

# Severe Congenital Hyperinsulinism in a Neonate Homozygous for Two Novel Missense Mutations in the KCNJ11 Gene

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## BACKGROUND

Congenital hyperinsulinism (CHI) is a heterogenous disorder characterized by hyperinsulinemic hypoglycemia. In severe forms of the disease it may present in the neonatal period. Molecular defects involving 8 genes has been described so far. Herein we report a case of severe, diazoxide unresponsive CHI in the AR form caused by two homozygous novel missense mutations in the KCNJ11 gene.

## CASE REPORT

An 8-day old girl was referred for hyperinsulinemic hypoglycemia. She was the first child of first degree cousins. She had hypoglycemia on the first day of life. Unresolved repeated hypoglycemia despite high glucose infusion rates (GIR) and an elevated insulin (47 mcIU/ml) suggested CHI and the patient was started on diazoxide (15 mg/kg/d). She continued to have bouts of hypoglycemia, considered to be diazoxide unresponsive and referred for pancreatectomy. Upon arrival to our clinic she had hepatomegaly. Cardiac ECHO revealed ASD, PDA, pulmonary hypertension as well as concentric left ventricular hypertrophy.

Blood glucose was kept in the normal range initially using diazoxide (15 mg/kg/d), hydrochlorothiazide (2 mg/kg/d), octreotide (20-40 mcg/kg/d) and glucose infusion (10-12 mg/kg/min). On 20<sup>th</sup> postnatal day, she developed heart failure and was digitalized, diazoxide was replaced with glucagon (20 mcg/kg/d). On 22<sup>nd</sup> day of life PDA was ligated, and 36<sup>th</sup> day of life near total pancreatectomy was carried out. Five days after pancreatectomy hypoglycemia recurred and she was put on octreotide. Neurological examination on 58<sup>th</sup> day of life showed failure to fix and follow objects, axial hypotonicity, and spasticity in the extremities. At the age of 30 months she is still using octreotide (15 mcg/kg/d) with rare hypoglycemia and latest HbA1c is 5,3 %.

Pathological examination of the pancreas showed diffuse hyperplasia, hypertrophy and nucleomegaly in the islet cells. Molecular analysis revealed that the patient was homozygous for two novel missense mutations (p.R221H and p.Q299H) in the KCNJ11 gene. Both parents were heterozygous for the same mutations.

