Predicting the impact of PHEX, FGF23 and DMP1 gene variants found in Malaysian Malay patients with Hypophosphataemic Rickets through in silico analysis of protein function and mRNA secondary structure

ABSTRACT

Hypophosphataemic Rickets (HR) is a rare bone disorder characterised by chronic hypophosphataemia caused by defective phosphate reabsorption in the renal tubules. Variants in phosphate-regulating endopeptidase homolog, X-linked (PHEX), fibroblast growth factor-23 (FGF23) and dentin matrix protein-1 (DMP1) genes contribute to X-linked dominant, autosomal dominant and autosomal recessive forms of HR, respectively. In this study, four Malaysian patients' DNA samples were subjected to polymerase chain reaction and Sanger sequencing to identify the types and locations of the variants. Then, in silico study was conducted based on the variants found to predict the effects of amino acid substitution on protein functions using SIFT and PolyPhen-2 software and RNAfold was used to construct the mRNA secondary structure. Mutational analyses had revealed two variants in PHEX; c.10G>C (E4Q), c.1970A>G (Y657C), one mutation in FGF23; c.716C>T (T239M) and three variants on DMP1; c.309A>T (S69C), c.1322C>T (S406S), c.1334G>A (E410E). The variants in these Malay patients were previously reported in different ethnic HR patients. Protein prediction programs suggested that the PHEX Y657C and DMP1 S69C variants may affect protein function. All variants were predicted to alter the secondary mRNA structure. These findings suggest that these missense and silent variants may lead to changes in protein function and mRNA secondary structure that are associated with the manifestation of HR phenotype.

Keyword: Hypophosphataemic Rickets; PHEX; FGF23; DMP1; In silico analysis