Molecular analysis of a large cohort of MODY patients by Next Generation Sequencing

R. Artuso1, V. Orlandini2, V. Palazzo1, L. Giunti1, S. Landini2, A. Provenzano3, A. La Barbera4, S. Giglio1,2, S. Stagi2
1. Medical Genetics Unit, Meyer Children’s University Hospital, Florence; 2. Medical Genetics Unit, Department of Clinical and Experimental Biomedical Sciences “Mario Serio”, University of Florence; 3. Department of Science’s Health, Meyer Children’s University Hospital, Florence

INTRODUCTION AND OBJECTIVE

Maturity-onset diabetes of the young (MODY) is a mono-genic non-autoimmune form of diabetes mellitus characterized by absence of ketosis, autosomal dominant inheritance, a young age of onset (<25 years) and primary defect in the function of the beta cells of the pancreas. MODY accounts for 2-5% of all cases of diabetes mellitus type 1 and 2 (T1D, T2D), but probably the true prevalence is underestimated as MODY shares clinical features with the more common forms of diabetes T1D and T2D. It is a phenotypically and genetically heterogeneous disorder with at least 14 subtypes.

However, in about 50% of MODY patients, causative mutations in known genes (MODYx) have been described. Recent advances in next-generation sequencing (NGS) technologies make it affordable to search for rare and functional variants for common complex diseases systematically. On the bases of this observation, we decide to analyse 100 MODY patients through NGS approach.

METHODS

Target resequencing in about 100 cases with diagnosis of MODY and/or T2D.

Design array custom for a set of 182 genes

We selected the coding and regulatory regions of genes: implicated in MODY and different type of diabetes disorders; implicated in T2D; implicated in the pancreatic β cells pathway; causative of diabetes in mice models.

RESULTS

MODY patients with two or more mutations in different genes

In this study we found, in association with known heterozygous/homozygous SNPs associated with diabetes, rare and pathogenic variants in the 66% of cases. Interestingly, in 40% of positive cases, we identified, in addition to MODY genes, two or more mutations in other different genes. These results suggest a complex aetiology of MODY, in contrast with reports that consider it caused by mutations in single genes. The advent of high-throughput sequencing (HTS) has made simpler to identify that monogenic disease could present digenic (D) or more complex inheritance. The complexity of DI transcends the genetics. To construct a compelling proof that the inheritance is digenic rather than monogenic may require a multidisciplinary team that can apply techniques to understand the two/more genes and proteins specifically and their interaction. This approach, in formidable way, can contribute not only to a correct genetic counseling, but especially for the choice of the personalized treatment. In fact, patients with diabetes often are treated similarly, with little consideration of individual characteristics that might affect clinical outcome and therapeutic response. Our study provides a highly sensitive method for identification of variants in new causative genes associated with diabetes and draws the best way for a tailored medicine.