Four nucleotide deletions of exon 47 in Dystrophin gene: A case report of a Kelantanese Duchenne Muscular Dystrophy patient

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Muscular dystrophy is a group of diseases that result in progressive muscle weakness and atrophy. Duchenne Muscular Dystrophy (DMD) is classified as dystrophinopathy and is an X-linked recessive disease. It is caused by alterations in the dystrophin gene at Xp21.2 encoding 79 exons [1]. It is characterised by progressive muscle wasting that begins at 3 to 5 years, delay in motor development and eventually wheelchair confinement followed by premature death at about 30 years from cardiac or respiratory complications [2]. Genetic etiology of cases of DMD in Malaysia are still scarcely reported. Here, we report the genetic cause in the case of an 11-year-old Kelantanese Malay boy who has progressive muscle weakness since 5 years old. He has difficulty in getting up from sitting and supine position also in climbing up stairs until 1st floor. He has a strong family history of DMD and musculoskeletal problems. His younger brother was diagnosed with DMD by molecular analysis and his maternal uncle died at the age of 16 with musculoskeletal problems but was never investigated. Physical examination revealed no dysmorphic features, positive Gower sign with absent tounge fasciculation. On neurological examination, tendon reflexes and muscle tone for limbs were normal. Muscle power for bilateral upper limbs were normal, however, bilateral lower limbs showed slight reduction in muscle power with calf hypertrophy.

Genomic DNA was subjected to multiplex ligation-dependent probe amplification (MLPA) screening of all of *Dystrophin* exons employing two sets of probes (SALSA-MLPA P034-A3 and P035-A3) (MRC Holland, Amsterdam, The Netherlands) and direct DNA sequencing. MLPA and Direct DNA sequencing result showed deletion of four nucleotides in exon 47: c.6803delACAA, p.K2268NFsX2269 leading to premature stop codon (Fig. 1 & Fig. 2).

Deletion accounts for 60% of the mutations within the 79 exons of the dystrophin gene. Deletions of exons 49, 50 and 51 were reported as the most frequent (71.43%) in Malaysian population [3]. To the best of available knowledge this is the first case reported in Malaysia involving nucleotide deletions leading to shifting of normal reading frame within exon 47. This case represents a frameshift deletion whereby the 4-base deletion lead to the appearance of termination codon prematurely at exon 47, 32 exons short of the normal transcript. It results in the formation of a truncated dystrophin protein and in consequence obliterates the production of dystrophin in muscles. MLPA does improve the diagnostic technique [4] especially in detecting small mutations as it has increased the detection rate up to 70% of the DMD/BMD cases [5-7], the remaining 30% of patients with small mutations require further analysis, such as Sanger sequencing. Parental genetic screening is advised as risk for phenotypic abnormalities differs between familial or de novo mutation.

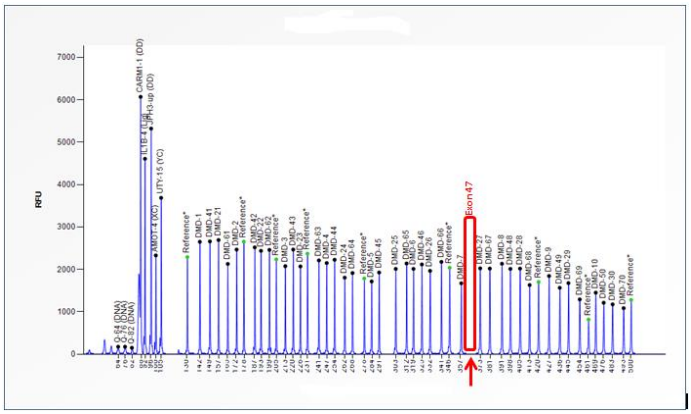

Fig. 1: Electrogram showing deletion of exon 47 in dystrophin gene

Fig. 2: DNA sequencing revealed deletion of 4 nucleotides in exon 47 (c.6803delACAA) resulting in the formation of premature termination codon (TAA)

Keywords: Duchenne Muscular Dystrophy, dystrophin, MLPA, DNA sequencing

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