**Functional investigation of rare variants in *HNF1A* to characterize risk factors for type 2-like diabetes in a general population**

Genomic sequencing of randomly selected individuals from three population-based cohorts recently revealed that 2% of individuals carry rare non-synonymous variants in one of seven maturity-onset diabetes of the young (MODY) genes, and the majority of carriers remain euglycemic through middle age. To evaluate their risk for developing type 2-like diabetes later in life, detailed analysis of each MODY gene variant is necessary to determine their true pathogenic nature. We have investigated the functional effect of all *HNF1A*-MODY gene variants recently reported in randomly selected individuals from the Framingham and Jackson Heart Studies, and cases and controls from Finnish and Swedish cohort (T2D cohort). *In silico* prediction tools, literature screening and family pedigree analyses were supplemented by functional analysis studying variant effect on HNF-1A-transcriptional activity, DNA binding and nuclear transport/localization. Of the 27 rare and three common *HNF1A* variants investigated a total of seven variant proteins (i.e. V103M, R131Q, E274del, Y322C, H469Y, H514R and T515K) were classified as having reduced transcriptional activity (<50%) and/or significantly reduced DNA binding of a HNF1A-containing rat albumin DNA fragment, or impaired nuclear localization, compared to wild-type HNF-1A. Among these seven variants, only R131Q and E274del were predicted as likely pathogenic, while the remaining five were classified as uncertain or likely not pathogenic by sequence variant classification. Comparing the clinical phenotype in the randomly selected individuals with the different variants showed that functionally affected variants are significantly associated with a diabetes phenotype (p=0.001, OR=6.92). Thus, functional characterization of *HNF1A* variants can supplement bioinformatics in ascribing pathogenicity, and seems to be most helpful for variants classified as uncertain. Such functional analyses may improve diagnostics of individuals carrying *HNF1A* variants, which may be at risk of developing type 2-like diabetes.