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Case Report

tRNA methyltransferase homologue gene TRMT10A mutation in young adult-onset diabetes with intellectual disability, microcephaly and epilepsy

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Abstract

Background A syndrome of young-onset diabetes mellitus associated with microcephaly, epilepsy and intellectual disability caused by mutations in the tRNA methyltransferase 10 homologue A (TRMT10A) gene has recently been described.

Case report We report two siblings from the fourth family reported to have diabetes mellitus as a result of a TRMT10A mutation. A homozygous nonsense mutation p.Glu27Ter in TRMT10A was identified using targeted next-generation sequencing and confirmed by PCR/Sanger sequencing. Diabetes was diagnosed while the subjects were in their 20s and was characterized by insulin resistance. Epilepsy and intellectual disability were features in common. Mild microcephaly was present at birth but their final head circumferences were normal.

Conclusion Our report provides independent confirmation of the role of TRMT10A mutations in this syndrome and expands its phenotypic description. TRMT10A sequencing should be considered in children or adults with young-onset diabetes who have a history of intellectual disability, microcephaly and epilepsy. This report also shows the advantages of using a targeted panel to identify previously unsuspected monogenic diabetes among young-onset non-insulin-dependent diabetes in the absence of obesity and autoimmunity.

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Introduction

Recently, a novel syndrome of young-onset diabetes mellitus or abnormal glucose homeostasis associated with microcephaly, epilepsy and intellectual disability attributable to homozygous mutations in the tRNA methyltransferase 10 homologue A (TRMT10A) gene was reported in two families [1,2]. In another report, an individual with TRMT10A deletion with failure to thrive, delayed puberty, intellectual disability and diabetes was described [3].

In the present paper, we report two siblings with young adult-onset diabetes, associated with intellectual disability, microcephaly in childhood and epilepsy, as a result of a third homozygous mutation in the TRMT10A gene.

Case report

The proband was the first child born to non-consanguineous white parents (Fig. 1). The pregnancy was uneventful and the child was born at term without postnatal problems. The child’s birth weight was 2700 g (-1.6 SD), length was 47.2 cm (-1.7 SD) and she had mild microcephaly [head circumference 32.5 cm (-2 SD)]. She had mild intellectual disability, first noticed when she attended primary school, but other developmental milestones were normal. She was diagnosed with grand-mal epilepsy at 5 years old. MRI of the brain was normal. Her head circumference was 49 cm (-2 SD) at 6 years 9 months old but improved to 50.3 cm (-1.3 SD) at 9 years 5 months old. Her final head circumference was normal at 53.1 cm (-1.3 SD). Growth in terms of height and weight was normal. Diabetes was diagnosed at 24 years old [plasma glucose 25.1 mmol/l, HbA1c 142 mmol/mol (15.1%), BMI 24.2 kg/m2 (weight 62.8 kg, height 1.61 m)]. She had a buffalo hump but features of familial partial lipodystrophy and Cushing’s syndrome were absent. She did not have ketoacidosis and was negative for antigu glutamic acid antibodies.

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acid decarboxylase and anti-islet antigen-2 antibodies. She was treated with insulin (1.0–1.2 units/kg/day) and metformin. Her HbA1c ranged from 50 to 85 mmol/mol (6.7 to 9.9%). Fasting C-peptide, measured 8 years after diagnosis, was detectable at 540 pmol/l. She had severe preproliferative retinopathy at 4 months after diagnosis, suggestive of long-standing hyperglycaemia, but has no nephropathy or neuropathy to date.

