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# Predicting Muscular Dystrophy through Genetic testing – A Study

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***Abstract:*** *A pathologic condition impairs the normal function or structure of an organ in human beings. In the current genomic era, the identification of the disease is paramount. Genetic diseases are caused by the abnormalities in the inherited genes. Muscular dystrophy is an inherited genetic disorder that is rooted by the huge number of sequence variants found in large sets of genes. There are about 9 major forms in muscular dystrophy and a better understanding is needed to predict this genetic disease. The mutation in the genes causes most of these disorders. There are currently no effective treatments to halt the muscle breakdown in muscular dystrophies. A new approach is to be designed to predict the muscular dystrophy disease subtypes effectively. As the growth of biological data increases, storage and analysis become incredible this in turn increases the processing time and cost efficiency. This paves the way for challenges in computing. The objective of machine learning is to dig out valuable information from a corpus of data by building good probabilistic models. In this paper, a preface to muscular dystrophy, traditional and innovative approaches involved in identifying this disease are discussed.*

***Keywords****:* Genes, DNA, Mutation, Codon, Genetic disease, Amino acids, Allele

## INTRODUCTION

Muscular dystrophy is a monogenic disease [1] that is caused by mutations in the genes which are in charge of the regular muscle function. Progressive muscle weakness that affects limb, axial and facial muscles are the foremost cause of muscular dystrophy. The other muscles that function in respiratory, cardiac and swallowing are affected in some specific types of muscular dystrophy. In a rare variant, the brain, inner ear, eyes, or skin is impaired by muscular dystrophy disorder [2]. Muscular dystrophy is believed as a genetic ailment flow in a family, even if only one blood relation in the ancestor is affected.

Autosomal recessive, dominant and X-linked are the three patterns of inheritance that causes muscular dystrophy. The recessive pattern of a disease requires two copies of inherited defective genes, one from each parent where both will be carriers of the disease but usually not affected by the disease. The dominant pattern involves, only one copy of the genetic defect to cause the disease. Anyone in the family with the gene mutation can pass the disorder to children. In the case of X-linked, the disease is passed only from mother to their children. In females, two pairs of X chromosomes are present and therefore the daughters turn out into carriers, and generally not affected by the disease. The male comprises of only one X chromosome and gets flawed by muscular dystrophy and hence in most cases the trait is identified in male children. Duchenne, Becker, Emery-Dreifuss, Limb-girdle, Facioscapulohumeral, Myotonic, Spinal, Distal and Charcot Marie tooth disease are the few rare forms of muscular dystrophy [3].

Duchenne muscular dystrophy (DMD) is the X-Linked and most common form of muscular dystrophy is caused by the mutations in the dystrophin gene located on the X chromosome. Dystrophin is the massive human gene that is 2.5MB long and encompasses of 79 exons. The absence of dystrophin gene occurs when a large number of exons are deleted, which is the major cause of DMD [4]. DMD



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causes out frame deletions that happen in the piece of the codon and the sequence read cannot be done. The patients affected by DMD are diagnosed around children in five years of age when the physical ability deviates obviously from their companion. When untreated, the strength of the muscle strength gets worse, and boys are wheelchair dependent at their early stages of the life. The other complications like respiratory, orthopedic, and cardiac emerge, that shortens the life of the patients [5].

Becker muscular dystrophy (BMD) is the X-Linked caused by the mutations in the dystrophin gene located on the X chromosome. It upholds muscle fiber strength, reduces muscle rigidity and increases sarcolemmal deformability. Less defective mutations in the dystrophin gene result display a much milder dystrophic phenotype in affected patients, known as Becker's muscular dystrophy [4,5]. BMD causes in frame deletions that take place beyond the codons and the sequence still can be read after deletions.

Emery-Dreifuss muscular dystrophy (EMD) can be affected in patients, typically in their childhood and in the early adolescent years with muscle contractures. The symptoms include cardiac conduction defects, muscle weakness and arrhythmias. If the patients left untreated in the early stage, it leads to increasing the risk of stroke and sudden death. The mutations in the Emerin (EMD) and Lamin A/C (LMNA) genes cause Emery- Dreifuss muscular dystrophy. Mutations like point mutations, insertions and deletions in the genes direct to EMD. X-Linked, autosomal dominant and autosomal recessive are three subtypes of EMD muscular dystrophy disease. Each type varies in their prevalence and symptoms.

