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A Novel Phenotype of GCK c.781G>A Variant Causing Neonatal Refractory Hyperinsulinaemic Hypoglycaemia

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Short running title: GCK c.781G>A and neonatal hyperinsulinaemic hypoglycaemia

A Novel Phenotype of GCK c.781G>A Variant Causing Neonatal Refractory Hyperinsulinaemic Hypoglycaemia

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Ethical Approval

This study was approved by the Ethics Committee of Pengpai Memorial Hospital (Approval No. PPJNYY20260115). Written informed consent was obtained from the patient's parents for publication of this case report.

Conflict of Interest

The authors declare no financial or non-financial competing interests. No funding was received for this work.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Jianfeng Lin and Yiqun He contributed equally to this work as co-first authors.

Jianfeng Lin: Conceptualization, clinical data collection, manuscript drafting, writing—review & editing, correspondence, and final approval.

Yiqun He: Genetic analysis and structural biology, data interpretation, and final approval.

All authors have approved the final version and agree to be accountable for all aspects of the work.

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Abstract

Glucokinase (GCK) mutations are well-known causes of maturity-onset diabetes of the young type 2 (MODY2) and hyperinsulinaemic hypoglycaemia type 3 (HH3). The GCK c.781G>A (p.Gly261Arg) variant has been exclusively reported in MODY2. We describe a term male infant with severe refractory neonatal hypoglycaemia and inappropriately elevated insulin. Genetic analysis identified a heterozygous GCK c.781G>A variant inherited from his father. Protein modelling supported a gain-of-function effect. The infant responded well to diazoxide and discontinued treatment two weeks after discharge. This is the first report of GCK c.781G>A presenting as neonatal HH3, expanding the known phenotypic spectrum of this variant.

Introduction

Glucokinase (GCK) is a key glucose sensor in pancreatic β-cells. Loss-of-function GCK mutations typically cause maturity-onset diabetes of the young type 2 (MODY2), while gain-of-function mutations lead to congenital hyperinsulinaemic hypoglycaemia type 3 (HH3), characterized by severe persistent neonatal hypoglycaemia.

The GCK c.781G>A (p.Gly261Arg) variant has previously been reported only in

MODY2 patients. To our knowledge, this variant has never been associated with a hyperinsulinaemic hypoglycaemia phenotype. We present the first case of GCK c.781G>A causing severe refractory neonatal HH3, highlighting the phenotypic complexity of GCK variants and providing important clinical implications for diagnosis and treatment.

Case presentation

A male infant was born at 38^{+5} weeks of gestation with a birth weight of 2.43 kg (small for gestational age). He developed severe refractory hypoglycaemia shortly after birth, with the lowest blood glucose level of 0.34 mmol/L. Laboratory tests showed inappropriately elevated serum insulin and C-peptide levels, consistent with hyperinsulinism. Meconium aspiration syndrome and patent foramen ovale were also noted.

Next-generation sequencing identified a heterozygous missense variant GCK c.781G>A (p.Gly261Arg), which was confirmed by Sanger sequencing and shown to be inherited from the asymptomatic father. Protein structure modelling revealed additional hydrogen bonds in the mutant protein, consistent with enhanced enzyme affinity and a gain-of-function effect.

The infant was treated with diazoxide combined with hydrochlorothiazide, and blood glucose levels rapidly stabilized. Medication was safely discontinued two weeks after discharge. Long-term follow-up demonstrated normal blood glucose regulation and age-appropriate neurodevelopment.

Discussion

This is the first report of GCK c.781G>A presenting as neonatal hyperinsulinaemic hypoglycaemia (HH3), whereas previous literature linked this variant exclusively to MODY2. This dual phenotypic expression illustrates the complex functional consequences of GCK variants and challenges traditional genotype–phenotype correlations.

Protein structural analysis helped clarify the molecular mechanism: the p.Gly261Arg substitution enhances hydrogen bonding, increasing glucokinase activity and leading to unregulated insulin secretion. Early genetic diagnosis allowed prompt initiation of diazoxide, preventing neurological complications. Notably, short-term treatment was sufficient, and the patient achieved clinical remission without long-term medication.

This case expands the known phenotypic spectrum of GCK c.781G>A and emphasizes the importance of genetic testing in unexplained refractory neonatal hypoglycaemia. It also provides evidence that some HH3 patients may not require lifelong therapy.

