# Biallelic *DNAJC3* variants in a neuroendocrine developmental disorder with insulin dysregulation

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***DNAJC3*, a co-chaperone of BiP, is a member of the heat shock protein family. These proteins are produced in the endoplasmic reticulum (ER) to counter cell stress resulting from healthy functional protein processing. Dysregulation of unfolded proteins within the ER is implicated as a mechanism of genetic disease. Examples include Marinesco–Sjogren and Wolcott–Rallison syndromes that share similar clinical features, manifesting neurodegenerative disease and endocrine dysfunction. Recently, loss of function mutations in *DNAJC3* was associated with syndromic diabetes mellitus in three families. The full phenotype included neurodegeneration, ataxia, deafness, neuropathy, adolescent-onset diabetes mellitus, growth hormone deficiency and hypothyroidism. A subsequent report of two unrelated individuals extended the phenotype to include early-onset hyperinsulinaemic hypoglycaemia. Here, we describe two siblings that recapitulate this extended phenotype in association with a homozygous novel mutation in the final exon of *DNAJC3* [c.1367_1370delAGAA (p.Lys456SerfsTer85)] resulting in protein elongation predicted to abrogate the functional J domain. This report confirms *DNAJC3* as a cause of syndromic congenital hyperinsulinaemic hypoglycaemia. Currently, PanelApp only includes this gene on diabetes mellitus panels. We propose *DNAJC3* should be promoted from a red to a green gene on a wider number of panels to improve the diagnosis of this rare condition. *Clin Dysmorphol* 31: 11–17** **Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.**

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## Introduction

Neurodegeneration is the progressive loss of normal cell function within the nervous system (Dyken and Krawiecki, 1983). For many paediatric neurodegenerative disorders, a link has been shown between these conditions and neurometabolic disturbance (Pierre, 2013). Previous study has characterised the protective role of heat shock proteins against neurodegeneration (Leak, 2014). This ubiquitous family of molecular chaperones, some highly expressed in endocrine tissues (Fagerberg *et al*., 2014), are produced to counter the detrimental effects of cell stress on healthy functional protein production (Kourtis and Tavernarakis, 2018). Disruption in the function of heat shock proteins may result in the accumulation of misfolded proteins, and ultimately result in human disease. This mechanism is implicated in the pathogenesis of certain genetic multisystem disorders, which manifest neurodegenerative and endocrine disorders concurrently (Synofzik *et al*., 2014). Autosomal recessive conditions such as Wolcott–Rallinson and Marinesco–Sjogren syndromes result from mutations in EIF2AK3 and SIL1, respectively, both of which are implicated in the regulation or repair of unfolded proteins within the endoplasmic reticulum (ER) (Iyer *et al*., 2004; Senderek *et al*., 2005;Synofzik *et al*., 2014).

The *DNAJC3* gene encodes the DNAJC3 protein, a co-chaperone that attenuates protein synthesis under ER stress (Ladiges *et al*., 2005). Previous publications on six individuals from three families, with loss of *DNAJC3* gene function, revealed a clinical phenotype of diabetes mellitus with multisystemic neurodegeneration (Synofzik *et al*., 2014; Bublitz *et al*., 2017). A subsequent report of two unrelated individuals extended the phenotype to include

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a prodrome of hyperinsulinaemic hypoglycaemia in infancy prior to the adolescent-onset of diabetes mellitus (Ozon *et al.*, 2020). We describe two siblings homozygous for a novel mutation in *DNAJC3* that recapitulate this phenotype and confirm *DNAJC3* as a syndromic cause of congenital hyperinsulinaemic hypoglycaemia (Table 1).

## Methodology

Siblings patient 1 and patient 2 were recruited, with written informed consent, from the South West Thames Regional Genetic Services at St George's University Hospitals National Health Service (NHS) Foundation Trust into the 100 000 genomes project of Genomics England. Phenotypic data were obtained from a review of clinical, radiology and laboratory records.

Whole-genome sequencing and sequencing of the mitochondrial genome were undertaken as outlined in a previous publication (Wei *et al.*, 2019).

The Genomics England bioinformatics pipeline tiered variants in applied panels into tier 1 high impact for example truncating variants and tier 2 moderate impact for example missense variant. Remaining rare variants are in tier 3 or untiered. The Exomiser tool is also applied to the data irrespective of panel using human phenotype ontology terms to prioritise variants according to frequency, pathogenicity, inheritance pattern and genotype to phenotype associations in known human diseases, model organisms and protein–protein interactions to known human disease genes. Each variant is scored and ranked with the highest rank being 1.