## MOLECULAR STUDIES

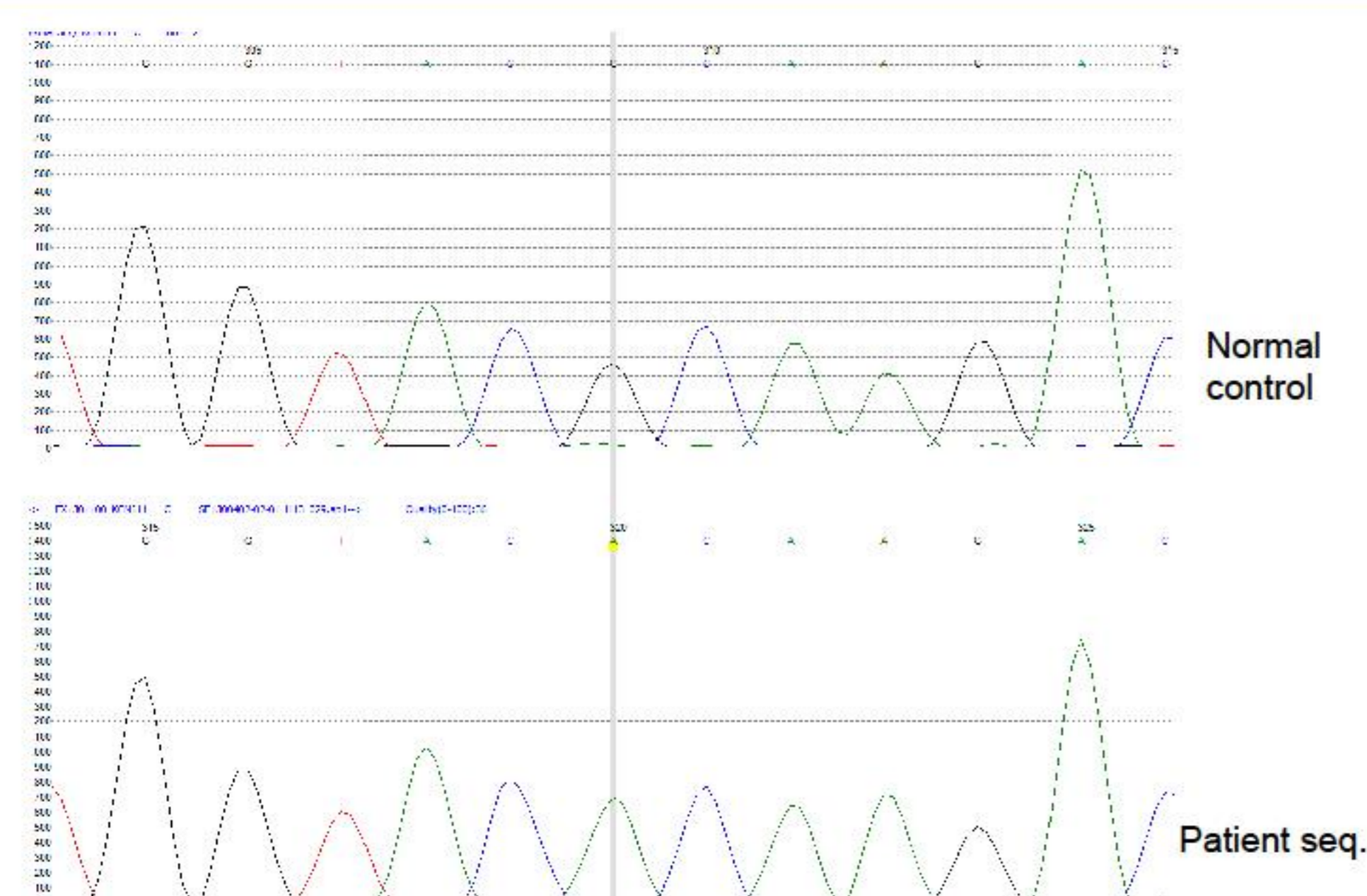


Fig. 1a. KCNJ11, p.R221H c.662G>A/c.662G>A control and patient results

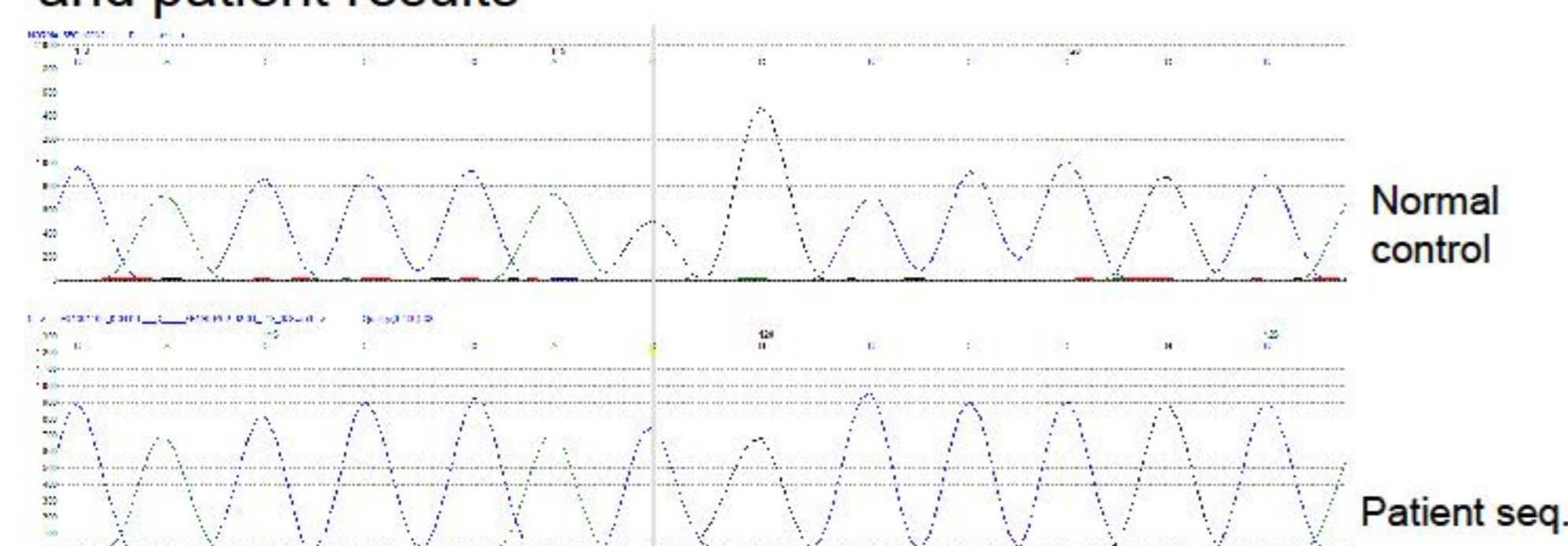
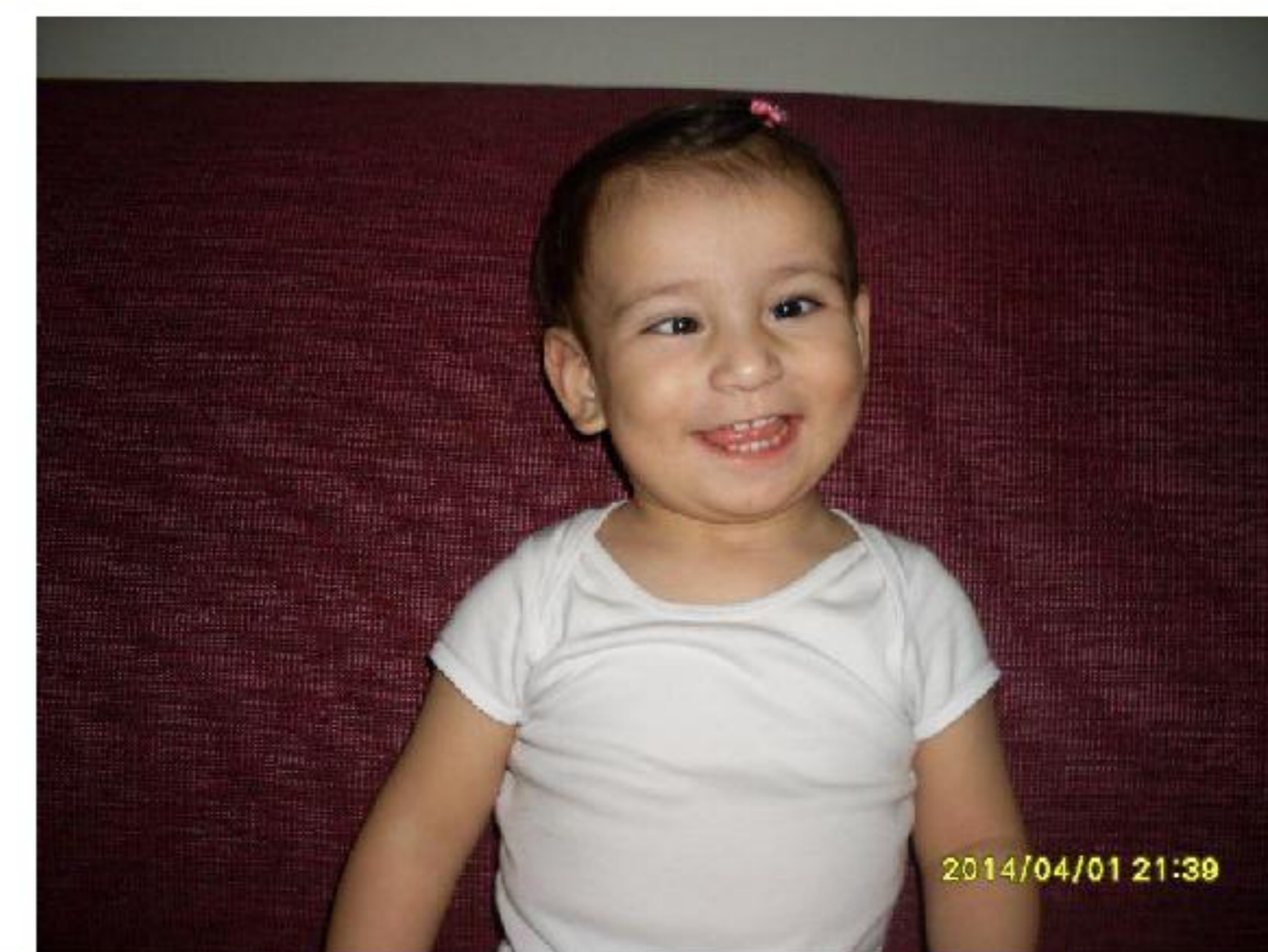


Fig. 1b. KCNJ11, p.Q299H c.897G>C/c.897G>C control and patient results

Molecular analysis revealed that the patient was homozygous for two novel missense mutations (p.R221H and p.Q299H) in the KCNJ11 gene. Both parents were heterozygous for the same mutations.