Limb-girdle muscular dystrophy (LGMD) can be seen in both boys and girls. Nearly mutations in 18 genes are the reason of LGMD. The defects in LGMD show a related distribution of muscle weakness that has an effect on both upper arms and legs. The different patterns of inheritance in LGMD are autosomal and recessive. Missense, insertions and deletion mutations in the genes route to LGMD.

Charcot Marie tooth disease (CMT) includes a number of disorders with an assortment of symptoms grounds damages in peripheral nerves. The disorder affects the peroneal muscle in the lower leg and hence the disease also is known as hereditary motor and sensory neuropathy (HMSN) and peroneal muscular atrophy [6]. CMT causes mild and also severe muscle degeneration, which is dependent on its mutation. There may be mild problems limited to skeletal muscle and also a severe problem like muscle degeneration corresponding with upshot on the brain. More than 30 forms of CMT are noticed and 30 genes are concerned, some may show severe brain malformations, such as lissencephaly and hydrocephalus and hearing loss [7].

The Facioscapulohumeral Muscular Dystrophy (FSHD) is an autosomal dominant neuromuscular disorder. The deletions of D4ZA microsatellite repeats in DUX4 gene on chromosome 4q cause Type 1 FSHD. Mutations such as missense, splice site and small deletions in SMCHD1 gene reflects in Type2 FSHD. The weakness of muscles in the face that slow progress in the shoulder, upper arm muscles and shoulder girdle, down to the stomach and lower limbs [8].

The Myotonic dystrophy is also known as Steinert's disease. The expansion of an unstable CTG trinucleotide repeat in the DMPK gene on chromosome 19 is the basis for this disease. The normal individual has the repeats ranging between 5 and 37. If the repeats exceed 50 then it the cause for myotonic dystrophy. CTG repeat sizes in patients range from 50 to 4000 [9].

Distal muscular dystrophy (DD) also known as Distal myopathy is a group of disorders that mainly affect distal muscles. The distal muscles that are located in the hands, feet, lower arms or lower legs are flawed in this type of muscular dystrophy. There are about eight forms of distal myopathy caused by the defects in various genes.

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease that results in progressive proximal muscle weakness and paralysis exemplify by degeneration of alpha motor neurons in the spinal cord. On the basis of the age of onset the patients SMA is classified into four types. In the range of the ages lie between Type 1 (0-6 months), Type II (7-18 months), Type III (> 18 months), Type IV (>18 years). The SMN1 gene is responsible for this genetic alteration that results in a reduction of survival motor neuron (SMN) protein [10,11].

Muscular dystrophy is a genetic disorder that is caused by the mutations in a variety of genes. When a mutation occurs in the gene the resultant protein product will be missing or altered. The change of protein in the muscles leads to alteration or malfunction of the muscles that reveal muscular dystrophy.
Muscular dystrophy is progressive and they tend to worsen with time. The factors like age of onset and rate of progression generally fluctuate from one disorder to another. Some these disorders can affect life expectancy. In the summary of all types of muscular dystrophy, the defects in some forms will cause contractures or inflexible joints, and few are accompanied by scoliosis or spinal curvature. Even though the majority muscular dystrophies don't affect the brain, some are accompanied by brain changes that cause learning disabilities that range from slight to severe. Finally, several forms of muscular dystrophy also impinge the heart. It is observed that each disorder has its own special locale of anxiety.

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## DNA MUTATION

Amend in the genetic code that causes a permanent change in the DNA sequence is termed as mutation. DNA mutations perceptibly root to genetic diseases. Single character change in a gene makes an impact on the gene which in turn changes the function of the gene. Muscular dystrophy is a genetic disease caused by the mutations in the genes. A mutation in DNA may do no harm in protein sequences in some of the mutations. Substitution is an exchange of one base to another, such as swapping a base from A to G. Missense mutations are the substitution in a codon that encodes a different amino acid and cause a small change in the protein. For example, missense mutation 347T>C indicates that codon changes CTC-CCC in the dystrophin gene results in DMD, where the protein Leu is altered to Pro [12].