## Results

### Case report

Patient 1 is a 10-year-old boy, born to consanguineous Pakistani parents both of whom are affected by adult-onset hypothyroidism. He was small for gestational age at the 20-week scan and was born at 41 weeks by emergency lower section caesarean section (LSCS) for fetal distress weighing 3.3 kg (+0.5 SDS). Birth head circumference was just below the 2nd percentile. At 8 months all growth parameters were on the 0.4th percentile. He smiled at 5 weeks, sat at 9 months and began cruising from 16–18 months. At 4 years he had a significant global developmental delay with motor and cognitive impairment. His vocabulary was limited to 4–5 word sentences with primarily echolalic speech. At 9 years, ophthalmic examination and visual electrodiagnostic assessment suggested retinal dystrophy (rod and cone photoreceptor dystrophy), bilateral myopia and a small uveo-retinal coloboma below the right optic disc. Audiogram detected bilateral sensorineural hearing loss. Fewer than five café au lait lesions on the chest and abdomen and joint hyperlaxity were noted with significant hypotonia of the lower limbs with an ataxic gait.

He had persistent neutropenia (range $0.6–0.8 \times 10^9$/l) with no apparent clinical manifestations. Thyroid function tests were consistent with primary hypothyroidism and at 13 months he was started on thyroxine resulting in biochemical correction of thyroid function. Persistent asymptomatic hypoglycaemia was detected precluding further investigation of growth hormone deficiency. A trial of growth hormone treatment had a poor response and a subsequent glucagon stimulation test showed a normal growth hormone (GH) peak response thus ruling out GH deficiency (Table 2). Pituitary function was normal, skeletal survey showed wormian bones in the skull consistent with hypothyroidism and 13 ribs. Bone age at 10 years was delayed at 6.8 years. Array CGH, *GJB2* gene screen, chromosome breakage, congenital infection and metabolic screen were normal. Nerve conduction studies showed a demyelinating sensorimotor neuropathy (Table 2). MRI scan of the brain and internal auditory meatus at 5 years showed only a subjectively small anterior pituitary (Fig. 1).

Patient 2 is the 5-year-old brother of patient 1. At 20-weeks gestation there was intrauterine growth restriction and oligohydramnios. He was born at 36 weeks by elective LSCS with a birth weight of 2.06 kg (–2.88 SDS) and head circumference of 29.8 cm (–3.96 SDS). Hypoglycaemia was detected but responded to the treatment in the special care baby unit. Newborn hearing screen detected bilateral sensorineural hearing loss. The developmental trajectory followed that of his older sibling with global developmental delay and similar growth parameters (weight –2.88 SDS, length –4.03 SDSand head circumference –3.96 SDS). He was hypotonic with absent deep tendon reflexes. An ophthalmic assessment revealed mixed astigmatism but no clinical evidence of retinal dystrophy or uveo-retinal colobomata. Further shared features with his sibling included hypothyroidism and neutropenia. Growth hormone stimulation test (glucagon test) at 2.8 years was normal (Table 2). At this time persistent asymptomatic hypoglycaemia was also detected. Biochemical features of hyperinsulinaemic hypoglycaemia were observed during a diagnostic fast (Table 2). He responded to diazoxide and chlorothiazide. Baseline pituitary function tests, on thyroxine, were normal (Table 2). MRI scan of the brain at 3 years showed a low volume anterior pituitary and generalised delay in the maturation of myelin (Fig. 1).

### Genetic findings

Intellectual disability and mitochondrial disorders panels were applied. A four base pair deletion was identified in the *DNAJC3* gene c.1367_1370delAGAA (p.Lys456SerfsTer85) affecting exon 12, the final exon, of the gene and that encodes the J domain of the protein. This variant was absent from the Genome Aggregation Database (gnomAD) (Karczewski *et al.*, 2020). The affected siblings were homozygous for this variant whereas parents were heterozygous. The variant was not flagged in tier 1 or 2 as the *DNAJC3* gene was not on either of the applied panels. However, it was ranked as the Exomiser 1 variant- based on a publication of *DNAJC3* mutant mice