Case at the age of 9 and 30 months.

## PATHOLOGICAL EVALUATION

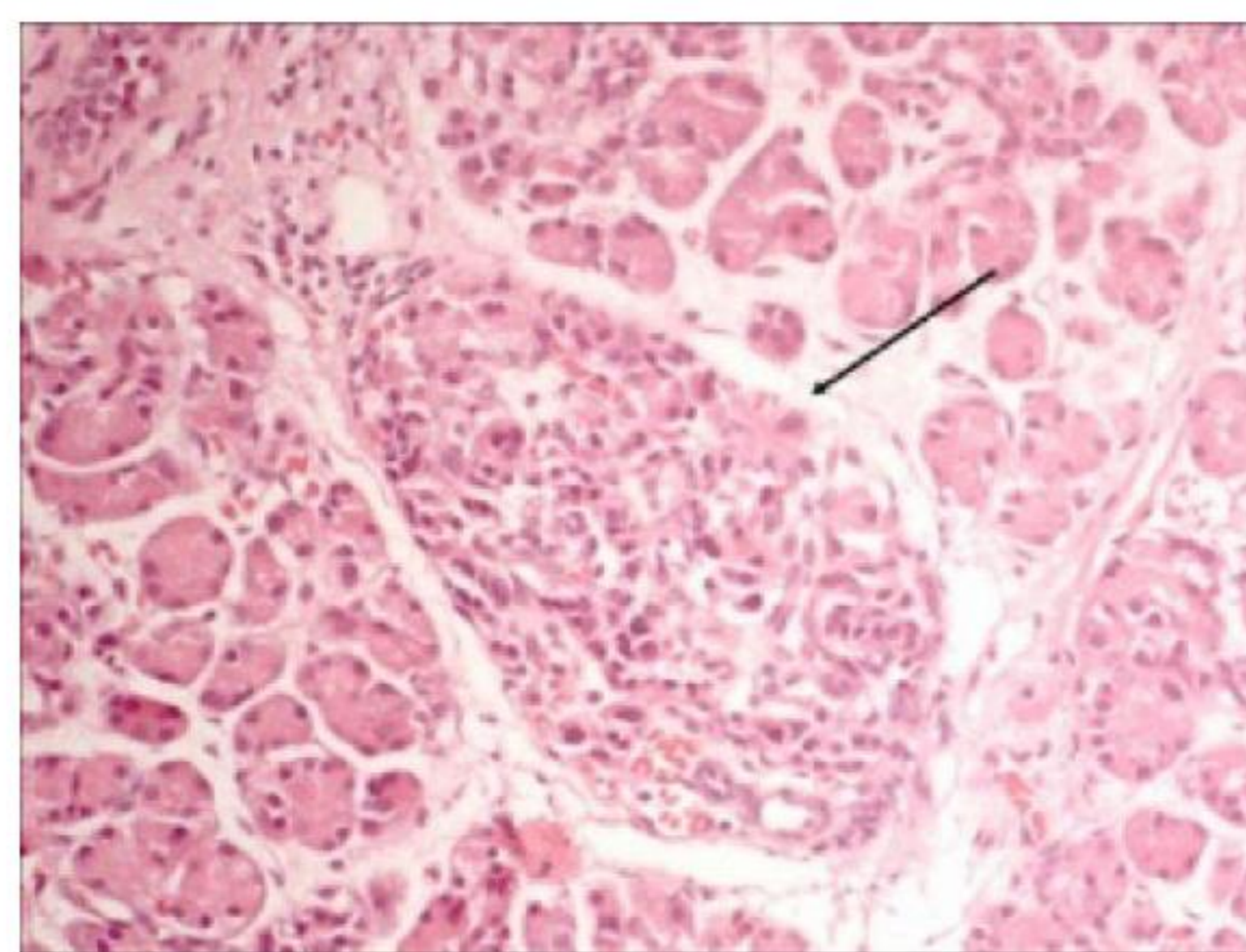


Fig. 2a. Hyperplastic Langerhans islet (arrow) is observed (HE, original magnification x100)

