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**Genotype-Phenotype Correlations in Patients with Osteogenesis Imperfecta**

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**ABSTRACT**

Osteogenesis imperfecta (OI) is a rare genetic bone disease. It is primarily characterized by bone fragility and low bone mass. Majority of OI patients have mutations in COL1A1 or COL1A2 genes. However, increase number of genes associated with OI has made the molecular diagnosis of OI more difficult. Therefore, this study aimed to characterize the mutations involved in Malaysian OI patients. A total of 29 patients from UKM Medical Centre and Hospital Putrajaya were recruited. Genomic DNA was extracted from peripheral blood and targeted sequencing of 14 genes panel was performed for mutational analysis. The sequencing reads were mapped to the human reference genome (hg19) using Ion Torrent Suite software. The mutations were annotated using ANNOVAR and the candidate mutations were predicted to be deleterious or not using in-silico tools. Significant variants were validated using Sanger sequencing and evaluated against the Dalgleish’s osteogenesis imperfecta mutation database. Statistical analysis was performed using SPSS software version 22. A mean sequencing depth of 433x with average of 176,253 reads per sample was achieved. Twenty-five variants were identified in 29 patients with OI type I, III, IV and V. Mutations in collagen type I genes (COL1A1, n=12 and COL1A2, n=6) accounts for 72% of all molecular diagnosis, followed by IFITM5, P3H1, BMP1 and SERPINF1 genes. Sixteen patients with collagen mutations had helical substitutions within the triple helix domain and 5 patients had haploinsufficiency mutations caused by frameshift, nonsense or splice site mutations. Most patients with OI type III had helical mutations and associated with severe phenotypes compared to haploinsufficiency mutations in mild type of OI (p < 0.05). We have identified mutations in COL1A1 and COL1A2 genes in our local OI patients. Targeted sequencing for genes involved in OI could be used for genetic testing of this disease.