Conclusion

The GCK c.781G>A variant can cause severe neonatal hyperinsulinaemic hypoglycaemia as a gain-of-function mutation, beyond its known association with MODY2. Early genetic diagnosis and diazoxide treatment result in an excellent prognosis, and drug withdrawal may be feasible after clinical stabilization.

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Figure legends

Figure 1. Scatter plot of blood glucose levels in the neonate during the first week after birth. The red dashed line marks the lower limit of normal blood glucose for term neonates (2.6 mmol/L).

Figure 2. Sanger sequencing chromatograms showing the heterozygous GCK c.781G>A (p.Gly261Arg) variant in the proband and his father. The red arrow points to the position of the G>A nucleotide substitution at chr7:44185837 (GRCh37/hg19). The upper panel displays the sequencing result of the proband, the middle panel displays the result of his father, and the lower panel shows the wild-type sequence from his mother, confirming that the variant is inherited in an autosomal dominant manner.

Figure 3. Pedigree of the family with the GCK c.781G>A variant. The arrow indicates the proband (index case). Squares represent male family members, circles represent female family members, filled symbols represent individuals carrying the heterozygous GCK c.781G>A variant, and open symbols represent wild-type individuals.

Figure 4. Predicted three-dimensional protein structural changes underlying the gain-of-function effect of the GCK c.781G>A (p.Gly261Arg) variant. Panel A shows

the wild-type GCK structure, and Panel B shows the mutant structure, with the altered hydrogen bond network indicated by blue dashed lines.

Conflict of Interest Statement

The authors declare no financial or non-financial competing interests that could influence the conduct or reporting of this study. No funding was received for this work.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The individual genetic sequencing data and clinical records of the neonate are not publicly available due to privacy and ethical restrictions, but are available from the authors with the permission of the patient's legal guardian.

