

Gene dosage changes in the GCK gene not detected by Sanger DNA sequencing in two patients with phenotypic MODY 2

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BACKGROUND

Maturity onset diabetes of the young 2 (MODY2) is phenotypically characterized by elevated fasting and post-prandial blood glucose (BG), and no diabetes auto-antibodies. Inheritance is autosomal dominant, and it is caused by variants in the glucokinase (GCK) gene with resetting of the pancreatic glucose sensor to a higher level. It is essential to detect MODY 2 patients as they do not require treatment.

OBJECTIVE AND HYPOTHESIS

The objective of the study was to present two phenotypic MODY 2 patients with gene dosage changes in the GCK gene, not detected by Sanger sequencing.

METHODS

Two patients with phenotypic MODY2 were included. Genetic methods: Sanger DNA sequencing and Multiplex ligation-dependent probe amplification dosage assay (MLPA).

RESULTS

Patient one. Patient one was a slim boy referred for diabetes mellitus (DM) 7.5 yr., with two fasting BG of 7.0 and 8.0 mmol/L, respectively, and a haemoglobin A1c (HbA1c) of 47 mmol/mol (6.4 %). His parents were non consanguineous. The father and grandfather had type 2 DM. BG profiles showed BG of 6.5 – 10 mmol/L. The boy tested negative for GAD65 and IA2 antibodies. Sequencing of all GCK exons did not reveal any gene variations, but MLPA detected a heterozygous whole GCK gene deletion (figure 1B), which could not be demonstrated in his parents (figure 2A), indicating that the deletion was a de novo variant.

Patient two. Patient two was a slim girl referred for DM 9.7 yr., with two HbA1c of 49 mmol/mol (6.6 %) and 48 mmol/L (6.5 %), respectively. Her parents were non consanguineous, and no family members had DM. BG profiles showed BG of 6.1 - 9.3 mmol/L. The girl tested negative for GAD65, IA2 and Zink Transporter 8 antibodies. Sequencing of all GCK exons did not reveal any gene variants, but MLPA detected a heterozygous duplication of exon 3 and 4 (figure 1C). The father, but not the mother, was carrier of the same duplication in the GCK gene (figure 2B): The fathers HbA1c was 43 mmol/mol (6.1%). The gene variant of patient 2 has not previously been reported in the human genome database.

