A Case of a Special Type of MODY-X: Clinical Report and Genetic Analysis (Post-Print)

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Abstract

Objective To report the clinical features and genetic testing results of a pedigree with suspected maturity-onset diabetes of the young (MODY). Methods We analyzed the clinical features, laboratory findings, and whole-exome sequencing (WES) results of a patient with a special type of diabetes and family history admitted to the Department of Endocrinology, First Affiliated Hospital of Anhui Medical University on September 10, 2018, and conducted clinical data analysis and Sanger sequencing validation of variants in the patient' s pedigree. Results The proband was a 21-year-old male who was admitted emergently due to diabetic ketosis after having diabetes manifestations for over 2 years. Laboratory examinations indicated insulin-resistant (type 2) diabetes. We analyzed the medical history of 17 members across four generations of this pedigree, with seven confirmed diabetic patients among paternal members. WES identified that the proband harbored both a heterozygous IRS2 c.1586delC frameshift variant and a heterozygous PPARG c.147T>G missense variant, both novel variants identified for the first time and potentially associated with inherited glucose metabolism disorders, while excluding other potentially pathogenic related gene variants; both variants were validated in 11 other family members, showing no strict co-segregation with clinical phenotypes; among six IRS2 c.1586delC-positive individuals, five were diagnosed with diabetes (83%, 5/6). Conclusion Current findings demonstrate that monogenic diabetes pedigrees often exhibit incomplete penetrance and/or variable expressivity, resulting in non-co-segregation of variants and phenotypes within the same pedigree, which may be attributed to the combined effects of pathogenic variants with differences in other gene polymorphisms among individuals, environmental factors, and lifestyle variations. This case identified a novel pathogenic IRS2 variant, and its gene function, reported diseases, variant pathogenicity, and patient phenotype all indicate that IRS2 is a candidate disease-causing gene for MODY.

Full Text

Preamble

IRS2 May Be Associated with Maturity-Onset Diabetes of the Young (MODY): Clinical Features and Molecular Genetic Analysis in a Pedigree with a Special Type of MODY

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Abstract

Objective: To report the clinical features and genetic test results of a family with suspected maturity-onset diabetes of the young (MODY).

Methods: We analyzed the clinical characteristics, laboratory findings, and whole-exome sequencing (WES) results of a patient with a family history of a special type of diabetes who was admitted to the Department of Endocrinology at The First Affiliated Hospital of Anhui Medical University on September 10, 2018. Sanger sequencing was performed in family members for candidate variant verification.

Results: The proband was a 21-year-old male who presented to the emergency department with diabetic ketosis after developing diabetic manifestations for more than two years. Laboratory tests indicated insulin-resistant (type 2) diabetes. We analyzed the medical history of 17 members across four generations of the family, identifying seven paternal members with confirmed diabetes. WES identified two novel heterozygous variants in the proband: an IRS2 c.1586delC frameshift variant and a PPARG c.147T>G missense variant, both previously unreported and potentially associated with abnormal glucose metabolism. Other potentially pathogenic gene variants were excluded. The two variants were verified in 11 additional family members, revealing no strict co-segregation with clinical phenotype. Among six members positive for IRS2 c.1586delC, five were diagnosed with diabetes (83%, 5/6).

Conclusion: Families with monogenic diabetes characterized by diabetes mellitus often exhibit incomplete penetrance and/or variable expressivity, resulting in non-co-segregation of variants and phenotypes within the same pedigree. This

may reflect the combined effects of pathogenic variants with individual differences in other gene polymorphisms, environmental factors, and lifestyle habits. The gene function, reported diseases, variant pathogenicity, and patient phenotypes identified in this case indicate that IRS2 is a candidate causative gene for MODY.

Keywords: Monogenic diabetes; Maturity-onset diabetes of the young (MODY); IRS2 gene; PPARG gene; Diagnosis

Introduction

In recent years, with rapid economic development and lifestyle changes, the global prevalence of diabetes has increased annually, with a notable trend toward earlier onset. Maturity-onset diabetes of the young (MODY) represents a heterogeneous group of monogenic diabetes disorders characterized by β-cell dysfunction. The clinical diagnostic criteria for MODY include: a family history of diabetes spanning at least two generations, with at least one case diagnosed before age 25; impaired insulin secretion with minimal or no insulin action defects (in the absence of concurrent obesity); and an autosomal dominant inheritance pattern, making it the most common form of monogenic diabetes. To date, 14 MODY subtypes have been identified based on different causative genes, though no IRS2-MODY cases have been previously reported.

In this study, we identified a novel pathogenic IRS2 variant through exome sequencing in a family with eight diabetic members and validated it in 11 family members. Through analysis of variant pathogenicity, familial co-segregation, and comprehensive clinical phenotypes, we propose IRS2 as a new candidate gene for MODY. Additionally, we performed familial validation and discussion of the suspected missense variant PPARG c.147T>G identified in the proband.