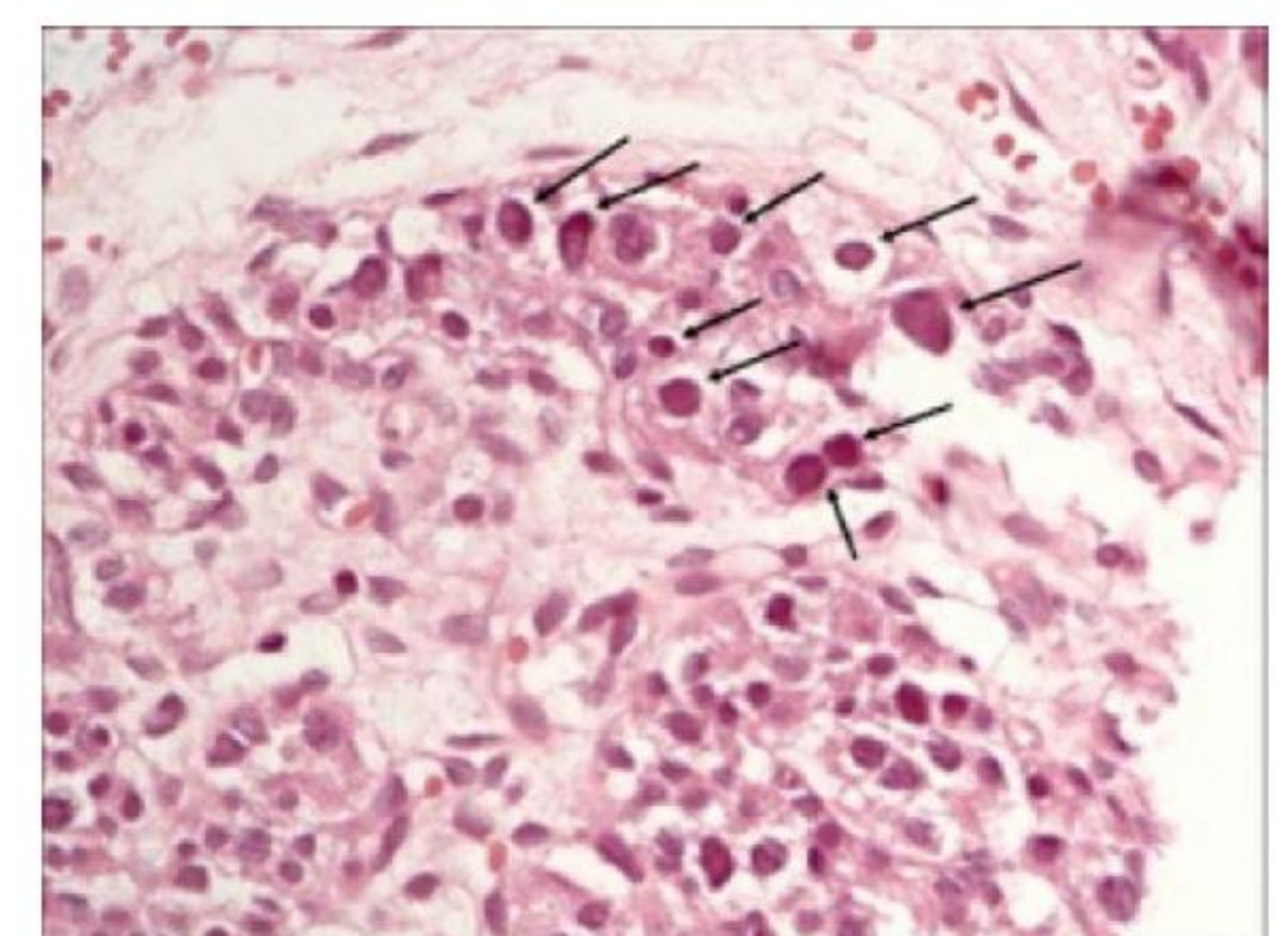


Fig. 2b. Hypertrophy and nucleomegaly (arrows) in islet cells (HE, original magnification x200)

Pathological evaluation showed diffuse hyperplasia, hypertrophy and nucleomegaly in the islet cells.

## CONCLUSIONS

Pathology and molecular findings suggested autosomal recessive CHI in the current patient. The arginine residue at codon 221 and the glutamine residue at codon 299 are conserved across species. It is therefore likely that one or both of these mutations are pathogenic.