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**Table 1** **Presence or absence of previously documented and newly reported features of DNAJC3 mutation in all reported individuals**

| | Current Family | | Family 1 (Synofzik *et al.*, 2014) | | | Family 2 (Synofzik *et al.*, 2014) | | Family 3 -cousin of family 1 (Bublitz *et al.*, 2017) | Family 4 (Ozon *et al.*, 2020) | Family 5 (Ozon *et al.*, 2020) | Family 6 (Lytrivi *et al.*, 2021) | Family 7 (Lytrivi *et al.*, 2021) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient 1 | Patient 2 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| DNAJC3 variant | c.1367_1370delAGAA (p.Lys456SerfsTer85)hom | | c.580C>T (p.Arg194*)hom | | | 72kb del ex 6-12hom | | c.580C>T (p.Arg194*)hom | (c.393 + 2 T > G)hom | (c.393 +2T> C)hom | (c.1036C>T, p.R346*)/ (c.1A>G, p.M1V) | (c.1177C>T, p.R393*)hom. |
| Age at publication | 10y | 5y | 39y | 40y | 20y | 41y | 20y | 14y | 6y | 9y | 30y | 18y |
| Sex | Male | Male | Male | Female | Male | Female | Female | Female | Male | Female | Female | Male |
| Short stature | + | + | + | + | + | + | + | + | + | + | + | + |
| Low BMI | + | + | + | + | + | + | + | + | + | + | – | + |
| (Sensorineural) Hearing loss | + | + | + | + | + | + | – | + | + | + | + | + |
| Gait ataxia | + | + | + | + | + | + | + | + | + | + | + | NR |
| Demyelinating neuropathy | + | U/N | + | + | + | + | + | + | + | + | + | NR |
| Atrophy cerebrum, cerebellum, brain stem, spinal cord | – | U/N | + | NR | NR | + | NR | + | + | + | + | NR |
| IDDM onset teens | – | – | + | + | + | + | + | + | + | + | + | + |
| Hypothyroidism | + | + | NR | NR | NR | NR | NR | + | + | + | + | + |
| Learning difficulties | + | + | NR | NR | NR | NR | NR | + | + | + | + | NR |
| Additional features | | | | | | | | | | | | |
| Neutropenia | + | + | NR | NR | NR | NR | NR | NR | – | NR | NR | NR |
| Hyperinsulinaemia | + | + | – | – | – | – | – | NR | + | + | ? | NR |
| Microcephaly | + | + | NR | NR | NR | NR | NR | NR | + | + | + | NR |
| Retinal dystrophy | + | U/N | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

Full electrodiagnostic investigations have not been undertaken
NR, not recorded; hom, homozygous; U/N, Unknown.

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**Table 2 Results of baseline pituitary function tests, hypoglycaemia screen and nerve conduction studies in our cases, confirming hyperinsulinism and normal anterior pituitary function**

| Investigations | Patient 1 | Patient 2 | Reference Range |
|---|---|---|---|
| Hypoglycaemia screen | | | |
| Insulin | 3.8 mu/L ↑ | 4.6 mu/L ↑ | <2 (at the time of hypoglycaemia) |
| Beta-hydroxybutyrate | <0.05 mmol/L ↓ | <0.05 mmol/L ↓ | 1–2 mmol/L |
| Non-esterified fatty acids | 0.35 mmol/L ↓ | 0.3 mmol/L ↓ | 1–2 mmol/L |
| Glucose | 2.1 mmol/L ↓ | 2.5 mmol/L ↓ | 3–7 mmol/L |
| Urinary ketones | Negative | Negative | |
| Baseline pituitary function tests | | | |
| Peak growth hormone* | 9 ug/L | 16.8 ug/L | > 7 ug/L |
| IGF1 | 61 ng/ml | 116 ng/ml | 47–231 ng/ml |
| IGFBP3 | 2.79 mg/L | 3.25 mg/L | 1.1–5.2 mg/L |
| Thyroid stimulating hormone | 10.54 mIU/L ↑ | 7.32 mIU/L | 0.62–8.05 mIU/L |
| Free T4 | 8.5 ng/dL | 8.4 ng/dL | 6.2–30.1 ng/dL |
| Free T3 | 5.5 ng/dL | 5.5 ng/dL | 2.4–9.8 ng/dL |
| Prolactin | 88 mU/L | 140 mU/L | 57–717 mU/L |
| LH | <0.1 IU/mL ↓ | 0.1 IU/mL ↓ | 0.7–6.5 IU/mL |
| Follicle stimulating hormone | 0.3 IU/mL | 1.2 IU/mL | 0.1–5.8 IU/mL |
| Baseline Cortisol | 320 nmol/L | 332 nmol/L | 150–500 nmol/L |
| Adrenocorticotropic hormone | 12.1 ng/L | 17.1 ng/L | 10–50 ng/L |
| Nerve conduction studies† | | | |
| Peroneal motor nerve conduction velocity | 31 m/s ↓ | U/N | |
| Superficial peroneal sensory nerve | 28.4 m/s ↓ | U/N | |