The proband’s brother was born at 43 weeks gestation. Microcephaly was described at birth but the head circumference was not recorded. His birth weight was 3274 g (-0.7 SD). He started walking at 3 years old and could first speak in phrases at 6 years old. He attended special school because of intellectual disability. Epilepsy was diagnosed at 4 years old and he had delayed puberty. His final head circumference was normal at 54.5 cm (-0.4SD). Diabetes was diagnosed when screened at 28 years using a 75-g oral glucose tolerance test (OGTT; plasma glucose 8.8 mmol/l at 0 min, 19.8 mmol/l at 120 min). His HbA1c level was 60 mmol/mol (7.6%) and his BMI was 28.4 kg/m² (weight 89.0 kg, height 1.77 m). Physical examination was normal. Fasting C-peptide level was 1000 pmol/l. The HbA1c level improved to 43 mmol/mol (6.1%) after 3 months of metformin therapy.

Neither the proband nor her brother had spontaneous hypoglycaemia. Both of them had mildly elevated LDL cholesterol and normal liver function tests. Skeletal surveys showed attenuated frontal skull vaults in both of them, in keeping with the history of microcephaly, but epiphyseal dysplasia was absent. Both their parents had normal heights, head circumferences and BMI, no epilepsy, intellectual disability, diabetes or prediabetes (normal OGTT results). Their maternal grandparents, now deceased, had Type 2 diabetes diagnosed after their 60s; their genotypes are not known.

All subjects provided written informed consent for blood sample collection and studies, as well as for the writing and publication of this report. The proband had participated in the UNITED (Using Pharmacogenetics to Improve Treatment in Early-Onset Diabetes) study when analysis of her HNF1A and HNF4A genes did not identify any mutation. Testing for mutations in all of the known or putative monogenic diabetes genes as part of the study was undertaken using targeted next-generation sequencing as previously described [4]. Sequencing was performed with a HiSeq2000 system (Illumina, San Diego, CA, USA; 48 samples per lane) and 100 bp paired end reads. Mutation confirmation was performed by PCR/Sanger sequencing. Subsequently, samples of the proband’s brother and parents were tested for TRMT10A mutation using PCR/Sanger sequencing. Plasma glucose and insulin was measured in the proband’s brother and parents at 0, 30, 60, 90 and 120 min in the 75-g OGTT. As a comparator, surrogate indices for insulin resistance and β-cell function of the brother were compared with the means of four age- and BMI-matched healthy control subjects.

Results

Metabolic studies

The OGTT results of the proband’s brother are shown in Fig. 2. He was newly diagnosed with diabetes. The findings were suggestive of insulin resistance (Matsuda index 1.46;
Microcephaly was a feature in common to all the reported cases, but the degree of severity appeared to vary. Microcephaly is defined as an occipito-frontal head circumference of >2 SD or >3 SD below the mean for age and sex [9,10]. Similar to those reported by Gillis et al. [2], our patients just met the criteria for mild microcephaly at birth; however, their head circumferences normalized as they grew and achieved normal final head circumferences. This was in contrast to the more marked microcephaly, which persisted to adulthood in the individuals reported by Igoillo-Esteve et al. [1] and Zung et al. [3]. All the individuals had intellectual disability, and epilepsy was common except in the individual reported by Zung et al. Contrary to the previous reports, our patients did not have short stature, although the proband did have a buffalo hump, as described in one patient previously [1].