Figure 1

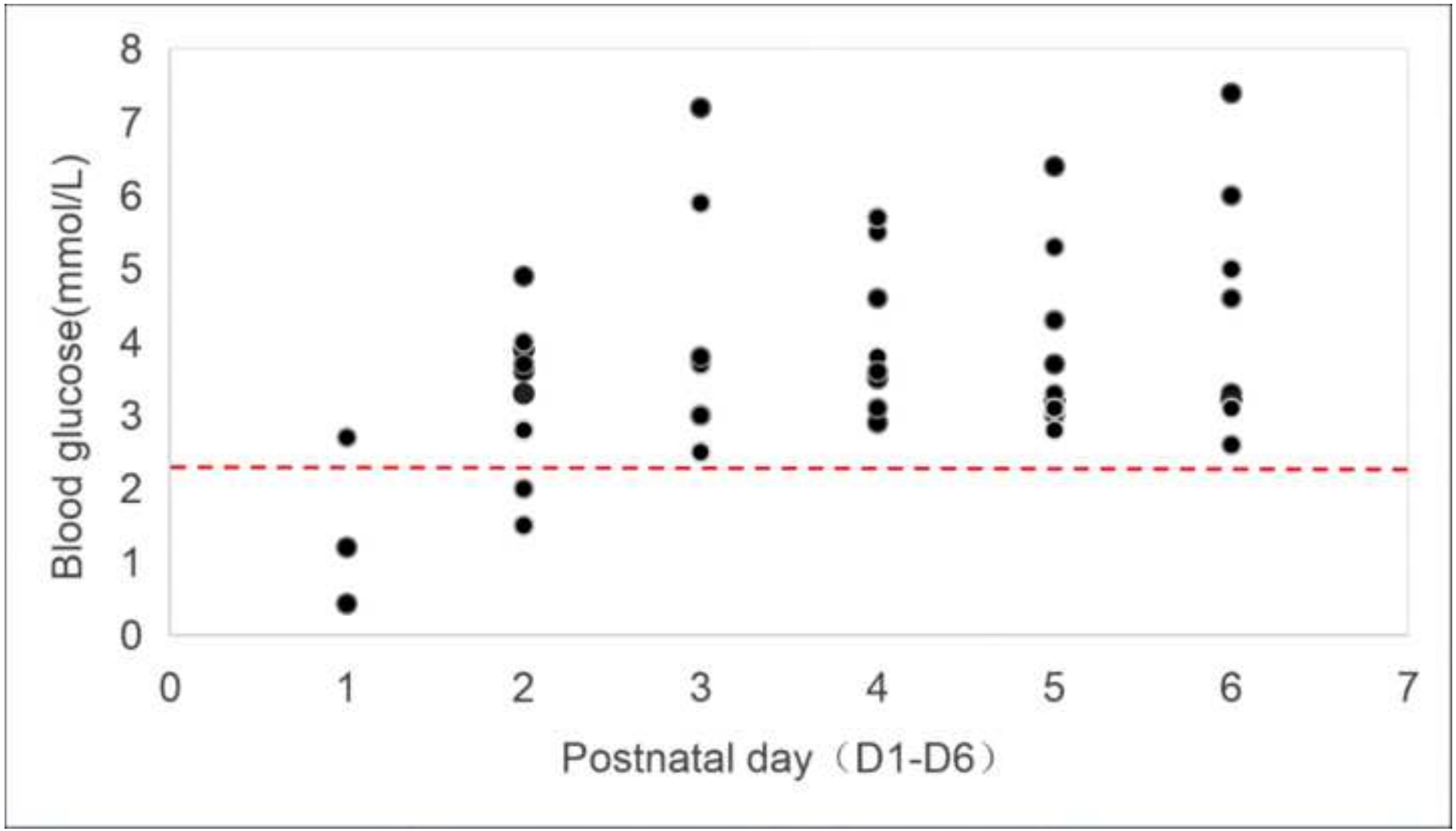

Blood glucose(mmol/L)
8
7
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7
Postnatal day（D1-D6）

