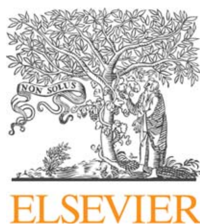

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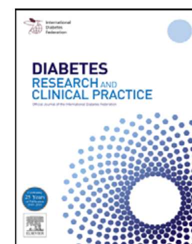

Three novel mutations in MODY and its phenotype in three different Czech families

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ABSTRACT

Aims/hypothesis: MODY (Maturity Onset Diabetes of the Young) is an autosomal dominant inherited type of diabetes with significant genetic heterogeneity. New mutations causing MODY are still being found. A genetically confirmed diagnosis of MODY allows application of individualized treatment based on the underlying concrete genetic dysfunction. Detection of novel MODY mutations helps provide a more complete picture of the possible MODY genotypes.

Materials and methods: We tested 43 adult Czech patients with clinical characteristics of MODY, using direct sequencing of HNF1A (hepatocyte nuclear factor 1-alpha), HNF4A (hepatocyte nuclear factor 4-alpha) and GCK (glucokinase) genes.

Results: In three Czech families we identified three novel mutations we believe causing MODY—two missense mutations in HNF1A [F268L (c.802T > C) and P291S (c.871C > T)] and one frame shift mutation in GCK *V244fsdelG* (*c.729delG*). Some of the novel HNF1A mutation carriers were successfully transferred from insulin to gliclazide, while some of the novel GCK mutation carriers had a good clinical response when switched from insulin or oral antidiabetic drugs to diet.

Conclusion: We describe three novel MODY mutations in three Czech families. The identification of MODY mutations had a meaningful impact on therapy on the mutation carriers.
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1. Introduction

MODY (Maturity Onset Diabetes of the Young) belongs to the group of monogenic diabetes and is characterized by autosomal dominant inheritance, non-insulin dependency and early onset of diabetes in at least one family member [1,2]. Haploinsufficiency is the most common model of pathogenicity. Based on the affected gene, nine types of MODY have been described to date [3–6]. The most common types are MODY 3 and MODY 2 which are caused by mutations in the HNF1A (hepatocyte nuclear factor 1-α) gene and GCK (glucokinase) gene, respectively. Hundreds of different mutations in the responsible genes have been found, while others are still presumed [7]. New studies have shown the existence of a correlation between the type of mutation within one gene and the severity of the associated diabetes [8]. The phenotype of

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Abbreviations: MODY, maturity onset diabetes of the young; HNF1A, hepatocyte nuclear factor 1-alpha; HNF4A, hepatocyte nuclear factor 4-alpha; GCK, glucokinase; PAD, peroral antidiabetic drugs.

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Table 1 – Primers.

