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Copy number variation in MODY diabetes - familial case presentation

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Abstract

MODY (Maturity-Onset Diabetes of the Young) is an autosomal dominant form of diabetes that usually have onset in adolecence. This type of diabetes is caused by defects in the primary insulin secretion. Different types of MODY which are monogenic diseases result from mutations in a single gene. The most common types of MODY are MODY 2 and MODY 3 (with mutations in GCK and HNF1A genes, respectively). In our study we identified very rare MODY 7 type of diabetes in three family members by MLPA analysis.

Keywords

MODY, Diabetes mellitus, KLF11, Family

Introduction

Diabetes mellitus is a group of metabolic syndromes that have a common symptom of high blood sugar or blood glucose either due to insulin resistance or inability to produce insulin by the Langerhans pancreatic islet (Alam et al., 2014; Guthrie & Guthrie, 2004; Bell & Polonsky, 2001). There are three major types of diabetes that differ in their time of onset, severity of symptoms and the prognosis: type 1; type 2 and gestational diabetes (American Diabetes Association, 2012). In addition to these three main types, there are two more "less known" types of diabetes: MODY (Maturity Onset Diabetes in Young) and LADA (Latent Autoimmune Diabetes in Adults) (American Diabetes Association, 2015). Type 1 and LADA type of diabetes are recognized as autoimmune diseases since there is an autoimmune reaction in the blood and antibodies that destroy the Langerhans cells in the pancreas are created. Thereby, the production of insulin is precluded which leads to the occurrence of this disease (Thomas & Philipson, 2015). MODY diabetes is presented with reduced insulin secretion

and normal insulin resistance, so this type cannot be classified as type 2 diabetes, although it had been previously considered so (Anik et al., 2015). Type 2 diabetes has different etiology than other types of diabetes because autoimmune reaction is absent; instead, reduced insulin sensitivity and increased insulin resistance are main underlying causes of type 2 diabetes (American Diabetes Association, 2015). The difference between MODY and type 2 diabetes mellitus is that patients with type 2 diabetes produce enough insulin but have high insulin resistance, which is not the case with MODY type. The term "maturity onset diabetes in young" or MODY relies on the dated classification of diabetes divided into juvenile and adult-onset diabetes, while according to the new classification, it belongs to the group in "genetic defects of the beta cell function" with subclassification according to the affected gene (American Diabetes Association, 2015; Thomas & Philipson, 2015).

MODY is an autosomal dominant form of diabetes with onset usually in adolescence. Except for early onset of the disease, other symptoms are similar to type 2 diabetes, with normal c-peptide levels and insulin resistance. MODY diabetes accounts for around 1% of all diabetes mellitus cases (Kleinberger & Pollin, 2015). Copy number variations are found in most of the patients with MODY diabetes, as well as point mutations (Bansal et al., 2017; Weinreich et al., 2015; Thomas et al., 2016).

Currently, there are eleven types of MODY, the most common of which are types MODY 2 and MODY 3 with mutations on GCK and HNF1A genes, respectively (Siddiqui et al., 2015; Heuvel-Borsboom et al., 2016; Bishay & Greenfield, 2016; Haliloglu et al., 2016; Karaca et al., 2017).

Distinguishing MODY diabetes from other types of diabetes is relevant in conjecture with personalized therapy and new therapeutic advances in diabetes management and care (American Diabetes Association, 2015).

Misdiagnosing can lead to inadequate therapy choices, poorly managed diabetes and overall lower quality of life in diabetes patients (Thomas & Philipson, 2015; Shepherd et al., 2009; Pearson et al., 2000; Ajjan & Owen, 2014; Shepherd & Hattersley, 2004).

Here we present case of family with rare MODY type.

Materials and methods

Three family members with diagnosed diabetes mellitus were referred to the Institute for genetic engineering and biotechnology, University of Sarajevo for MODY genetic characterization. Proband patient in this family was the mother, with diagnosed diabetes mellitus type 2. Family physician referred her two children who were also diagnosed with type 2 diabetes mellitus. Sample used for genetic analysis was DNA isolated from 3 ml of whole blood, which was collected from all three family members. The family history and some clinical data were also recorded.

