# Birth weight and diazoxide unresponsiveness strongly predict the likelihood of congenital hyperinsulinism due to a mutation in *ABCC8* or *KCNJ11*

**TI Hewat [1], D Yau [2], JCS Jerome [1], TW Laver [1], JAL Houghton [3], BM Shields [1], SE Flanagan [1], KA Patel [1, 3]**

1. University of Exeter Medical School, Exeter, UK
2. Royal Manchester Children's Hospital, Manchester, UK
3. Department of Molecular Genetics, Royal Devon & Exeter Hospital, Exeter, UK

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

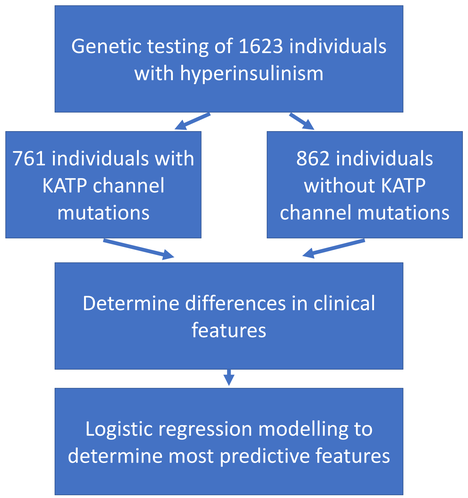
## INTRODUCTION

- Mutations in the KATP channel genes (*ABCC8 & KCNJ11)* cause ~80% of monogenic cases of hyperinsulinism [1, 2]
- Identifying a KATP channel mutation can inform on medical management [3]
- Clinical features may help to establish the likelihood of a KATP channel mutation at diagnosis

## AIM

Assess whether clinical features at presentation can predict the likelihood of a KATP channel mutation

## METHOD




## RESULTS

| | Birth weight (g) | Diazoxide responsive | Diagnosed first week of life | Insulin (pmol/l) | Female sex | Consanguineous | Caucasian |
|---|---|---|---|---|---|---|---|
| **KATP** | 4333 | 32% | 85% | 162.2 | 46% | 52% | 30% |
| **Non-KATP** | 3512 | 88% | 72% | 115.4 | 36% | 34% | 52% |
| **P value** | $6 \times 10^{-94}$ | $2 \times 10^{-84}$ | $1 \times 10^{-9}$ | $1 \times 10^{-8}$ | $5 \times 10^{-5}$ | $2 \times 10^{-12}$ | $3 \times 10^{-18}$ |

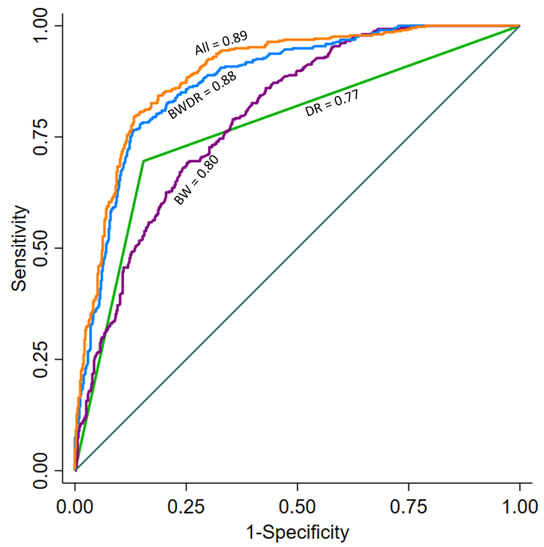



*Figure 1 - Receiver operating curves analysis showing the discriminating ability of clinical features to identify individuals with KATP hyperinsulinism from those with unknown aetiology. DR = diazoxide responsiveness. BW = birth weight. All = BW, DR, age at diagnosis, sex, insulin level at diagnosis, ethnicity, consanguinity.*

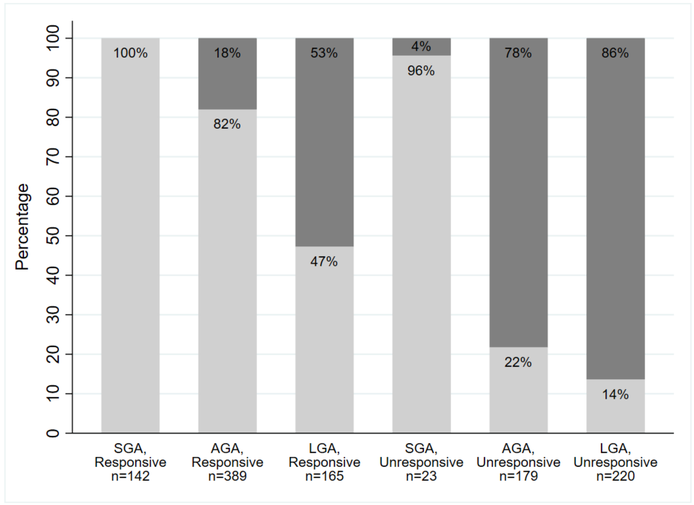



*Figure 2 - Proportion of KATP hyperinsulinism by diazoxide responsiveness and birth weight categories. Light grey bars = percentage of individuals without KATP channel mutation, dark grey bars = percentage of cases with KATP channel mutation. S/A/LGA = Small/Appropriate/Large for Gestational Age*

- Seven clinical features differed between individuals with KATP channel mutations and those with an unknown genetic aetiology (Table 1)
- Birth weight and diazoxide response are independent and additive for predicting KATP channel mutations (Figure 1)
  - ROC AUC = 0.88 when model used birth weight and diazoxide, ROC AUC = 0.89 when adding other clinical features
- A KATP channel mutation was most likely in individuals who were diazoxide unresponsive and born large (86%) or appropriate (78%) for gestational age (Figure 2)

## CONCLUSIONS

- Birth weight and diazoxide response are highly predictive for congenital hyperinsulinism caused by KATP channel mutations
- Individuals born appropriate or large for gestational age who do not respond to diazoxide treatment are most likely to have a KATP channel mutation
- Thorough monitoring of clinical features at presentation in individuals with congenital hyperinsulinism can help to guide diagnosis, genetic testing, and future management

## REFERENCES

1 - Kapoor RR *et al*. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol 2013 168 557-564.

2 - Snider KE *et al*. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab 2013 98 E355-363.

3 - Banerjee I *et al*. The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. Eur J Endocrinol 2011 164 733-740.

## ACKNOWLEDGEMENTS

Wellcome Trust, Royal Society, and Research England for funding this work

Congenital Hyperinsulinism International for funding genetic testing for individuals from low- and middle-income countries

Patients, parents, and guardians for participating in this study

## CONTACT INFORMATION

www.hyperinsulinismgenes.org
@HIgenes
@TIHewat