Case Report

1.1 General Information

The patient was a 21-year-old male who presented to the Department of Endocrinology at The First Affiliated Hospital of Anhui Medical University on September 10, 2018, with complaints of "polydipsia, polyuria, and dry mouth for two years, and elevated blood glucose for one day." This study was approved by the hospital ethics committee, and informed consent was obtained from the patient and participating family members.

1.2 Present Illness

Two years prior, the patient developed polydipsia, polyuria, and dry mouth without apparent cause, consuming approximately 8 L of water daily with 5-6 daytime voids and 3-4 nighttime voids, each approximately 400-500 ml, accompanied by 14.5 kg weight loss over two years, which he did not address. On

September 9, 2018, his fasting blood glucose was 16.2 mmol/L at a local hospital. For further evaluation, he presented to our outpatient clinic on September 10, 2018, where fasting blood glucose was 24.6 mmol/L and urinalysis showed ketones 3+, glucose 15.7 mmol/L, K+ 3.66 mmol/L, and HCO3- 3+. He was admitted emergently with "diabetic ketosis." During the course of illness, he denied chills, fever, dizziness, headache, nausea, vomiting, abdominal pain, diarrhea, limb numbness, cold extremities, or visual disturbances. His appetite and sleep were adequate.

1.3 Physical Examination

Height: 170 cm; weight: 72 kg; BMI: 24.91 kg/m^2. The patient was alert but in poor spirits, with dry skin and poor elasticity. No superficial lymphadenopathy was noted. The thyroid was not enlarged. Neck was supple, pharynx not erythematous. Lung breath sounds were clear without rales. Heart rate: 105 beats/min, regular rhythm, no murmurs. Abdomen was soft, liver and spleen not palpable, no tenderness or rebound tenderness. No renal percussion tenderness. No lower extremity edema, normal skin temperature, normal dorsalis pedis pulses. Knee reflexes were elicitable, Babinski signs negative bilaterally.

1.4 Family History

[Figure 1: see original paper] shows the pedigree of the proband. Family members with diabetes included II-2 (grandmother), II-3 (great-aunt), II-4 (great-uncle), III-2 (father), III-3 (elder uncle), III-9 (younger aunt), and IV-5 (younger aunt' s son). All living family members underwent laboratory glucose testing for confirmation; members II-2 and II-3 could not be retrospectively confirmed as they had deceased, with information based on family reports. Clinical characteristics of all confirmed diabetic patients were recorded and summarized in Table 1 .

1.5 Laboratory Examinations

Laboratory examination results for family members are presented in Table 2 .

1.6 Genetic Testing and Diagnostic Results

After obtaining informed consent from the proband and family members, 3.0 mL of venous blood was collected in EDTA anticoagulant tubes from each participant on September 26, 2018. DNA was extracted and sent to Zhiyin Dongfang (Beijing) Translational Medicine Research Center Co., Ltd. (Beijing) for whole-exome sequencing. Exome library construction used the xGen Exome Research Panel v1.0 (IDT, USA) capture chip, with high-throughput sequencing performed on the NovaSeq 6000 platform (Illumina, USA). Data cleaning, quality control, alignment to the reference genome (hg19), and screening for point mutations and insertions/deletions <50 bp were completed following manufacturer protocols, achieving $ $99% target sequence coverage. Variant

annotation and automated pathogenicity and disease association analysis were performed using the Comprehensive Genetic Disease Precision Diagnosis Cloud Platform system (Zhiyin Dongfang, https://cloud.chigene.org:18081/). Variant pathogenicity was classified according to American College of Medical Genetics (ACMG) guidelines into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. Reference transcripts used for IRS2 and PPARG annotation were NM_{003749}.3 and NM_{138711}.6, respectively.

Results showed the proband harbored a heterozygous IRS2 frameshift variant c.1586delC (p.P529Rfs*15) and a heterozygous PPARG missense variant c.147T>G (p.H49Q). The proband' s father (III-2, diabetic), younger aunt (III-9, diabetic), and younger aunt' s son (IV-5, diabetic) also carried both the IRS2 c.1586(exon1)delC frameshift variant and PPARG c.147(exon3)T>G missense variant (both heterozygous). The elder uncle (III-3, diabetic) and elder uncle' s son (IV-2, phenotypically normal) carried only the IRS2 c.1586(exon1)delC frameshift variant (heterozygous). The proband' s mother (III-1, phenotypically normal), second uncle (III-5, phenotypically normal), second uncle' s daughter (IV-3, phenotypically normal), elder aunt (III-7, phenotypically normal), elder aunt' s son (IV-4, phenotypically normal), and great-uncle (II-4, diabetic) were wild-type for both pathogenic genes (summarized in [Figure 2: see original paper]).