Nonsense mutations are the substitution in a codon that results in premature termination of protein. TAG ("amber"), TAA ("ochre"), TGA ("opal" or "umber") are the three stop codons. For example, a nonsense mutation in the dystrophin gene 433C>T, point out that the codon change CGA-TGA and the protein arg is terminated with amber stop codon and results in BMD [13].

Single character change in a gene makes an impact on the gene which in turn changes the function of the gene. In some cases, a DNA mutation may do no harm in protein sequences. It depends on the sort of DNA mutation and where it is located. A change in codon encodes the same amino acid and causes no change in the protein is called silent mutations [14]. Consider an example, in CAPN3 gene 246G>A specifies CCG-CCA and the protein pro is not misrepresented, but it routes to the LGMD type 2 disease.

During small insertions, a new base is added into the sequence that alters the function of a gene. An increase in the number of the same nucleotides in a location is termed as duplications. For example, EMD disease is caused by the duplications in the emerin gene for the nucleotide change 650_654dupTGGGC [15].

Small deletions occur in the genes when a base is deleted from a sequence that truncates the function of genes. For example, 253delG deletes G in 253 position in the SH3TC2 gene that directs for Charcot-Marie-Tooth disease 4C. Gross insertions and gross deletions occur when the whole number of exons is involved in the insertions are deletions.

Frameshift mutations alters the position of nucleotides in the reading frame, and that forms unrelated amino acids into the protein, generally followed by a stop codon.

For example consider a DNA sequence

Codon: Thr Pro Glu Glu Glu Thr

Sequence: ACT CCT GAG GAG GAG ACT

**Missense mutation**

Codon: Thr Pro Glu Glu Glu Thr

Sequence: ACT CCT GAG GAG GAG ACT

Sequence: ACT CCT GTG GAG GAG ACT

Codon: Thr Pro Val Glu Glu Thr

In the above noted example, a single nucleotide change from A to T and thus it codes for Val instead of the amino acid Glu.

**Nonsense mutation**

Codon: Thr Pro Glu Glu Glu Thr

Sequence: ACT CCT GAG GAG GAG ACT

Sequence: ACT CCT GAG TAG GAG ACT

Codon: Thr Pro Val Stop Glu Thr

**Silent mutation**

Codon: Thr Pro Glu Glu Glu Thr

Sequence: ACT CCT GAG GAG GAG ACT

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Sequence: ACT CCA GAG GAG GAG ACT

Codon: Thr Pro Glu Stop Glu Thr

In the 6th position the nucleotide changes from T to A with no change in their amino acid. These mutations are termed as Silent mutations.

**Frameshift mutations**

Sequence: ACTCCTGAGGAGGAGACT

Sequence: ACTCCTCTGAGGAGGAGACT

The base pairs CT are inserted in the 7th position.

Sequence: ACTCCTGAGGAGGAGACT

Sequence: ACTCCTGAGGAAGACT

The base pairs GG are inserted in the 9th position.

**MUSCULAR DYSTROPHY DIAGNOSIS**

There is no fruitful remedy for muscular dystrophy disorder and the diagnosis of this disease is a tedious process. The disease can be diagnosed with the results of muscle biopsy, electromyography, electrocardiography and DNA analysis.

Serum creatine kinase is a straightforward and economical indicative test for severe forms of dystrophy. The analysis is done by measuring the serum concentration of creatine kinase. The higher concentrations of serum creatinine kinase than normal values suggest a disorder. A specific disorder is not found out by this laboratory analysis. In DMD, serum creatine kinase concentrations are elevated from birth, and the early diagnosis is done by testing in neonates which helps in reduction of disease further in the family. This method does not diagnose all forms of dystrophy [16,17].

Electromyography testing (EMG) is done in two phases. In the first phase a small needle that is gently inserted into the electrical patterns of the muscles in the arm or thigh. The second phase determines how soon the messages are being sent from the brain to nerves by stimulating the nerves of either arm or leg through a small electrical pulse being sent from the brain to the nerves. EMG test is uncomfortable, painful, lengthy procedure. EMG testing is less favored for children and it is mostly performed only on adults for disease identification. EMG tests are done mainly for the investigation in myotonic dystrophy. The performance of EMG is not satisfied for the patients having less creatinine kinase.

