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Next Generation Sequencing-based Discovery of Novel Genetic Markers in the Vitamin D Receptor Gene correlated with Osteoporotic Fracture among Older Filipino Women

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Objectives: This study aimed to discover novel genetic variants in the entire 101 kB vitamin D receptor (VDR) gene for osteoporotic fractures in a group of older Filipino women using next generation sequencing approach in a case-control study design.

Materials and Methods: A total of fifty women with and without osteoporotic fracture seen at the Philippine Orthopedic Center were included. Blood samples were collected for determination of serum vitamin D, calcium, phosphorus, glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase and as primary source for targeted VDR gene sequencing using the Ion Torrent Personal Genome Machine. The variant calling was based on the GATK best practice workflow and annotated using Annovar tool.

Results A total of 1496 unique variants in the whole 101-kb VDR gene were identified. Novel sequence variations not registered in the dbSNP database were found among cases and controls at a rate of 23.1% and 16.6% of total discovered variants, respectively. Noteworthy is the discovery of two disease-associated novel heterozygous frameshift deletions (Pearson chi square p-value. Neither of the two SNPs was found in control patients nor in the dbSNP. Furthermore, two novel exonic variants were predicted to be damaging and may have increased the probability of acquiring osteoporotic fracture.

Conclusion: These findings show the power of Next Generation Sequencing in identifying sequence variations in a very large gene and the surprising results obtained in this study greatly expand the catalog of known VDR sequence variants that may represent an important clue in inter-individual response to vitamin D treatment for osteoporotic fracture.