Both the IRS2 c.1586delC frameshift variant and PPARG c.147T>G missense variant were novel, with no reports in SNP databases or literature. According to ACMG guidelines, IRS2 c.1586delC was classified as pathogenic (PVS1+PM2+PP1), while PPARG c.147T>G was classified as uncertain significance (PM1+PM2+PP1). Using the diagnostic cloud platform, other potentially pathogenic gene variants consistent with the diabetes phenotype were excluded (Table 3). Sanger sequencing using an ABI3730 sequencer (Thermo Fisher Scientific, USA) validated the DNA sequence point mutations for IRS2 and PPARG. PCR primers for Sanger sequencing were: IRS2 c.1586delC: F-CTGCAACACAGCCGCTCCATGTC, R-ACAGTGGCTCAGGGGCCTGTC; and PPARG c.147T>G: F-GGGTTACTGAGAGATGAGTCCAAT, R-GAAATGACCATGGTTGACACAGAG (results shown in [Figure 3: see original paper]).

Literature Review and Discussion

Monogenic diabetes is a rare form of diabetes caused by defects in single genes that result in pancreatic β-cell dysfunction and impaired insulin secretion. It is subdivided into three main types: maturity-onset diabetes of the young (MODY), neonatal diabetes, and syndromic diabetes, with MODY being the most common form.

In 1975, Tattersall and Fajans first proposed clinical criteria for MODY diagnosis: (1) early-onset diabetes before age 25; (2) at least two, ideally three, family members with diabetes (autosomal dominant inheritance pattern); (3)

non-insulin dependence (no insulin requirement even five years after diagnosis); (4) absence of obesity; and (5) absence of diabetic ketoacidosis (DKA). However, as more MODY genes were identified, some were found not to strictly meet these criteria, as certain MODY patients may present with obesity and DKA.

MODY was initially defined as a clinical subgroup of early-diagnosed familial diabetes with onset before age 25, characterized by insulin independence and autosomal dominant inheritance. Initial linkage analysis in large families identified the first MODY gene encoding glucokinase (GCK), followed shortly by genes encoding hepatocyte nuclear factor 1α (HNF1A), hepatocyte nuclear factor 4α (HNF4A), and hepatocyte nuclear factor 1β (HNF1B). To date, 14 definitive MODY causative genes have been identified (Table 3), though newly identified MODY gene cases remain rare, indicating high genetic heterogeneity. The proband in this case developed diabetes manifestations before age 20 and was diagnosed at age 21 with a clear family history, meeting MODY diagnostic criteria.

The IRS2 gene is one of the most important regulatory molecules mediating hepatic insulin receptor signal transduction and participates in selective insulin resistance, where insulin' s lipogenic effects remain intact while glucose uptake and glycogen synthesis are impaired. Animal experiments demonstrate that IRS2 deficiency manifests as selective insulin resistance, and hepatocyte-specific IRS2 knockout activates gluconeogenic pathways. The PPARG (peroxisome proliferator-activated receptor gamma) gene, a member of the nuclear hormone receptor superfamily, is highly expressed in adipose tissue of obese individuals and regulates lipid homeostasis, thereby reducing type 2 diabetes mellitus (T2DM) risk in obese populations. Therefore, abnormalities in both IRS2 and PPARG genes can cause glucose metabolism disturbances and increase diabetes risk.

We report a special type of MODY pedigree with a pathogenic IRS2 variant c.1586delC. Fajans et al. (2001) reported 10%-40% penetrance for non-insulin-dependent diabetes, which could explain the 83% (5/6) penetrance of IRS2-MODY in our family. Additionally, MODY phenotype severity may relate to variable expressivity of genetic traits. Expressivity refers to the degree of manifestation of a genetic defect, with different expressivity levels representing varying phenotypic severity. Pathogenic variant carriers exhibit variable phenotypes of differing severity rather than no phenotype at all. Based on disease duration, phenotypes may not be detected in a single medical examination, instead appearing intermittently across multiple tests—a phenomenon termed incomplete expressivity. In our family medical record review, limitations of the era, individual health status, and lifestyle factors may have resulted in mild IRS2-MODY phenotypes that escaped diagnosis (low expressivity), absence of diabetic manifestations at testing (expressivity attenuation), or complete lack of phenotype (non-penetrance). For case II-4, who tested negative for IRS2 c.1586delC, the possibility of diabetes from independent causes cannot be excluded. Currently, no studies have established IRS2 as a definitive MODY causative gene, high-

lighting the novelty of our findings, though confirmation awaits identification of additional similar patients or pedigrees.

Author Contributions

Hu Honglin and Zhang Qiu conceived and designed the study and analyzed its feasibility. Ren Yumei collected and organized case data, analyzed and interpreted results, and drafted the manuscript. Xu Min was responsible for patient diagnosis, treatment, and provision of case data. Ye Meilei revised the manuscript. Hu Honglin was responsible for quality control, review, and overall accountability for the manuscript.

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Note: Figure translations are in progress. See original paper for figures.