Muscle biopsy and DNA testing are widely used tests to predict muscular dystrophies. A muscle biopsy is a surgical practice where a tiny sample of a muscle is extracted and analyzed. The removal of muscle tissue is done using a biopsy needle and microscopic analysis is done to examine the level of the genes that cause muscular dystrophy. A performing muscle biopsy is costly, it is invasive, and at most care should be taken after the surgery. A muscle biopsy might be considered if speedy and trustworthy genetic testing is unavailable.

Genetic testing is an initial step tested on a blood sample to spot the alteration in the genes so as to help in the diagnosis of muscular dystrophy without performing a muscle biopsy. The risk involved in DNA analysis or genetic testing is minimal and the traits can be identified effectively as the disease-causing genes are explicitly known. Carrier mothers, those who may be at risk of passing this disease on to their children are identified by genetic testing and preventive measures can be provided [18]. To find the mutations in the genes for the patients identified through muscle biopsy, the genetic testing is again performed to confirm the diagnosis. However, the muscle biopsy is optional for the patients diagnosed by genetic testing, to distinguish from other phenotypes [19].

## APPROACHES TO INFER MUSCULAR DYSTROPHY

### General approaches

The clinical diagnosis of DMD is done through the laboratory analysis of dystrophin. The methodologies engage in recent dystrophin diagnostic experiment includes multiplex PCR, Multiplex ligation-dependent probe amplification (MLPA), Southern blot analysis, Detection of virtually all mutations-SSCP (DOVAM-S). The demerits of these technologies are lengthy, painstaking procedure, and not able to detect duplication mutations precisely. In addition, to carry out carrier testing in females the entire family history should be examined [20].

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The exact mutation in the DMD gene can be analyzed using gene therapy and missense, nonsense, insertions, deletions and splicing mutations are identified through direct sequencing [21, 22]. Molecular diagnostic methods at nucleotide level are required. The direct sequencing analysis is considered to be laborious, expensive and time-consuming. In some cases, the MLPA reports will be negative and point mutation detected by the sanger method requires direct full gene sequencing, and hence the role of direct sequencing in diagnosis of DMD is increased [23].

Polymerase chain reaction (PCR) is now common and often indispensable technique used in medical and biological research labs in the diagnosis of hereditary diseases. PCR has the benefit of being minimally invasive, efficient and very specific for the detection of large gene deletions, The major drawbacks in this approach are a lack of antimicrobial sensitivity data, complexity of the assay, and the price of PCR equipment and kits [24].

Genetic testing is also an option to confirm a Muscular dystrophy disease. As each disease has several subtypes and there are different genes responsible for each subtype, it is important to narrow the possible type of disease as much as possible using the previously mentioned tests. If the gene change can be found and confirmed, this information can then be used to help in testing other family members to determine whether they are carriers of the disease [25].

**Computational Approaches**

Sequence-based features have significant differences between the sets of genes known to be involved in human hereditary disease and those not known to be involved in disease. These can be examined with the help of cDNA sequences for the OMIM Mendelian disorders [26]. A set of features was chosen from the gene sequences and classification is done with the machine learning techniques [26].

FSHD one form of muscular dystrophy is diagnosed through gene expression profiling. A gene expression data set consists of dozens of samples with more than thousands of genes. The Linear discrminant analysis is done [8]. Some of the limitations of microarray data to classify all forms of muscular dystrophy are (i) the cDNA probes plotted on the microarrays do not cover all of the genes expressed in skeletal muscle, (ii) the properties of probe cDNAs have not been not well-characterized, (iii) homologous genes of each target gene may cross-hybridize with the probes and because relatively large amounts of RNA are required, (iv) each microarray analysis requires pooled RNA samples from several patients [27].

Muscular dystrophy and its subtypes are classified by integrating protein-protein interaction (PPI) network, using interpretable gene set information and mRNA profiling data. Identification of gene sub-networks are done using a distance metric approach named affinity propagation clustering (APC) approach. The biomarkers are identified the functional gene set information is combined. Classification of muscular dystrophy is done with multi-class support vector machines (MSVMs) with the gene set features and subnetworks. Using this approach sub-networks and gene sets are identified that are more relevant to MD [28].

