Review article

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A BRIEF INSIGHT ON DUCHENNE MUSCULAR DYSTROPHY (DMD): A SHORT REVIEW

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Duchenne Muscular Dystrophy (DMD) is a devastating genetic disorder characterized by progressive muscular degeneration or muscle wasting. It is a rare X-linked recessive condition which is considered as one of the most common types of muscular dystrophy [1,2]. DMD typically affects males (1 in 3500 to 5000 new-born males) with an incidence rate of 200 per million births [1,3]. However, it also affects females in cases of skewed X-inactivation or other X-chromosome abnormalities [3]. The initial symptoms are clumsiness and difficulty in walking by the age of 4-5 years [4]. Gower's sign, pseudohypertrophy (false enlargement) of calf muscles, waddling gait, impeded motor development, muscle wasting and weakness, contracture, scoliosis and breathing difficulties are the prominent signs and symptoms of DMD [4]. Patients become wheelchair-bound and dependent, by the teen-age. The mean age at death is found to be ~19 years due to fatal complications including cardiomyopathy and respiratory failure [4].

DMD is caused by genetic mutations in Dystrophin (DMD) gene which possesses >2.5 million base pairs of genomic sequence [5]. The Xp21 locus bound Dystrophin gene is also considered as the largest human gene [5]. It covers ~0.1% of total human genome and ~1.5% of entire X-chromosome [5]. It is the first gene isolated by positional cloning and is considered as the most complex genetic locus [6]. It comprises 79 exons which altogether express a messenger RNA (mRNA) of 14 kilobases to yield a cytoskeletal protein, dystrophin, of 427 kDa that is expressed at muscle sarcolemma [3,7]. The 79th exon of dystrophin gene is considered as the longest exon of DMD gene that possesses 2.7 kilobases and contains full 3' UTR (untranslated region) [6]. DMD gene also comprises numerous large introns across its full length which are claimed to be one of the major causes of high mutation rate leading to develop two well-known mutation hot-spots (intron 7 and 44) of the gene [6]. With such extremely large size, DMD gene exhibits a complex mutational spectrum of >7000 mutations and high spontaneous mutation rate [7]. Though duplication, translocation, insertion and point mutations have been observed; the intragenic large deletions are the most commonly reported mutations (65%) in case of dystrophin gene [5,7,8]. It has been reported that mutations in translational reading frame of dystrophin transcript resulting to dystrophin protein deficiency or unstable dystrophin protein, subsequently develop DMD [3,8]. However, the functional or quantitative dystrophin abnormalities are found to be linked with Becker Muscular Dystrophy (BMD) [3,8].

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The dystrophin gene expresses a rod shaped dystrophin protein (Figure 1) that comprises four domains [8]. Its amino terminal binds with F-actin and its central coiled-coil rod contains 24 spectrin-like repeats and 4 hinge regions [8]. The cysteine rich domain binds to the β-dystroglycan (βDG) and C – terminal binds to syntrophin and dystrobrevin [7,8].

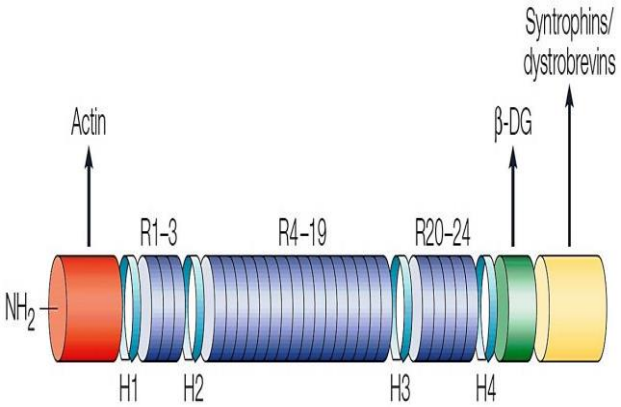

Figure 1: Structural domains of dystrophin protein [8].
The central coiled-coil rod consists 4 hinge regions (H1 – H4) and 24 spectrin like repeats (R1 – R24), located in three distinct sections.

Dystrophin protein forms a complex (dystrophin–glycoprotein) with integral membrane proteins (dystroglycan, sarcoglycan, syntrophin and dystrobrevin) and plays a vital role as a bridge

between basal lamina and inner cytoskeleton of muscle fiber to provide structural stability to the skeletal muscle [7,8]. The principle chore of the complex is to stabilize sarcolemma and protect muscle fiber from long term contraction-induced damages [8]. The loss of dystrophin leads to muscle fiber damage and membrane leakage which allows influx of calcium into sarcoplasma, protease and pro-inflammatory cytokines activation and mitochondrial dysfunction that eventually develops muscle fiber degeneration [7]. Eventually, the displacement of neuronal nitric oxide synthase, increased oxidative stress, increased muscle necrosis, fibrosis and fatty tissue replacement develop [7,8]. The progressive muscle weakness forces DMD patient to be wheelchair-dependent by the age of 12 and often between the age of 15–25, patient may die due to cardio-respiratory failure [4,8].

DMD may be diagnosed by serum Creatine Kinase (CK), electromyography (EMG), western blot analysis, immunofluorescence studies, multiplex Polymerase Chain Reaction (PCR) assays and southern blot analysis [4,6]. Limitations of medical science to provide only symptomatic treatment to DMD patients necessitate an effective cure despite its earliest description reported in the 1880 as monogenic disorder [4]. However, promises for affirmative changes towards DMD treatment have been observed recently. In August 2014, European Medicine's Agency granted conditional approval for Translarna (ataluren) for the treatment of nonsense mutation Duchenne Muscular Dystrophy (nmDMD) for ambulatory patients with age of 5 years or more [9]. Moreover, US FDA in September 2016 granted accelerated approval to Exondys 51 (eteplirsen) (Sarepta Therapeutics) for the treatment of DMD in patients with confirmed DMD mutation responsive to exon 51 skipping [10].

Majority of DMD patients would have to wait for a treatment due to the limited patient suitability for ataluren and eteplirsen. Therefore, extensive and decisive research is indeed necessitated for effective treatment of DMD in the area of biological, genetic and procedural interventions which are yet to be explored effectively.

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