# **Unveiling a Novel MT-TSI m.7479G>A Variant in Mitochondrial Diabetes: The Critical Role of mtDNA Sequencing in Atypical Presentations**

**Aim:** To describe a case of mitochondrial diabetes associated with a previously undescribed MT-TSI m.7479G>A variant, highlighting its clinical presentation, diagnostic challenges, and management implications.

**Methods:** A 71-year-old Caucasian female diagnosed with diabetes at age 50 underwent comprehensive clinical evaluation, including detailed family history, laboratory assessments (HbA1c, GAD/IA2 antibodies, C-peptide), and next-generation sequencing of mitochondrial DNA (mtDNA). Treatment outcomes and follow-up data over 21 years were analysed to assess glycaemic control and complications. Genetic counselling was offered to address maternal inheritance.

**Results:** The patient presented with new onset of diabetes associated with significant weight loss (BMI 26 to 17.1 kg/m²). She had a strong maternal family history of diabetes (mother, maternal uncle, and brother affected). Laboratory investigations at diagnosis revealed an HbA1c of 9.0% and fasting glucose of 11.1 mmol/L. At age 71 years, testing showed negative GAD/IA2 antibodies, and normal C-peptide (0.8 nmol/L), indicating preserved beta-cell function. Genetic testing identified a heteroplasmic MT-TSI m.7479G>A variant (13.90% proportion heteroplasmy), absent from the HmtVar database, and previously undescribed in the literature. In spite of limited functional studies, we believe this mutation is likely to be pathogenic due to the MT-TSI gene’s critical role in mitochondrial tRNA function and oxidative phosphorylation. Treatment with metformin (1000 mg daily) and sitagliptin (100 mg daily) maintained stable glycaemic control (HbA1c 6.5%) since diagnosis, without insulin or complications). Metformin was continued despite mitochondrial disease, supported by normal liver function and no lactic acidosis over 21 years. The patient has no children, but genetic counselling was offered to relatives.

**Conclusion:** The novel MT-TSI m.7479G>A variant likely underlies mitochondrial diabetes, emphasizing the importance of mtDNA sequencing in atypical diabetes presentations to enable accurate diagnosis, personalized treatment, and genetic counselling.