*Peak Growth Hormone level following glucagon stimulation test.
†<38 m/s indicates demyelinating neuropathy.

showing a gradual onset of glucosuria and hyperglycemia associated with increasing apoptosis of pancreatic islet cells (Ladiges *et al*., 2005). This four base pair deletion occurs in the last 10% of the protein, is out of frame and causes loss of the stop codon with elongation of the protein by 37 amino acids. The protein is likely to escape nonsense-mediated decay but is predicted to abrogate the function of the J domain with loss of function of the protein.

*DNAJC3* loss of function mutations have been reported to cause a multisystem disorder of combined cerebellar and peripheral ataxia associated with hearing loss and diabetes mellitus in several families. Three affected individuals of the first reported family, of Turkish origin, were homozygous for a premature termination mutation in exon 6 of the *DNAJC3*. c.580C>T mutation (p.Arg194*) (Synofzik *et al*., 2014). A subsequent report of another member of this family with a similar phenotype was also homozygous for (p.Arg194*) (Bublitz *et al*., 2017). A second family had a homozygous deletion of 72.747 bp involving exons 6–12 of *DNAJC3* inclusive of the 3 prime UTR and exon 39 of the adjacent gene orientated in the opposite direction (Synofzik *et al*., 2014). A further report documents syndromic juvenile-onset diabetes mellitus in two patients one homozygous for (*c.1177C>T, p.R393**) nonsense mutation and the other compound heterozygous for *(c.1036C>T, p.R346*)/(c.1A>G, p.M1V)* nonsense and missense mutations, respectively (Lytrivi *et al*., 2021). Of particular note most recently, two unrelated individuals presenting with a very similar phenotype to our siblings, that included hyperinsulinaemic hypoglycaemia, were found to be homozygous for different mutations at the same splice site c.393+2 T>G and c.393+2T>C (Ozon *et al*., 2020). These mutations are predicted to cause exon skipping and loss of protein function (Table 1).

## Discussion

Comparison of the phenotype in the siblings presented in this article reveals many features in common with the earlier reported families, including hearing loss, short stature, ataxia and neuropathy. By contrast with the earlier reports, these siblings also present with congenital hyperinsulinaemic hypoglycaemia as documented in the recent report by Ozon *et al*., (2020). Therefore the clinical phenotype resulting from loss of *DNAJC3* includes a spectrum of presentations of insulin dysregulation evolving from hyperinsulinaemic hypoglycaemia to diabetes mellitus and that appears to be age-related. The hypoglycaemia was reasonably well tolerated by the siblings reported here thus is it possible this may have been present in the families reported by Synofzik *et al*., (2014) and Bublitz *et al*., (2017)) but that this resolved without requiring treatment. Indeed one case in the Lytrivi article had documented symptomatic hypoglycaemia on fasting in infancy prior to onset of diabetes mellitus at 12 years. Ongoing monitoring for the features of diabetes mellitus in the siblings presented here will be required as they transition into adulthood. Genetic causes of insulin dysregulation with a wide range of age of onset are well recognised (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A* and *UCP2*) (Shah *et al*., 2017) and syndromic forms are also seen. MEHMO syndrome an X-linked condition due to mutations in *EIF2S3* is associated with intellectual disability, microcephaly, hypopituitarism, neonatal hypoglycaemia and early-onset diabetes (Stanik *et al*., 2018). One reported family initially presented with hyperinsulinaemic hypoglycaemia which resolved by 7 years of age, and later presented with noninsulin-dependent hyperglycaemia in their 2nd decade (Gregory *et al*., 2019).

