VARIANT IDENTIFICATION USING WHOLE EXOME SEQUENCING IN A FAMILY SUSPECTED WITH IRON-REFRACTORY IRON DEFICIENCY ANAEMIA

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Iron-refractory iron deficiency anaemia (IRIDA) is a rare type of anaemia that affects about 1 in 1 million people globally. The inheritance pattern is autosomal recessive, which is caused by a defective *Transmembrane Protease Serine 6 (TMPRSS6)* gene. Patients with *TMPRSS6* variants exhibit microcytic hypochromicity, low serum iron and transferrin saturation (TSAT), relatively low serum ferritin, normal to high hepcidin, and unresponsive to oral iron. Based on our knowledge, no genetic studies have been conducted on IRIDA in Malaysia. This study aims to describe the molecular genetic findings in a family suspected of IRIDA using whole exome sequencing (WES). Two male siblings with persistent and unexplained anaemia and three male family members who were not having symptoms were recruited for this study at the Anaemia Clinic, Hospital Ampang. DNA was extracted from blood samples and sent for WES service. Bioinformatic analysis was performed to identify the presence of gene variants related to IRIDA. Gennext software (Version: 0.1.0) was utilised for variant annotation, and various databases were used for the variant filtering and prioritisation process such as NCBI, OMIM, HPO, etc. Haematological parameters revealed that the two suspected sons had microcytic hypochromic anaemia, low haemoglobin and TSAT, and normal serum hepcidin. The proband had low serum iron and normal ferritin, while the other suspected son had relatively low serum iron and ferritin. All the other three male family members showed normal haematological parameters. Pathogenic variants were not found in the family members; however, common SNPs related to IRIDA were identified. All five family members carried homozygous *TMPRSS6*/rs855791 (NM_001289000.1:c.2246T>C) and *SLC11A2*/rs445520 (NM_001174130.2:c.17A>C). The two suspected siblings carried heterozygous *TMPRSS6*/rs2235324 (NM_001374504.1:c.730A>G) but not the *TMPRSS6*/rs78174698 (NM_001374504.1:c.1636C>T) that was found in the father and first son. In addition, the proband was found to carry a homozygous splice-site deletion variant, *TMPRSS6*/rs60484081 (NM_001374504.1:c.1842-6_1842-2delCTGGGG). The haematological parameters of the suspected siblings point towards the IRIDA phenotype. rs78174698 was reported to increase serum ferritin, whereas the absence of this variant probably reduces serum ferritin in the suspected siblings, an indication of IRIDA. rs60484081 could be a modifier SNP that causes reduced penetrance in the proband, showing less severe symptoms compared to his brother. These findings emphasised that WES can be used in diagnosing underlying IRIDA that affect this family. Thus, advancements in diagnostic tools help families in need get better treatment for IRIDA.

Keywords: IRIDA, *TMPRSS6,* SNP