Known and a novel mutation in *PHKA2* expand the phenotype of glycogen storage disease IXa to include idiopathic ketotic hypoglycaemia

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Conclusion: Patients with idiopathic ketotic hypoglycaemia may have a mild form of glycogen storage disease. Genetic analysis is encouraged to improve precision of treatment and prognosis, and to diagnose affected family members

Background

• Idiopathic ketotic hypoglycaemia (IKH) is the most common cause of hypoglycaemia in childhood. It is an exclusion diagnose when thorough investigations have been made

• Glycogen Storage disease (GSD) type IX is due to a deficiency in phosphoralyse kinase and comprises one quarter of all GSD's. GSD IXa, encoded by *PHKA2*, is the most frequent subtype with a majority of private mutations (n>100)

• Clinical features in children with GSD IXa include hepatomegaly, elevated liver enzymes, short stature and ketotic hypoglycemia. Wide variations in symptoms and severity exist without any known genotype-phenotype correlation

Methods

• Retrospective chart evaluation in three families with IKH patients

• Genetic analysis by whole exome sequencing or 29 gene GSD panel

Results

• Six children in three families were diagnosed with IKH (**Table 1.**) and were reclassified to have GSD IXa

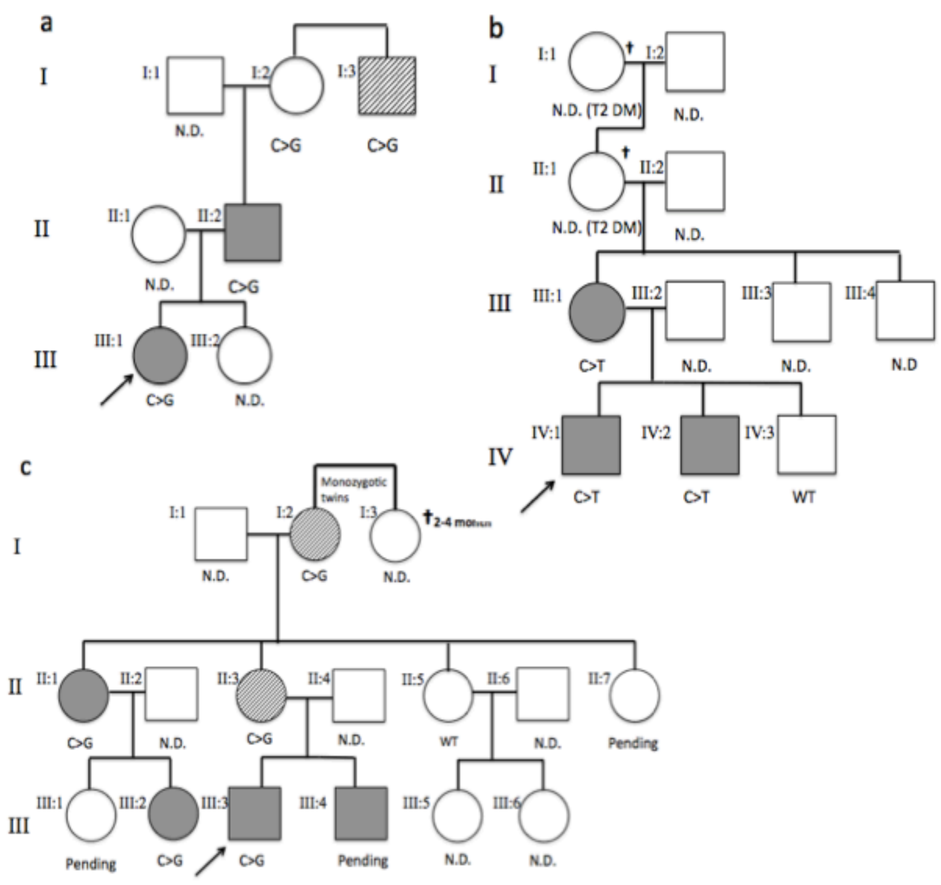

Figure 1. Pedigree of three families with IKH
Dark grey: Symptoms
Hachured: Symptoms in childhood
White: No symptoms

Circle: Female
Square: Male

Genetic investigations

• In family A and B Whole Exome Sequencing were made

• Two previously reported mutations in *PHKA2* were found:
c.2606C>G, p.Pro869Arg and c.1493C>T, p.Pro498Leu

Family history and the knowledge from family A and B prompted reevaluation of the IKH diagnosis in family C