The siblings reported here both had hypothyroidism and short stature in keeping with the case reported by Bublitz *et al*.,(2017) however, we did not see clear evidence of

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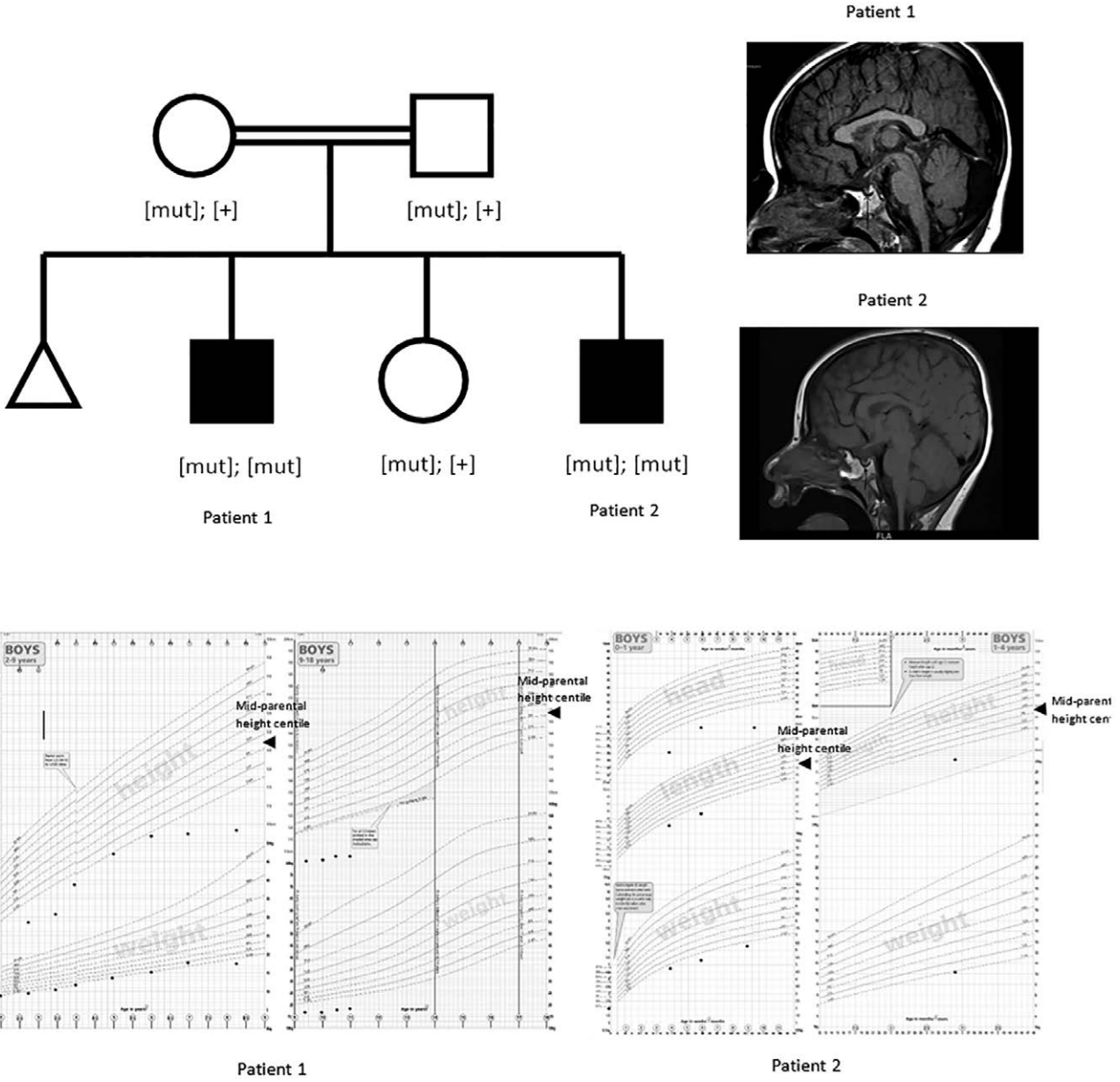
**Fig. 1**




Family pedigree showing that affected individuals are homozygous for the mutation. Mut=mutation, +=wild type, with growth charts of patients 1 and 2 demonstrating short stature and microcephaly (all measurements below the 2nd centile). MRI brain imaging of patient 1 at 5 years of age and patient 2 at 3 years of age which show subjectively small anterior pituitary glands. Growth Charts copyright © 2009 Royal College of Paediatrics and Child Health.

growth hormone deficiency. Microcephaly, a consistent feature of all families, and neutropenia, not documented previously, were also present in both siblings. Retinal dystrophy was seen in only one of the siblings although this feature may evolve in the younger sibling or be affected by variable expression. Given the consanguinity, we did consider the possibility of a second genetic disorder explaining these novel features; however, the whole-genome sequencing variant review did not identify an alternative explanation. The phenotypic differences are therefore likely to be due to phenotypic variability.

