A genetic retrospective study of Maturity-Onset Diabetes of the Young (MODY) in two population health studies

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Background: Maturity-Onset Diabetes of the Young (MODY) has been reported to account for 1-2% of all diabetes cases. Like most rare diseases, MODY is usually underdiagnosed with reports that up to 90% of MODY cases are misdiagnosed as Type 1 or Type 2 Diabetes. Properly diagnosing MODY has medical implications as the first line of treatment is usually different for MODY patients who may not require insulin medication. MODY is generally inherited in an autosomal dominant manner, with variants in GCK, HNF1A and HNF4A explaining more than 80% of reported cases.

Aims: The aims of this retrospective study were: (i) to provide the frequency of known pathogenic or likely pathogenic variants, as well as predicted loss-of-function variants in the population; (ii) to estimate the penetrance of these variants; and (iii) to assess the potential medical implications of screening the general population for pathogenic variants in these three genes.

Methods: We analyzed the exome sequence data of 70,000 individuals, with 50,000 individuals from the UK Biobank and 20,000 from the Healthy Nevada Project (HNP), irrespective of their ancestry. Participation was not based on a personal or family history of diabetes. We used ClinVar to select known MODY pathogenic and likely pathogenic variants and Variant Effect Predictor version e!95 annotations to identify predicted loss-of-function variants in GCK, HNF1A, and HNF4A. Electronic health records were available for all individuals analyzed. We looked in particular at (i) ICD10 codes related to diabetes, (ii) medication codes for insulin and metformin, as well as (iii) the age of diabetes diagnosis.

Results: The frequency of known pathogenic or likely pathogenic variants (n=14 in HNP; n=42 in UK Biobank), or predicted loss-of-function variants (n=4 in HNP; n=12 in UK Biobank) in these three genes was about 1 in 1,000 individuals (0.1%). Less than 25% of the individuals carrying a pathogenic or likely pathogenic variant had a diagnosis of MODY (2 in HNP; 10 in UK Biobank). Moreover, none of the other individuals carrying a pathogenic or likely pathogenic variant had a diagnosis of diabetes. We further characterized the phenotypes of these individuals with regard to glucose and HbA1c levels. These results also allow to refine the classification of pathogenic and likely pathogenic variants for MODY.