchenne muscle dystrophy diagnosed by professor Duchenne who described it on clinical diagnosis basis ,later on pathological and genetic studies have been done to fully diagnose both the Duchenne muscle dystrophy and the milder female form: Becker's caused by decreased not quite absence of the Dystrophin gene leading to decreased Dystrophin protein formation, there is a group of Dystrophin associated proteins called: the Dystrophin associated proteins Complex composed of: Dystroglycan and the Dystroglycan Complex, other extracellular matrix proteins, Sarcoglycan complex, Synotrophins and the Dystrobrevin.

Duchenne and Becker's' are diagnosed according to: Clinical basis, histological features, muscle biopsy and testing including genetic testing. Other Dystrophinopathies such as: Manifesting female carriers, Cramps and Myalgia, contiguous Gene syndromes, Outliers and cramps and myalgia syndromes and Duchenne Muscle Dystrophy (DMD)-associated dilated cardiomyopathy (DCM) are diagnosed on clinical basis and genetic testing only. ***Conclusion:*** PCR is recommended to be used in Dystrophin gene non-muscle (Blood samples) detection in Egypt.

Keywords:

Dystrophin gene

PCR

DMD

Introduction

Introduction

Dystrophin gene is the largest gene discovered. The Utrophin is the Dystrophin paralogue, which can be helpful in finding new methods of treatment using it, both the Dystrophin gene and its' protein, the Utrophin are discussed in details in **chapter 1.**

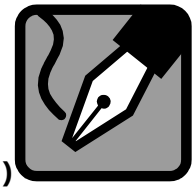
Disturbances in the Dystrophin gene and protein lead to a group of muscle dystrophies called: Dystrophinopathies, in cases of total absence of the gene it results in a severe sex linked muscle dystrophy in males called: Duchenne, while the decrease of the gene and protein lead to Becker's muscle dystrophy in females which is less severe than Duchenne, discussed in **chapter 3**.

Muscle dystrophies are just a category of muscle disorders which are being classified according to the WHO by the International classification of Disease-1 (ICD-10), according to the Muscle Dystrophy association, (MDA), according to the American Association of Neurology, according to site, etiology and other classifications that are discussed in **chapter 2**.

Being the most severe forms of muscle dystrophy it has been an increasing necessity to diagnose Duchenne, Becker's and detect carries, and in order to do that there are many diagnostic basis including: clinical diagnosis, genetic testing, EMG and muscle US, but the detection of the Dystrophin gene remains a core stone in the diagnostic procedure and its' detection was performed by taking a muscle biopsy, until recently some easier methods are being used to detect the gene from a blood sample and are as accurate as a muscle biopsy, which makes it more easier for the physician and the patient and decreases the cost by more than 3 times or

so according to the laboratory cost ranges, recent non- muscle Dystrophin gene detection methods are discussed in **chapter 4**.

Finding hope for treating or even just improving cases of Duchenne muscle dystrophy means hope for all other myopathic and dystrophic cases, being the most severe type, according to such fact many trials for management of Duchenne and researches are being performed such as gene therapy and stem cells therapy, in order to try to find a hopeful treatment for such severe cases, recent treatment trails for muscle dystrophies are discussed in **chapter 5**.



Chapter (1)

Dystrophin

Dystrophin

On the year 1909 the term "gene" was first used and the chemical composition of DNA was discovered. According to the official Guidelines for Human Gene Nomenclature which were first published in 1979 *from The* human gene nomenclature committee, the philosophy of the HGNC remains "that gene nomenclature should evolve with new technology rather than be restrictive as sometimes occurs when historical and single gene nomenclature systems are applied" that is why updates are added to gene symbols ***(Mitelman et al., 1995).***

According to the last updated guidelines a gene is defined as:

"A DNA segment is that contributes to a phenotype and or a function. In the absence of demonstrated function a gene may be characterized by sequence, transcription or homology" ***(Hester-Wain et al., 2002).***