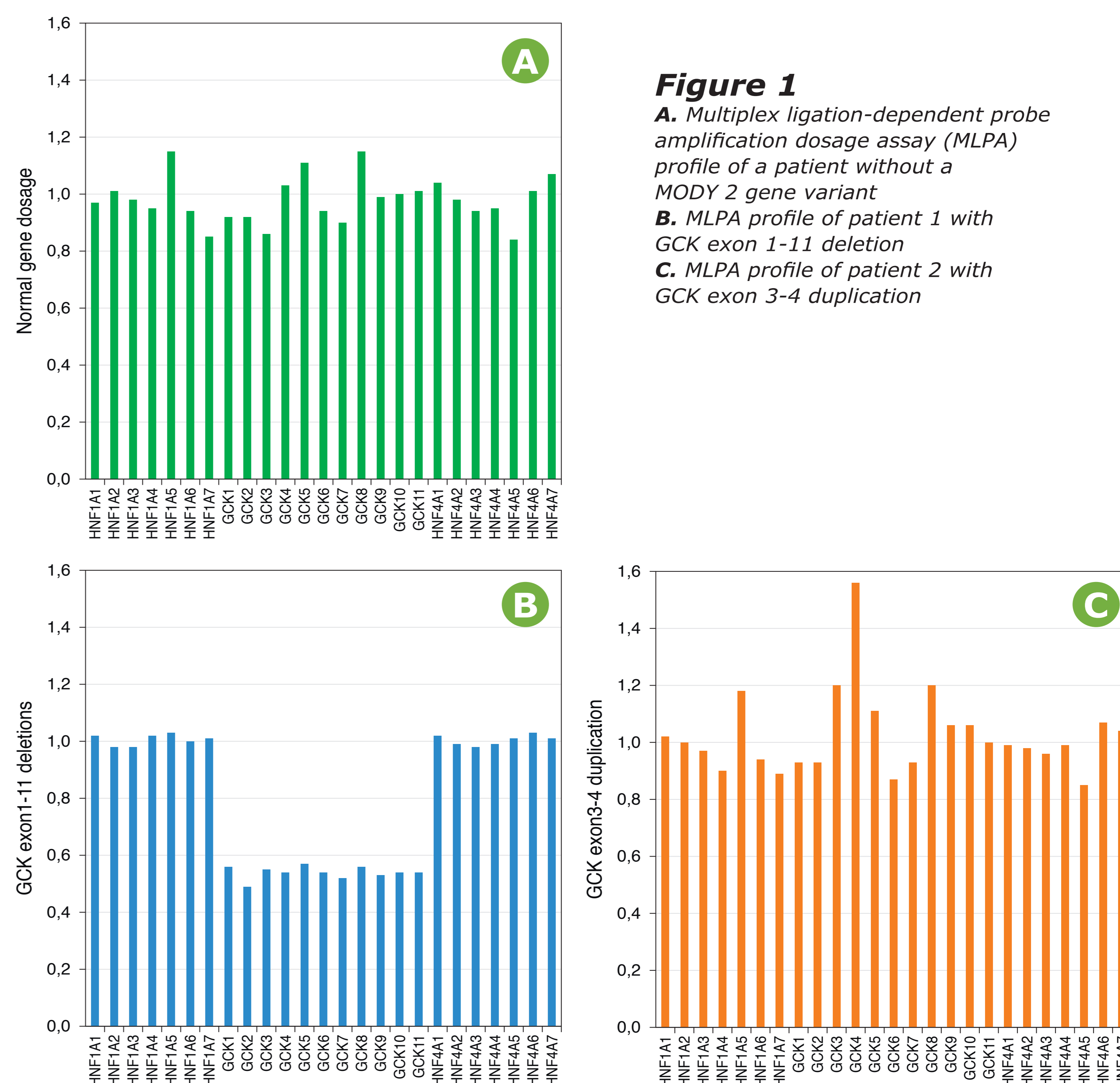


Figure 1
A. Multiplex ligation-dependent probe amplification dosage assay (MLPA) profile of a patient without a MODY 2 gene variant
B. MLPA profile of patient 1 with GCK exon 1-11 deletion
C. MLPA profile of patient 2 with GCK exon 3-4 duplication

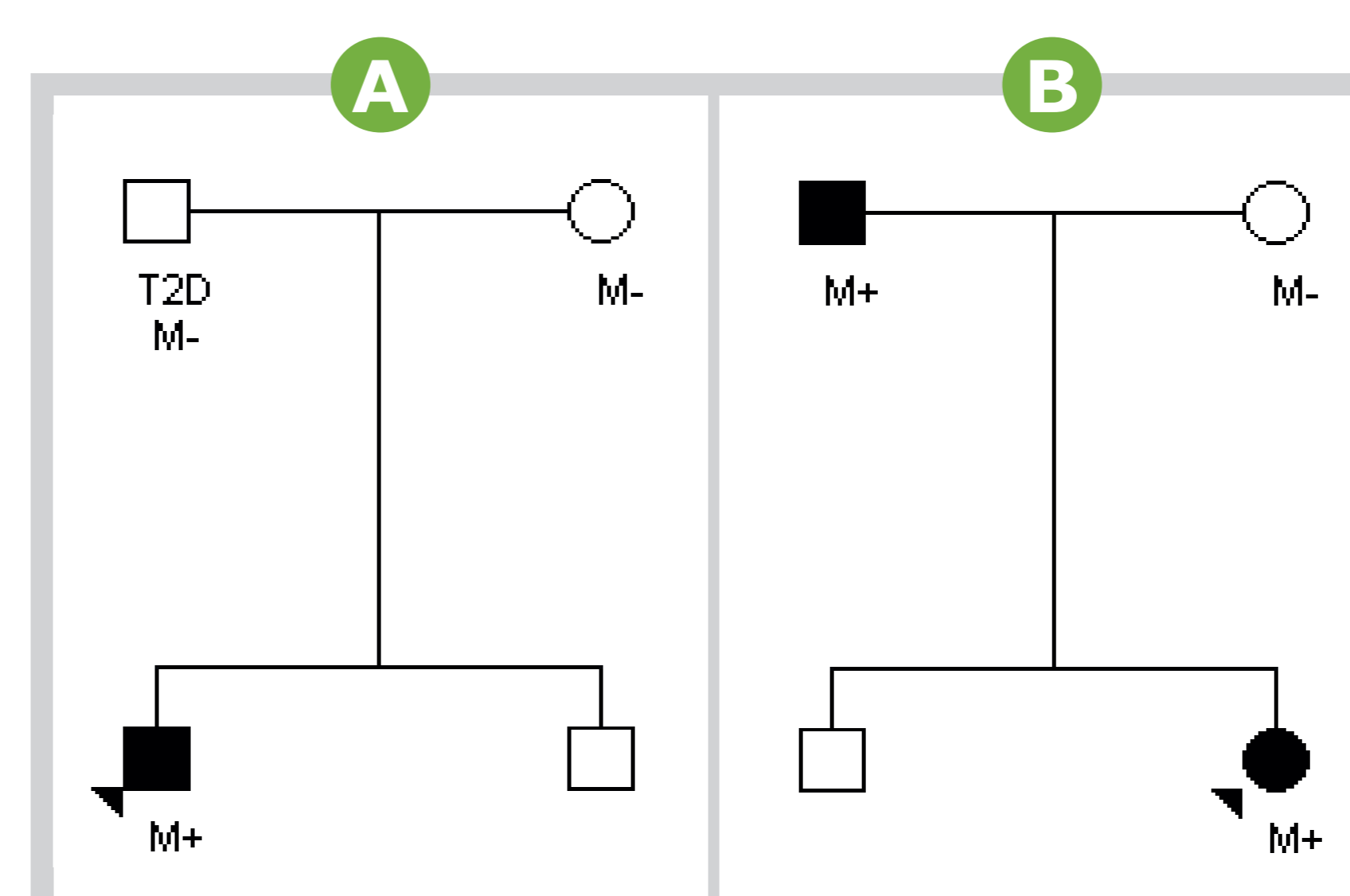


Figure 2
Pedigree of the closest relatives of patient 1(A) and patient 2(B)
M+ with arrow = patient 1 and patient 2
M+ = family member with a MODY 2 gene variant
M- = family members tested, but with no MODY 2 gene variant
T2D = type 2 diabetes

CONCLUSION

These cases emphasize the importance of gene dosage analysis by MLPA in patients suspected for a GCK variant, when no variant is identified by direct sequencing. Detection of a GCK variant has implications for the patient as well as for family members carrying the same gene variant, as MODY 2 patients generally do not need treatment. Further, pregnant women with a MODY 2 gene variant should not have their blood glucose normalised as this may be deleterious for a fetus with the MODY 2 gene variant.