Machine learning techniques have been successfully applied to identifying disease-associated genes [29]. The problem is formulated as a supervised learning problem, where the task is to make the classifiers to learn from training data and the prediction is made from the learned classifier [30].

Schizophrenia is a genetic disease and also a heterogeneous syndrome characterized by perturbations in language, perception, thinking and social relationships [31]. There is no set of symptoms finalized to categorize this disease other than the genetic factors. Disease gene association studies focused on SNP (Single Nucleotide polymorphism) aids in predicting the disease [31]. Twelve machine learning techniques and seven datasets are considered to classify the disease.

Numerous supervised learning techniques and various types of gene or protein annotation data have been used to solve the disease gene classification problem. Supervised algorithms such as k-Nearest Neighbor, Decision tree learning, Artificial Neural Networks, Naive Bayes and Support Vector Machines are compared and their performance is analyzed for predicting the disease.

The classification of muscular dystrophy continues to evolve with the advances in understanding of their molecular genetics. A huge number of muscular dystrophy related defective genes and proteins are identified, but no effective treatments are known for many of its subtypes. At present, there is no effective method to identify and classify all types of muscular dystrophy. The proportion of mutations in deletions, duplications and point mutations differs in each type of disease and to date, no genetic testing has been developed to cover this whole mutational spectrum in a single platform. Large size and number of genes for all types of muscular dystrophy requires considerable effort, cost and time for direct sequencing. The direct sequence analysis of this spectrum involved in all kind muscular dystrophy requires a high level of the laboratory. However, it is more important to know the exact mutation site and type to predict prognosis and, therefore, all the mutation sites should be analyzed effectively.

## OBSERVATIONS AND DISCUSSION

From the study, it is observed that few forms of muscular dystrophy are identified through computational methods based on full direct sequencing and microarray data. Usage of microarray gene expression data is convincing when multiple genes involved in a disease and also hereditary traits cannot be detected efficiently. It was observed that the discussed approaches involve more cost for classifying the disease sequences and to predict the type of muscular dystrophy and also accuracy may not be achieved.

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Tests for only a few types of muscular dystrophy disease are already in clinical use. The apparent benefit of hereditary testing aids in identifying and understanding of risk for a certain type of disease. Predictive hereditary tests for all types of muscular dystrophy need to be done.

The current advancements in gene testing helps in identifying people at a risk of getting a disease in advance in ahead of any symptom appears. An accurate gene test result in finding the disease-related gene mutation.

As the vulnerability of the disease is high the tests helps in detecting the possibility of the disease in carrier mothers so that there is a possibility of finding the disease in carrier son/daughter at the earliest before birth. The traditional method of testing is time consuming and incurs cost overhead.

Identification of genetic factors in complex diseases like muscular dystrophy is a far more difficult task with the standard methods as it is difficult to analyze the data. The complex diseases provide a lot of challenges to standard data analysis techniques.

Therefore, it is essential to model and represent this knowledge in a computational form with minimal loss of biological context through a gene sequences based approach. Disease-gene associations need to be designed and a suitable classification algorithm should be identified to handle this type of data.

With the help of sequence based information, a model can be created based on supervised learning techniques to infer the genetic disease effectively.

## CONCLUSION

In this recent survey research on the muscular dystrophy disease identification through computational intelligence is reviewed. This paper elucidates the introduction of DNA mutations, the vulnerability of muscular dystrophy disease and various techniques involved in identifying the disease briefly. From the observations, it is concluded that usage of the available clinical methods is not able to process huge data. Microarray gene expression data and protein-protein interaction methods help in identifying disease when multiple genes involved. Inferring a muscular dystrophy using the mutated gene sequences should be carried out to spot the disease efficiently. To deal with a large number of sequences, new disease identification model should be designed and developed based on the advanced learning techniques like deep learning. A distributed environment should be created with the big data technologies like Hadoop and its components that support in predicting the disease effectively using a large number of mutated gene sequences.

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