On the year 1953 J. D. Watson and F. H. C*. Crick publish the double-helix model of DNA.****,10 years later on 1963:* ***Nobel Prizes in Physiology or Medicine are shared by J. D. Watson, F. H. C. Crick, and M. H. F. Wilkins for their studies on the three-dimensional structure of DNA. According to the Webster's New World™ Medical Dictionary, 3rd Edition*** *DNA is defined as:* ***DNA****: a molecule in the memorable shape of a double helix, a spiral ladder. Each rung of the spiral ladder consists of two paired chemicals called bases. There are four types of bases. They are adenine (A), thymine (T), cytosine (C), and guanine (G). As indicated, each base is symbolized by the first letter of its name: A, T, C, and G. Certain bases always pair together (AT and GC). Different sequences of base pairs form coded messages* ***(Sarah, 2003).***

***According to the Webster's** a Gene is defined as:*

Gene:** A gene is a sequence (a string) of bases. It is made up of combinations of A, T, C, and G. These unique combinations determine the gene's function, much as letters join together to form words. Each person has thousands of genes -- billions of base pairs of DNA or bits of information repeated in the nuclei of human cells --which determine individual characteristics (genetic traits)* **(Sarah, 2003).

Marshall W. Nirenberg is an American biochemist who shared the 1968 Nobel Prize in Medicine for his work on deciphering the genetic code .**Maxine Singer** also had great contributions in the deciphering of the genetic code*, both scientists described the gene structure that has been approved till the year 2008,current researches are performed to study population genetic structure differences in some societies.* ***Richard Tywman** described the Gene structure on the year 2003 describing two general types of genes in the human genome: non-coding RNA genes and protein-coding genes.*

Non-coding RNA genes represent 2-5 per cent of the total and encode functional RNA molecules. Many of these RNAs are involved in the control of gene expression, particularly protein synthesis. They have no overall conserved structure.

Protein-coding genes represent the majority of the total gene structure and are expressed in two stages: transcription and translation. They show incredible diversity in size and organization and have no typical structure. They have, however, several conserved features ***(Richard-Twyman, 2003).***

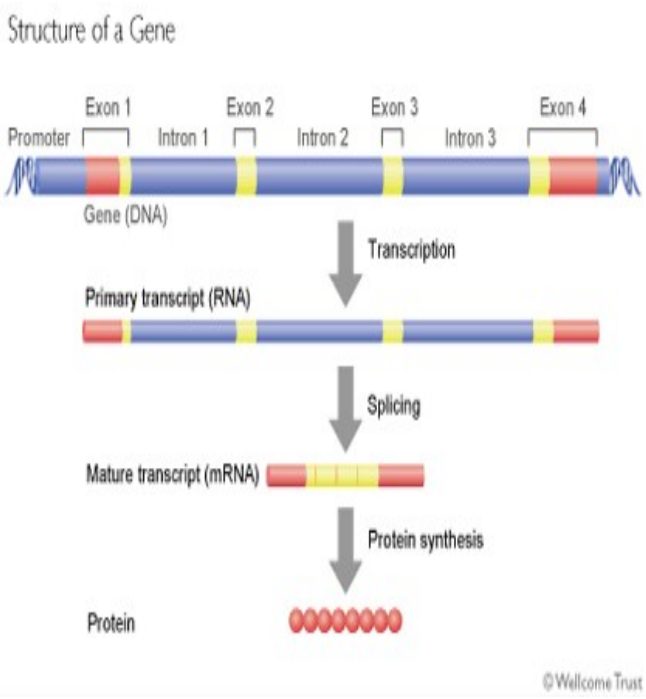


Fig. (1): Simplified overview of gene structure and expression. A protein-coding gene is defined by the extent of the primary transcript. The promoter and any other regulatory elements are outside the gene. The gene itself is divided into three types of sequence. The coding region (light blue) is the information used to define the sequence of amino acids in the protein. The un-translated regions (dark blue) are found in the mRNA but are not used to define the protein sequence; they are often regulatory in nature. Finally introns (white) are found in primary transcript but spliced out of the mRNA. They may interrupt the coding and un-translated regions.

The boundaries of a protein-encoding gene are defined as the points at which transcription begins and ends. The core of the gene is the coding region, which contains the nucleotide sequence that is eventually translated into the sequence of amino acids in the protein.

The coding region begins with the initiation codon, which is normally ATG. It ends with one of three termination codons: TAA, TAG or TGA. On either side of the coding region are DNA sequences that are transcribed but are not translated. These un-translated regions or non-coding regions often contain regulatory elements that control protein synthesis **(Fig. 1).**