A homozygous nonsense mutation, p.Glu27Ter, in the TRMT10A gene was identified in our patients. Data from the Exome Aggregation Consortium (ExAC) browser showed that the frequency of heterozygous TRMT10A nonsense mutations is ~1 in 4000, and the p.Glu27Ter mutation found in our family is the most common [11]. The family is unaware of any close common ancestor. In humans, TRMT10A is the orthologue most closely related to yeast TRM10, a protein that has tRNA m1G9 methyltransferase activity [12]. This nonsense mutation in TRMT10A at this location is likely to result in nonsense-mediated decay and reduced protein expression [13]. Reduced TRMT10A
| Report [reference] | Individual designation | Parental origin | Consanguinity between parents | TRMT10A mutation | Diabetes mellitus | Age when diabetes diagnosed (years) | Diabetes treatment | Endogenous insulin secretion | Microcephaly at birth | Low birth weight | Short stature | Epilepsy | Intellectual disability | Spontaneous hypoglycaemia | Brain imaging BMI (kg/m²) | Delayed puberty | Other clinical features |
|-------------------|------------------------|-----------------|------------------------------|------------------|------------------|-------------------------------|-------------------|---------------------------|------------------------|-----------------|----------------|---------|--------------------|----------------------|-------------------------|------------------|------------------------|
| Igoillo-Esteve et al. [1] | Individual 1 | Moroccan | Yes | c.379G>A p.Arg127Ter | Yes | 22 | Insulin | Detectable C-peptide | Unknown | Yes, severe | Yes | No | NR | NR | Normal | NR | Short neck, wide nose, low hairline, buffalo hump, retraction of right 5\(^{th}\) toe, scoliosis, joint laxity |
| Gillis et al. [2] | Individual 2 | Moroccan | Yes | c.379G>A p.Arg127Ter | Yes | 19 | Insulin | Detectable C-peptide | NR | No, severe | Yes | Yes | Yes | NR | Normal | NR | No |
| Zung et al. [3] | Individual 3 | Moroccan | Yes | c.616G>A p.Gly206Arg | Yes | 14 | Insulin | Detectable C-peptide | Yes, mild | Yes, mild | Yes, mild | Yes, mild | No, severe | NR | 26.9 | NR | No |
| Present report | Individual 4 | Jewish | No | c.379G>A p.Arg127Ter | No | 9 | Diet | – | Yes, mild | Yes, mild | Yes, mild | Yes, mild | NR | 21.7 | Yes | NR | No |
| | Individual 5 | Jewish | No | c.616G>A p.Gly206Arg | No | – | – | Present but insufficient relative to insulin sensitivity | Yes, mild | Yes, mild | Yes, mild | Yes, mild | No, severe | NR | 20.6 | Yes | NR |
| | Individual 6 | Jewish | No | c.616G>A p.Gly206Arg | No | – | – | Present but insufficient relative to insulin sensitivity | Yes, mild | Yes, mild | Yes, mild | Yes, mild | No, severe | NR | 24 | Yes | NR |
| | Individual 7 | Israeli Muslim | Yes | 4q23 deletion | Yes | 15 | Insulin | – | – | – | – | – | Yes, mild | NR | 28.4 | Yes | NR | No |
| | Individual 8 | Caucasian | No | c.79G>T p.Glu27Ter | Yes | 24 | Insulin, metformin | Detectable C-peptide | – | – | – | – | NR | NR | Unknown | No | Yes |
| | Individual 9 | Caucasian | No | c.79G>T p.Glu27Ter | Yes | 28 | Metformin | – | – | – | – | – | NR | NR | 24.2 | Yes | No |

NR, not reported. Mutations described in accordance with Human Genome Variation Society (HGVS) guidelines with the A of the ATG initiation codon numbered nucleotide c.1, using reference sequence NM_001134665.1 for TRMT10A.
mRNA expression and TRMT10A protein deficiency was previously shown to be the result of a p.Arg127Ter nonsense mutation [1]. TRMT10A protein is ubiquitously present but more abundant in human brain and pancreatic islets [1]. This was consistent with the selected involvement of brain (microcephaly, intellectual disability and epilepsy) and pancreatic islets (diabetes) in our patients. The robust insulin secretion in our case supported the in vitro findings that TRMT10A silencing did not appear to affect β-cell function but may induce β-cell apoptosis [1]. The mechanism by which the mutation is associated with insulin resistance remains to be investigated.

In summary, the present case report provides independent confirmation of the role of TRMT10A mutations in this newly described syndromic form of monogenic diabetes and expands its phenotypic description. It also highlights the newly described syndromic form of monogenic diabetes and confirmation of the role of \( \text{TRMT10A} \) mutations in young-onset diabetes and primary microcephaly in humans. The authors thank the family for their participation. We thank Prof. Andrew Hattersley from University of Exeter Medical School for critically reviewing the draft manuscript.

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