Primers for HNF4A gene sequencing analysis

Exon	Forward Primer	Reverse Primer
1	GATCTTCCCAGAGGACGGTTTG	CTCCCACCCCAAAGTTGAGTG
2	GCTCCCTTAGATGCCTGACA	CAAGTGTGCCCATTTCCCA
3	TTGTGTCTTCTCCATCCAACCA	TTGTAAATGACTGTCGGGGAGC
4	TCCCACTCCTCATCAGTCACAGA	CTGGGGAGAATGGAGGTGGA
5	TGTGCAGGGGACAGAGAGTG	TAAAATCAAGCCAGTCCACGG
6	ACTTGCCCAGCGTCACTGA	GAATCTCCTTGCCTGGGTGA
7	GTCAACCCAAGGTGACTTCCC	AGTCTGGCAGAGCGTTCTGGA
8	GGTCTTGACTCCCCAGATGC	AAGGAGCTGAGGGGTGAGC
9	AGGAAGATGGCGTCCCAAG	CACTTTCTCCTGCCTCCTGTCT
10	GAATTTTGAGCAGCCCCTGTC	TCTTCCTTTGCCGTGACCAC
Primers for HNF1A gene sequencing analysis		
Prom1	AGCCAGCACTGTTCTTGG	AGGGACAGGGAGCTATG
Prom2	TCCCATCGCAGGCCATAGCTC	CCGTCTGCAGCTGGCTCAGTT
1/1 part	TGGGTGCAAGGAGTTTGGT	CGTGAAGTCTTCCCCATCG
1/2 part	ACTGATCCAGGCACTGGGTG	TCAGAAGGGGGGCTCGTTA
2	GGGTTGACAAGGTTCCAGCA	TGCAGGTTGAATCCCACTGAC
3	AAGGTCAGGGGAATGGACG	CTGGACAGCCTTTTACAGGACC
4	ACAGGGTTCCTCTGAGCCTG	TGACTGCTGTCACTGGGACA
5	AAGTGCTGAGGGCTGTGGA	CTGCTCCAGAATCTCCCTGC
6 iso1	AGGGAGATTCTGGAGCAGTCC	TGAGTCCCAGTGGCTCTTCC
7 iso1	GCAGGGGTGGGATATAACTGG	CTGCATCCATTGACAGCCAAC
8 iso1	CCCTTTCCCCAGTCTTGAGG	CTCTGTCACAGGCCAAGGGA
9 iso1	TCCCTTGGCCTGTGACAGA	CCACAGTGACGGACAGCAAC
10-1 iso1	TGCCTCCCCATCCTGAGTAC	TGCATCAGAGCAGAGTGGG
10-2 iso1	CTGCTTGGGGGGTGATGAG	TGCCTGTGTGAGTAGGTGATGG
10-3 iso1	CCTGCCCCAACTCCTTCCA	GGTCACCTCTTTCTTCTCCTGGG
10-4 iso1	CTCACAAGGCAGCAAGGC	CCAAACCCCATCTGAATGA
Primers for GCK gene sequencing analysis		
Prom	ATGGGGATGGAGGCTCTTTG	TGTGGGGCTTAGTGTCCTTC
1a	TCCACTTCAGAAGCCTACTG	TCAGATTCTGAGGCTCAAAC
1b	GGGGCAGAGTATTTGAGCAG	TGCCCCCAGCCTTAGTTTTG
1c	CTCCACATCTACCTCTCCAG	AGGGGCTGAGGAGAGGAACA
2	TGTGCAGATGCCTGGTGACA	TTCTGTCTCGGGCTGGCTGT
3	TATCCGGGCTCAGTCACCTG	TGTGGGACTTGGGGACATG
4	AGGAATAGCTTGGCTTGAGGC	GCATTAGAGGTGGCAGGTGAC
5	GAGGTAGTGACAGGCCCTAGCA	CAAGGAGAAAGGCAGGCAGTG
6	TTTCTCCTTGGCTTCCAGCA	GTACACAGGGAGCCTCAGCAGT
7	CAGTGCAGCTCTCGCTGACAGT	TTGCTTTTCCCCAGAGTTGTTT
8	CCTCGTGCCTGCTGATGTAA	GTCGCCCTGAGACCAAGTCT
9	ATCGCCCCCATTTCTCCA	CCCACCTCATCCTCCACATTC
10	AGATTTGGGGGAAGGGTCG	GGCTGTCCCACCGAAAAACT

the specific type of MODY depends on the type of mutation, its location within the gene domain(s) and the number of affected isoforms [8,9]. Knowledge of genetic variants of MODY and its phenotypes help determine the impact of the disease and maximized treatment; this minimizes the progression of the disease and improves the quality of life of those affected [10]. Predictive testing of pedigrees can also be beneficial [11]. Identification of new mutations, which can cause MODY, together with the phenotypic description can be applied to further personalize genetic based treatment of affected individuals. We describe here three novel MODY mutations detected in three different Czech families.

2. Subjects, materials and methods

We examined 43 Czech probands and their family members fulfilling the inclusion criteria for genetic testing of MODY. The patients were referred from out-patient diabetic clinics as well as from hospitals. Inclusion criteria for testing was a classic MODY phenotype with a positive family history of diabetes in at least two generations and at least one of the following: (1) a negative test for anti-GAD and anti-IA-2 antibodies at the time of diabetic onset, (2) unusually low doses of insulin or oral antidiabetic drugs needed for diabetic compensation, and/or (3) absence of signs of metabolic syndrome; BMI < 31 kg/m^2.

Genomic DNA for genetic analysis was obtained from EDTA anticoagulated peripheral blood using QIAamp DNA blood kit. Primers (Table 1) of all exons of genes HNF1A, HNF4A and GCK were designed using Genamic Expression software; for promoter regions we used previously designed primers [12].

Primers were designed to control all exons and adjacent parts of introns. PCR products were purified using ExoSAP-IT® (USB Corporation). Direct sequencing reactions were performed using BigDye® Terminator v3.1, additional chemistry were removed using BigDye XTerminator® Purification Kit.

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