Syndromic hypoketotic, hypoinsulinaemic hypoglycaemia due to a mosaic activating phosphatidylinositol 3-kinase (PI3K) mutation

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Introduction

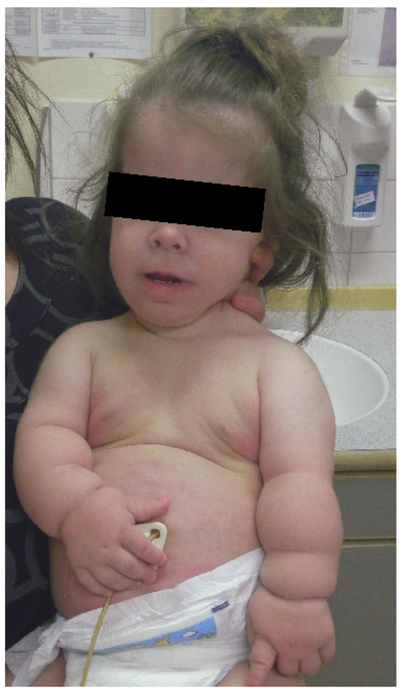
In contrast to hypoglycaemia due to congenital hyperinsulinsm, there are patients with a similar metabolic profile of **hypoketotic hypoglycaemia, but low insulin levels and relatively low glucose requirements** to maintain euglycaemia.

So far, four patients with **activating mutations in the insulin signal-transducing kinase AKT2** have been described, each also showing a syndromic phenotype including hemihypertrophy (1).

We present a 3.5 year-old girl with **similar metabolic and syndromic features, but no AKT2 mutation,** suggesting a possible mutation in another gene of the same pathway.

Case report

- Non-consanguineous German parents, birth weight 3230g (+2.03 SDS), length 52cm (+1.51 SDS), HC 37.5cm (+2.3SDS)
- **Recurrent hypoketotic, hypoinsulinemic hypoglycaemia**, unresponsive to diazoxide and somatostatin analogues, currently stable under starch-enriched meals and overnight PEG feeds.
- **Other syndromic aspects**: Large diastasis recti, syndactyly, short limbs and "chubby" appearance, ventriculo-peritoneal shunt due to Arnold-Chiari Malformation, epilepsy, generalised muscle hypotonia, hyperaemia of the face, dorsal haemangioma, fibrotic hepatopathy on liver biopsy

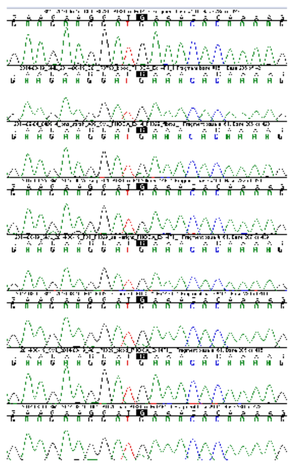


Metabolic Profile	Patient	Reference
Fasting glucose (after 11h fast)	2.5mmol/l (45mg/dl)	>4mmol/l (72mg/dl)
Fasting insulin (after 11h fast)	<0.2mU/l	undetectable
Ketonuria	negative	
Glucose infusion rate to maintain euglycemia	2.4mg/kg/min	in CHI: >10mg/kg/min
Glucagon stimulated glycogen release	Normal	
Glucose tolerance test	Normal	

Genetics

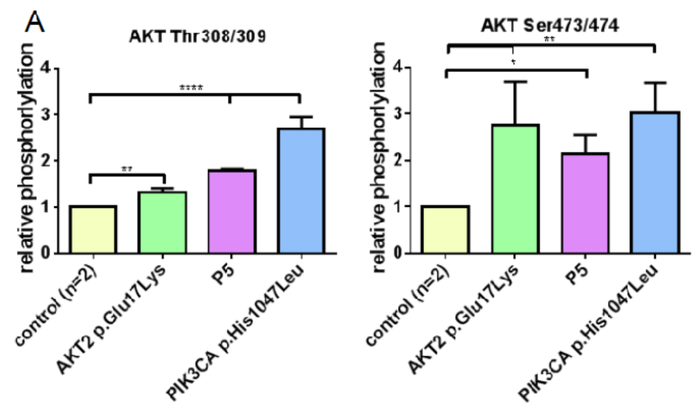
Exome sequencing undertaken in the proband and parents detected a **mosaic mutation (p.Glu726Lys) in PIK3CA**, encoding the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), in lymphocyte, hair bulb, fibroblast, cheek swab, and liver DNA from the patient but neither parent:

Sample	Mutation burden
Mother	<1%
Father	<1%
Fibroblasts	33-36%
Liver	42-44%
Blood	22-29%
Cheek swab right	20-23%
Cheek swab left	24-26%
Hair bulb	27-28%



Cellular Studies

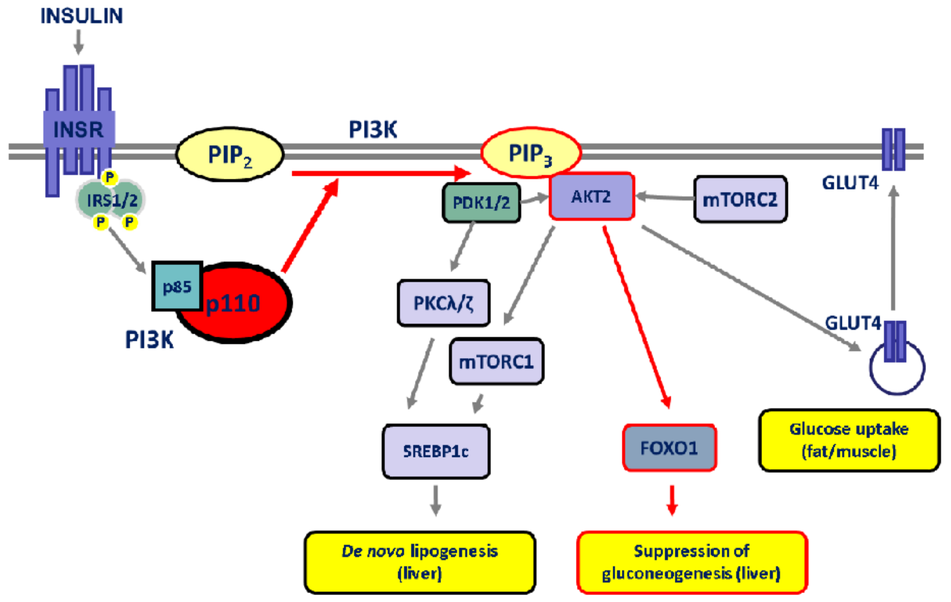
Primary dermal fibroblasts of the patient (P5) show a **small but significant increase in phosphorylation of downstream AKT** at Thr 308/309 and Ser 473/474, lying downstream of PI3K. This hyperphosphorylation level lies in between those observed in AKT2 mutation (1) and PIK3CA p.His1047Leu-associated segmental overgrowth (2).



ELISA, mean ± SEM, n=3, pooled data, *p<0.05, **p<0.01, ****p<0.0001

Discussion

Activating **PIK3CA mutations are known to cause a spectrum of segmental overgrowth disorders including Megalencephaly-Capillary malformation (MCAP) syndrome** (3), of which our patient shows several typical aspects. The phenotypic spectrum is substantially influenced by the mosaic pattern, e.g. the mutation burden in a respective tissue. So far, hypoglycaemia has not been described in MCAP syndrome.



Here, a **high mutation burden is present in liver tissue,** in which insulin signalling is constantly activated. This explains extensive **suppression of gluconeogenesis independent from blood glucose concentration and serum insulin**, leading to hypoketotic, hypoinsulininemic hypoglycaemia with relatively low requirements of glucose to maintain euglycaemia.

Conclusions

In contrast to hypoglycaemia due to congenital hyperinsulinsm, there are patients with a similar metabolic profile of **hypoketotic hypoglycaemia, but low insulin levels and relatively low glucose requirements to maintain euglycaemia based on mutations in the PI3K/AKT signalling pathway.** These patients provide a unique opportunity to study this pathway in vivo.

Acknowledgements and literature

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