• A novel GSD IXa mutation (HGMD, ClinVar and literature)
c.4C>G, p.Arg2Gly in *PHKA2,* maternal was found

• Allele frequency 4/100,000 (genomAD)

• *In silico* analysis: Deleterious(PolyPhen-2), deleterious (SIFT), disease-causing (Mutaster)

• Classification according to ACMG guidelines was likely pathogenic

Discussion

• IKH and GSD IXa can clinically overlap, as suggested by our report, why GSD IXa may be under-diagnosed

We hypothesize that IKH may represent milder variants of GSD, **Figure 2.**

• GSD gene panel and family testing is encouraged in IKH

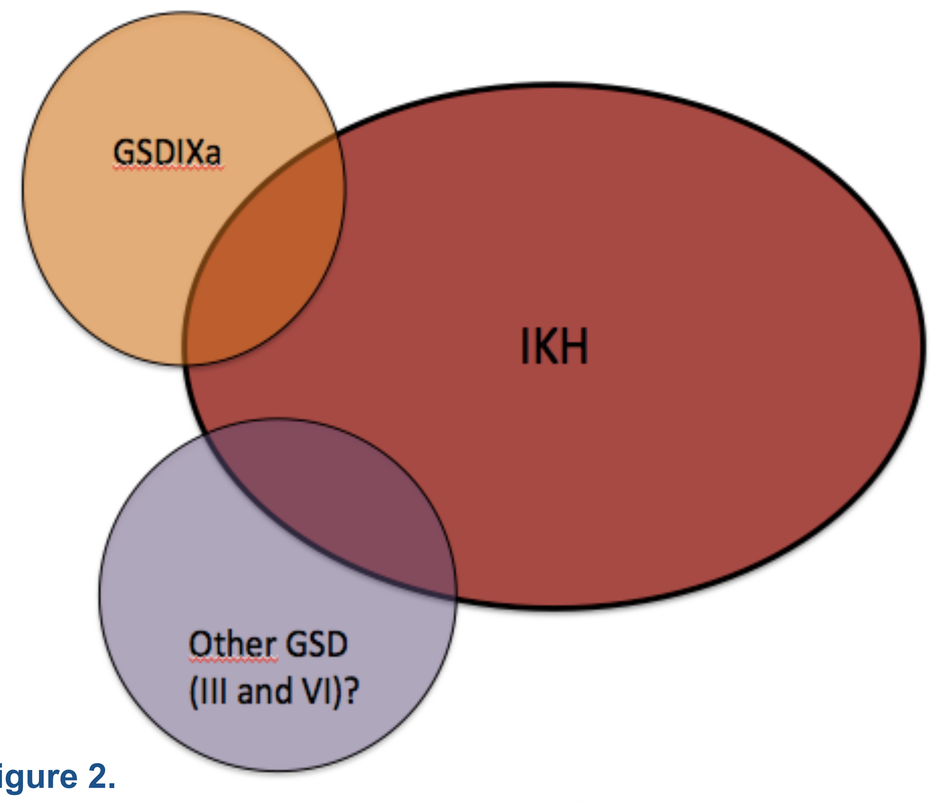

Figure 2.
Hypothesis: Mild affected children with GSD IXa may be misdiagnosed as IKH. The same may be true for other GSDs.

Patient	Onset	Sex	Hypoglycaemia (mmol/L) (lowest reported)	Ketosis (>1.0 mmol/L)	Hepatomegaly (Ultrasound or clinical)	Liver dysfunction	Growth retardation (< -2 SD)	Normal hormonal and metabolic investigations	Gene	Mutation
Family A										
III:1	17 mo.	F	2.5	Yes	No	No	No	Yes	*PHKA2*	p.Pro869Arg
Family B										
II:1	19 mo.	M	1.9	Yes	No	No	No	Elevated lactat + pyruvat	*PHKA2*	p.Pro498Leu
II:2	20 mo.	M	2.1	Yes	No	No	No	Elevated lactat + pyruvat	*PHKA2*	p.Pro498Leu
Family C										
III:2	6 y.	F	2.2	Yes	No	No	No	Yes	*PHKA2*	p.Arg2Gly
III:3	8 mo.	M	1.8	Yes	No	No	No	Yes (subnormal GH values)	*PHKA2*	p.Arg2Gly
III:4	3 y.	M	2.3	nd	No	No	No	nd	*PHKA2*	p.Arg2Gly

nd=no data, mo.=month, y.=year, F=female, M=Male

Table 1. Clinical details in IKH patients