Isolation of DNA was performed by DNeasy Blood & Tissue DNA extraction kit (Qiagen, USA), according to the manufacturer`s manual. The isolated DNA was quantified with Qubit 2.0 fluorometer, and diluted to concentration of 20 ng/μl, so the starting amount of DNA for MLPA analysis was 100 ng.

Identification of copy number variations was made with MLPA (Multiplex Ligase-dependent Probe Amplification) technique (Schouten & Eijk-Van Os, 2011), with MLPA kits P241 (MODY probemix-contains probes for HNF4A, GCK, HNF1A and HNF1B genes and is therefore specific for MODY 1, 2, 3 and 5) and P357 (contains probes for the PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4 and INS genes and is therefore specific for MODY 4 and MODY 6-10) (MRC – Holland, Netherlands).

Hybridization, ligation and PCR reaction were performed in Eppendorf Mastercycler gradient, and genotyping was performed in ABI PRISM 310 (Applied biosystems, USA) sequencer, according to the manufacturer's instructions. The data were analyzed using GeneMapper v.3.2 (Applied biosystems, USA) and Coffalyser.net (MRC-Holland, Netherlands) software. After fragment separation using sequencer, all raw data are checked for sloping, and samples and MLPA reaction quality were checked with Coffalyser.net software.

Results and Discussion

The family history and pedigree analysis revealed presence of diabetes mellitus in at least 3 generations