Figure 2

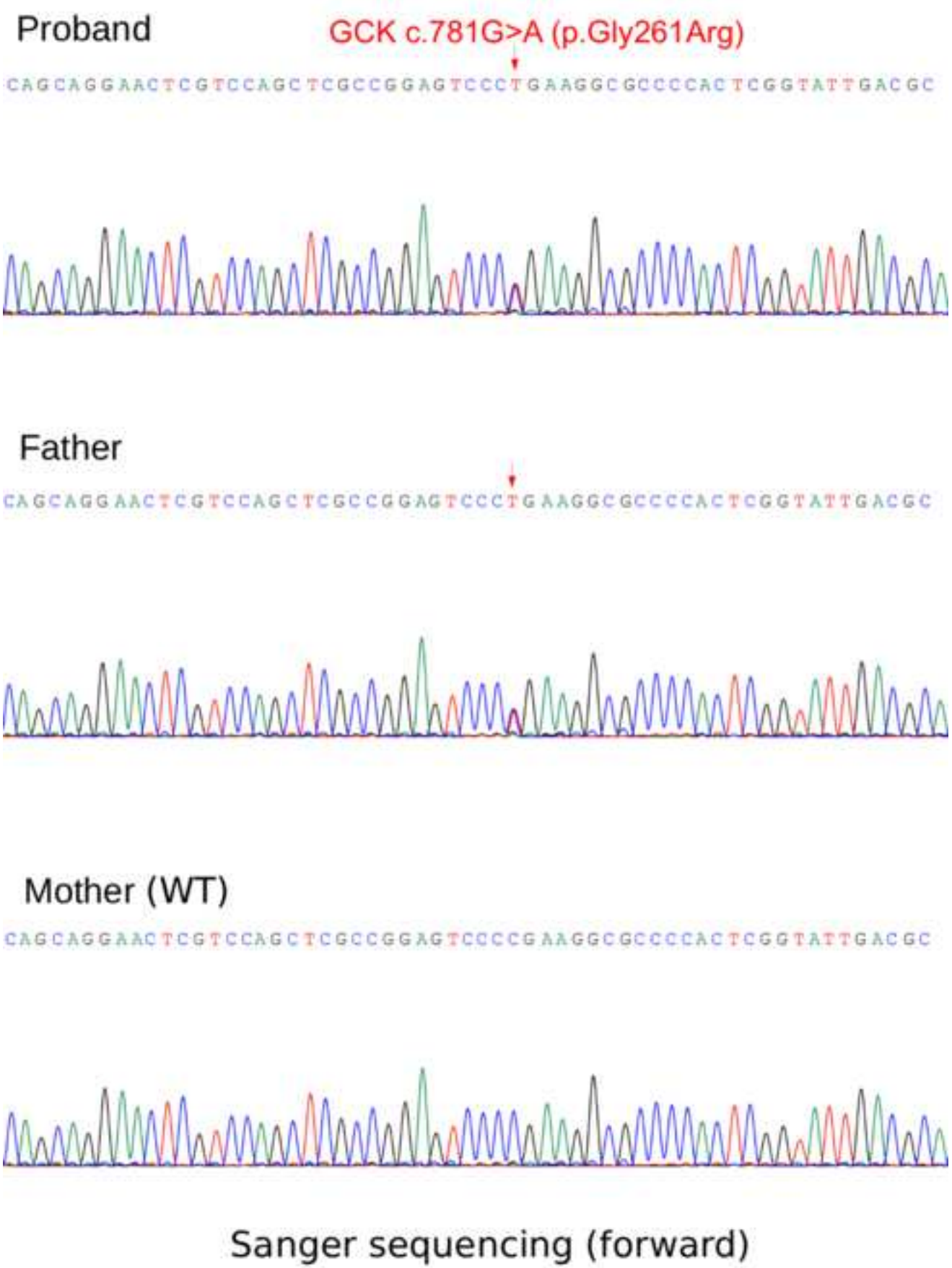

Proband
GCK c.781G>A (p.Gly261Arg)
CAGCAGGAACTCGTCCAGCTCGCCGGAGTCCCTGAAGGCGCCCCACTCGGTATTGACGC
Father
CAGCAGGAACTCGTCCAGCTCGCCGGAGTCCCTGAAGGCGCCCCACTCGGTATTGACGC
Mother (WT)
CAGCAGGAACTCGTCCAGCTCGCCGGAGTCCCCGAAGGCGCCCCACTCGGTATTGACGC
Sanger sequencing (forward)

