Monogenic Diabetes: the Impact of Making the Right Diagnosis

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Background: Maturity Onset Diabetes of the Young (MODY) is the most common type of monogenetic diabetes in Europe, with an estimated total of 20.000 patients in the Netherlands. However, the large majority of patients are still genetically unaccounted for. While diagnosing monogenic diabetes often has clinical consequences for the index patient and importance for family members.

Methods: We studied 1951 index patients with diabetes referred for genetic testing between 2015-2020 in the Netherlands. Genetic testing was performed using a custom gene-panel including 24 genes associated with monogenic diabetes.

Results: Pathogenic germline variants were identified in 287 of 1951 (15%) referred diabetic patients. The median age at diagnosis was 27 years (range, 0 to 80 years) in mutation carriers compared with 34 years (range, 0 to 83 years) in nonmutation carriers (p=0.000). Pathogenic germline variants were found in 17% of females compared to 11% of males (p=0.001). *GCK*-MODY and *HNF1A*-MODY were the largest MODY-subgroup with respectively 37% and 34% of all mutation carriers. Furthermore in 8% a variant of unknown significance was found in one of the MODY-associated genes.

Discussion/Conclusion: This nationwide study showed a mutation detection yield of 15% with our MODY-gene-panel, associated with younger age at diagnosis and female gender. In general, comprehensive testing increases efficiency both in terms of time and costs if more than one gene is related to a certain disease. The drawback of testing many genes is the complex interpretation of the results. Therefore, close collaboration between treating physicians and clinical geneticists is of utmost importance, including the interpretation of variants of unknown significance. Based on our data and literature; genetic analysis is recommended in individuals with diagnosis diabetes below age 35 years, in absence of clinical characteristics of diabetes type 1 (e.g. auto-antibodies) or diabetes type 2 (e.g. lifestyle risk factors) and/or positive family history of diabetes. These criteria would increase MODY detection, enabling optimal clinical management as well as genetic counseling of family members.