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Comprehensive Molecular Genetic Approach for Patients with Nephrocalcinosis and Suspected SLC34A3/SLC34A1 Damage

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Objectives : Pathogenic variants in SLC34A3 and SLC34A1 genes lead to hereditary hypophosphatemic rickets with hypercalciuria (HHRH) or hypercalcemia, infantile 2 (IHC2) respectively. Using just WES/WGS can't provide final diagnosis in half patients
Methods : 22 unrelated patients with clinical diagnose HHRH and 12 with IHC2 were referred for WES or WGS. For 11 patients NGS data were further reanalyzed with further RNA analysis, functional analysis or WGS.
Results : Primary NGS data analysis revealed both causative variants for 50% patients in each group. For other patients there were none or one variant found and comprehensive further analysis containing reanalyzes of NGS data, RNA analysis, minigene assay or allelic disbalance investigation were performed. 5 missed variants were found with reanalyzes of primary NGS data in cases of HHRH. Most variants were previously described, but were filtered out or not suspected during manual analysis in primary investigation. For 4 patients RNA analysis or allelic disbalance investigation ofSLC34A3 were performed in order to reveal a mechanism of pathogenicity of variants or in order to found second variant in the gene. For 2 patients WGS were performed as a second line of NGS diagnosis. In cases of IHC2 reanalysis detected 2 missed variants, with further minigene assay for one of them. Other one was missed 4 times in the WES analysis and was previously described, but was filtered out due to high global frequency. Such a comprehensive approach detected second pathogenic variant for 7 more patients with HHRH, improving a diagnostic yield up to 82%, and for 4 patients with IHC2, improving a diagnostic yield up to 83%.
Conclusions : Comprehensive approach using a NGS data reanalysis and functional study is highly important in cases with accurate clinical diagnosis and can significantly improve a genetic diagnostic yield in patients with suspected SLC34A1/SLC34A3 disease.