*DNAJC3* is a member of the heat shock protein 40 family (hsp40) which binds to BiP (hsp 70) to stimulate ATPase activity, thus activating BiP (Bonomo *et al.*, 2010). Active BiP, a player of the hsp70 chaperone machinery, interacts with polypeptides within the cell to attenuate cell stress through mechanisms, including protein folding, translocation and degradation (Frydman, 2001; Walsh *et al.*, 2004; Bonomo *et al.*, 2010). The structure of the J domain consists of four helices. Hydrophobic residues within this substrate-binding pocket are required for interaction with the corresponding hsp70 ATPase domain (Pellecchia

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*et al.*, 1996; Genevaux *et al.*, 2002). We hypothesise that the altered protein structure of the J-domain coded by the variant found in the current family disrupts ATPase activity, preventing activation of BiP and permitting the accumulation of misfolded proteins and the associated consequences of cell stress.

The mechanism by which increased cell stress results in neurodegeneration and glucose dysregulation is uncertain but tissues show increased vulnerability to *DNAJC3* loss. This gene is expressed maximally in endocrine tissues such as the thyroid, testis and pancreas (Fagerberg *et al.*, 2014). Histologic changes resulting from *DNAJC3* loss have been observed in the pancreatic islets (Ladiges *et al.*, 2005) which may explain the clinical endocrine consequences. Reliable data on the expression profile and effect of loss of DNAJC3 protein in the brain and pituitary gland is lacking.

Mice null for *DNAJC3* develop hyperglycaemia likely due to increased apoptosis of pancreatic beta cells (Ladiges *et al.*, 2005). However, an alternative explanation may be reduced pancreatic beta-cell proliferation as has been observed in Wollcott–Rallison syndrome, a related condition resulting from mutations in the metabolic stress sensing kinase *EIF2AK3* and associated with early-onset insulin-dependent diabetes mellitus (Feng *et al.*, 2009). Studies on null mouse models of another ER stress protein, *SIL1*, demonstrated that *SIL1* expression affected islet insulin content, islet sizing, glucose tolerance and glucose-stimulated insulin secretion (Ittner *et al.*, 2014). *SIL1* loss in humans causes Marinesco–Sjogren syndrome, for which as yet glucose dysregulation has not been reported.

These observations do not, however, explain the hyperinsulinism seen in the current family and that reported by Ozon *et al.*, (2020). It may be that there is an age-related penetrance with hyperinsulinism occurring in the first decade and hyperglycaemia in the second decade. Hyperinsulinism of infancy may be due to disturbance of islet cell remodelling that is of the balance of apoptosis and proliferation of the beta cells (Kassem *et al.*, 2000). Our clinical observations are in-keeping with this suggestion. As both children have grown their diazoxide requirement has decreased and they can fast appropriately for their age with no reported episodes of hypoglycaemia. Therefore their requirement for this treatment may cease. Close monitoring will reveal if they develop a requirement for antihyperglycemic medication in later life.

The finding of hyperinsulinism reveals the complexity of the effect of derangement of heat shock proteins on insulin regulation necessitating long-term endocrine input for such patients. The previously reported cases have been treated with insulin for diabetes mellitus, however, all showed some residual insulin production. Therefore, this condition may produce a form of diabetes mellitus amenable to oral antihyperglycemics such as seen with other genetic forms of maturity-onset diabetes of the young.

These siblings confirm the association of *DNAJC3* with congenital syndromic hyperinsulinism and in addition add neutropenia and retinopathy as possible further clinical features to the previously reported short stature, sensorineural hearing loss, gait ataxia, demyelinating neuropathy, hypothyroidism and learning difficulties (Synofzik *et al.*, 2014). Currently, PanelApp only includes this gene on diabetes mellitus panels (Lytrivi *et al.*, 2021). We propose *DNAJC3* should be promoted from a red to a green gene on a wider number of panels to improve timely diagnosis of this rare condition.

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Written informed consent for publication of their clinical details and/or clinical images was obtained from the parents of the patient.

### Conflicts of interest

There are no conflicts of interest.

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