

Background

Over 800 different mutations in *GCK* gene have been reported in the Human Gene Mutation Database, the vast majority of which result in monogenic diabetes (Maturity Onset Diabetes of the Young, MODY type 2). The missense mutation p.Leu122Val is listed in that database as “disease-causing”. However, the National Center for Biotechnology Information ClinVar database (Variation ID 585919) reports that this mutation is of “uncertain significance”. Both databases refer to an Italian pediatric patient reported by Massa *et al* in 2001.

Objective

To report a pedigree of 3 patients affected with *GCK* mutation c.364C>G (p.Leu122Val) to support the pathogenicity of this mutation.

Cases

Proband (case 1) is an African-American female who was diagnosed with diabetes at 3 years of age. She was initially treated for type 1 diabetes with basal/bolus insulin. Her diabetes autoantibodies were negative and she required low doses of insulin. Her insulin was discontinued upon discovery of a mutation in the *GCK* gene suggestive of MODY type 2. Her HgbA1c has since ranged from 6.8 - 7.2% without insulin therapy.

Case 2 is the younger half-sister of case 1. She was initially seen at 3 years of age for an elevated fasting glucose level of 6.55 mmol/L (118 mg/dL) and HgbA1c of 6.4%.

Case 3 is the mother of case 1 and 2. She had a history of insulin-requiring gestational diabetes with her second pregnancy, and received metformin therapy for 8 months post-partum. At a clinic visit with her daughters, she was found to have a fasting glucose of 7.16 mmol/L (128 mg/dL) and HgbA1c of 6.3%.

Results

Genetic analysis in the three cases revealed *GCK* mutation c.364C>G (p.Leu122Val). The maternal grandmother of cases 1 and 2 also had genetic testing performed that was negative for the mutation.

The potential pathogenic role of this mutation was evaluated *in silico* by several bioinformatic tools.

<i>in silico</i> analysis <i>GCK</i> mutation L122V	
PolyPhen2	Probably damaging
SIFT	Damaging
Mutation Taster	Disease causing

Conclusions

To our knowledge, the *GCK* mutation c.364C>G (p.Leu122Val) has only been reported in a pediatric patient in Italy and was without a phenotypic description. The description of these three family members over two generations strengthens the supposition that this mutation is indeed disease-causing and of clinical significance.

Reference

Massa O, Meschi F, Cuesta-Munoz A, *et al* 2001. *Diabetologia* 44:898–905.