Figure 3

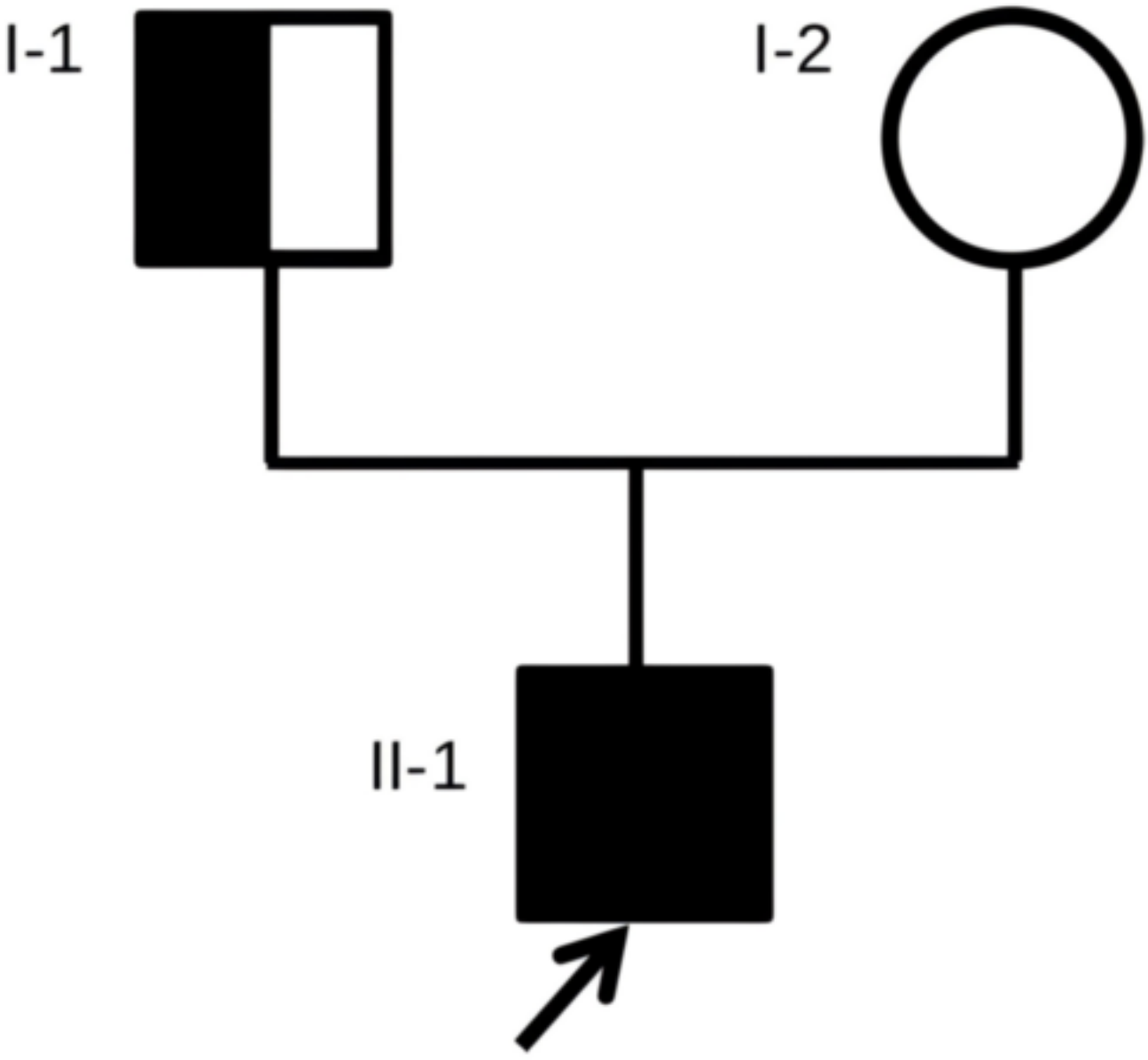
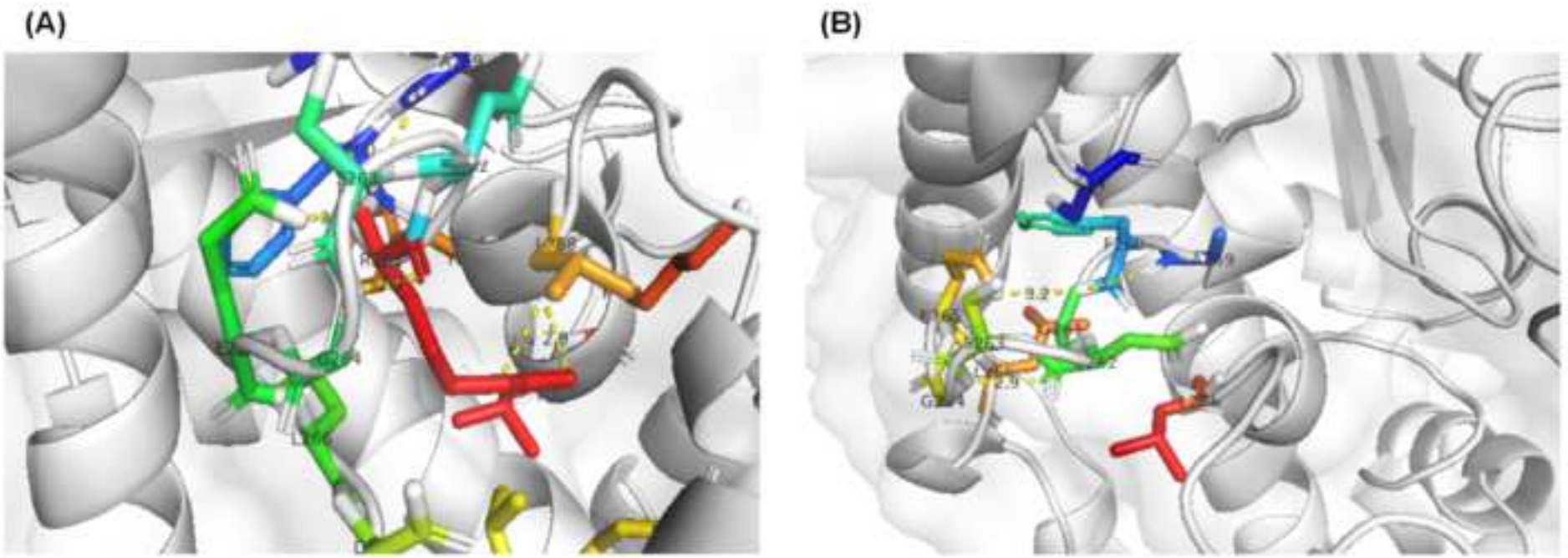


Figure 4



CONFLICT OF INTEREST STATEMENT

Manuscript Title: A Novel Phenotype of GCK c.781G>A Variant Causing Neonatal Refractory Hyperinsulinaemic Hypoglycaemia

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