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Novel mutations in *SLC16A2* gene in four unrelated Malaysian boys with MCT8 deficiency

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Abstract

Monocarboxylate transporter 8 (MCT8) deficiency is a disorder caused by impairment in the transcellular transport of thyroid hormones, which are essential for proper development and function of the brain. MCT8 is encoded by *SLC16A2* gene located on the Xq13.2 chromosome. *SLC16A2* gene is the only gene known responsible for causing the MCT8 deficiency. MCT8 deficiency is an X-linked disorder characterized by severe cognitive deficiency, infantile hypotonia, generalized muscle weakness and spasticity. Thyroid function tests in patients with MCT8 deficiency are usually abnormal with increased free 3,3′,5-triodothyronine (T3), normal to low free 3,3′,5,5′-tetraiodothyronine (T4) and normal to elevated thyroid stimulating hormone (TSH). **This study aims** to describes and characterize four novel mutations found in four unrelated MCT8 deficiency patients in Malaysia. Nineteen patients suspected with MCT8 deficiency were referred to our laboratory for *SLC16A2* gene mutation analysis. PCR and direct sequencing were performed on six coding exons and flanking introns of *SLC16A2* gene. Mutational analysis was then performed using Seqscape software v3.0 and the variants found were evaluated using the web-based software MutationTaster2 for pathogenicity predictions. Human Gene Mutation Database (HGMD) was used to check whether these mutations found have been previously reported. Mutational analysis of *SLC16A2* gene revealed four different novel mutations which include three hemizygous frameshift mutations (c.488dupT, c.1461dupC and c.244_245insTATA) detected in three different patients and one hemizygous missense mutation (c.626G>A) found in 2 siblings. Frameshift mutations are predicted to introduce premature stop codon which will produce a truncated protein, hence rendering the thyroid hormone transporter defective. The missense mutation c.626G>A was also predicted to be disease-causing by MutationTaster2. All five patients portrayed similar clinical characteristics that include developmental delay, hypotonia and deranged thyroid function tests. Four novel mutations in *SLC16A2* gene have been detected in four unrelated patients with similar MCT8 deficiency phenotype. MCT8 deficiency should be suspected in male patients with psychomotor retardation, hypotonia and deranged thyroid function tests with X-linked inheritance pattern. Genetic counselling should be provided to the parents of affected patients for future family planning.

Keywords: MCT8 deficiency; *SLC16A2* gene; novel mutations

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