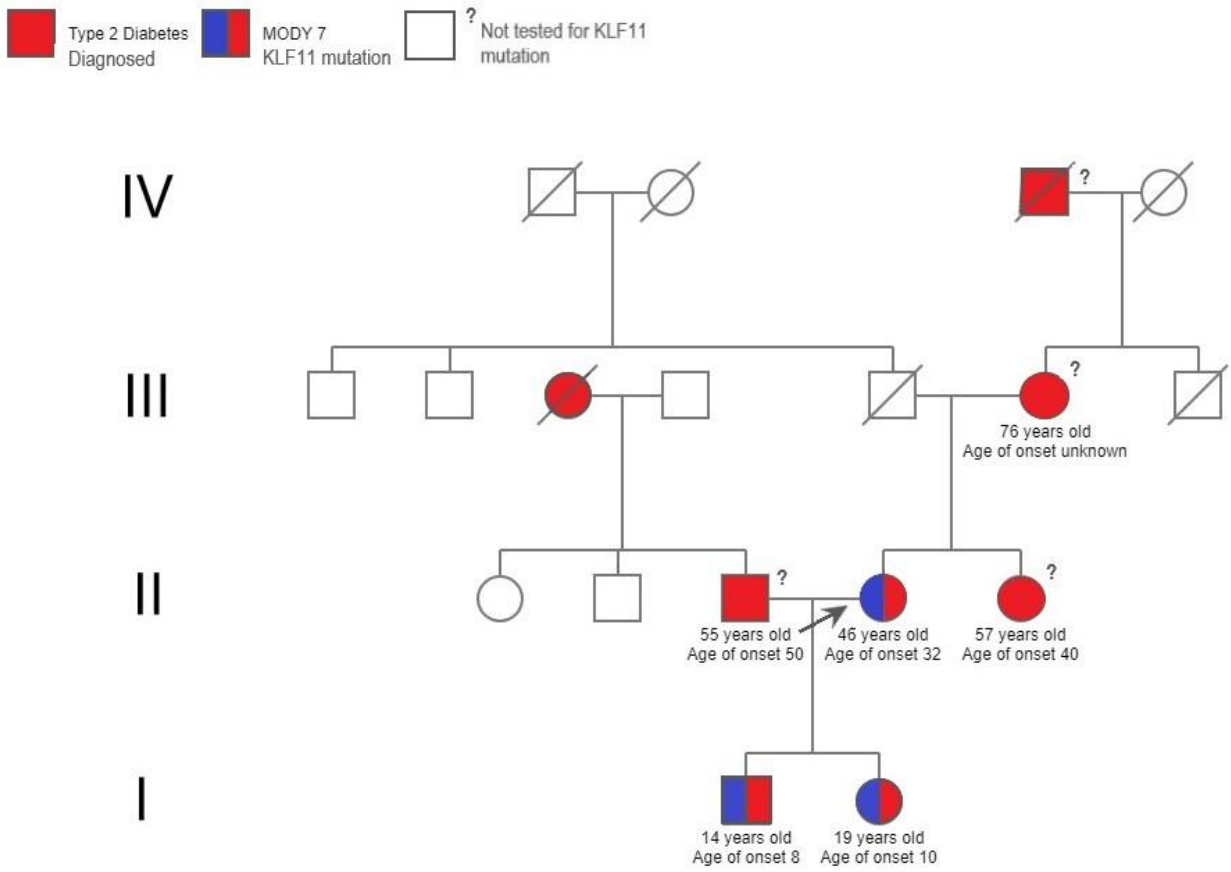

Figure 1. Family genealogy tree with collected data on diabetes mellitus

in the mother's family line (as depicted in Figure 1). As we can easily note, mother, her sister and maternal grandmother were at that time diagnosed with type 2 diabetes. Family confirmed that the father is also diagnosed with diabetes type 2, but he was unavailable for testing at that time. The father`s family history is not known. Regarding the age of the family members and the age of onset, the mother was 46 years old at the time of testing, with onset of the disease at 32. The daughter was 19 years old at the time of the testing, with onset at 10, while the son was 14 years old, with onset at 8.

All the tested family members had the value of last two HbA1c levels under 6.0 and, since they had normal C-protein levels and did not need insulin therapy, they were diagnosed with diabetes mellitus type 2. All three family members were under anti diabetic treatment with metformin hydrochloride. MLPA analysis revealed single heterozygous deletion of exon 4 of KLF11 gene in all family members (mother, daughter and son). This mutation is associated with MODY 7 type of diabetes (Fernandez-Zapico et al., 2009; Neve et al., 2005) as KLF11 gene carries information for zinc-finger transcription factor that is expressed in pancreatic islet cells (Kim, 2015). Clinical features for MODY 7 include most of the symptoms connected with type 2 diabetes and most likely it is misdiagnosed as such, and common therapy includes insulin and anti-diabetic medication. This type of MODY diabetes is rare with prevalence of less than 1% of confirmed MODY diabetes patients in Europe and the USA (Kleinberger & Pollin, 2015). In UK, GCK and HNF1A linked MODY diabetes are the most common types of MODY (Kleinberger & Pollin, 2015) with 52% MODY patients has HNF1A mutations and 32% patients has GCK mutations, respectively. Similar percentage of the above mentions mutations observed was patients in other European regions, including Netherlands, Sweden, Germany, France (Kleinberger & Pollin, 2015), with HNF4A as the third most frequent mutation (around 10%). It would certainly be interesting to establish whether the father also has some form of MODY diabetes.

Though there is not enough evidence to support that claim since his clinical findings or his sample were unavailable to us. Also, even though all three family members have the same copy number variation, they do not have the same age of onset (32, 10 and 8 years old, respectively). It can be argued that mother`s onset was earlier but was not recognized as diabetes due to other environmental and health causes. However, it is not likely that her onset was as early as that of her children. Children`s early onset could be multifactorial occurence, in regard of father`s diagnosis of diabetes mellitus type 2, but it could not be confirmed at this time.

Conclusions

In this study we assessed a genetic character of familial form of diabetes in a triad of mother and two siblings. There is an apriori high-risk for diabetes based on the extended family history that confirmed diabetes diagnosis in three generations. It would be beneficial for all patients diagnosed with multigenic disorders such as diabetes mellitus type 2 to collect as much data as possible, and not only patient`s data, but data of the patient`s family as well. If the family data was collected before the start of our study, MODY could be recognized before the proband`s onset of disease. In the molecular-genetic characterization of confirmed diabetes we applied copy number variation analysis using MLPA based method. This is fast and relatively cost effective method for screening for the large genomic rearrangements that can confirm diagnosis of MODY diabetes. In Bosnia and Herzegovina, most of the MODY diabetes patients are misdiagnosed at the moment, and new guidelines in MODY diabetes diagnosis are needed for our country.

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