SHORT REPORT

Chitayat-Hall and Schaaf-Yang syndromes: a common aetiology: expanding the phenotype of *MAGEL2*-related disorders

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ABSTRACT

Background Chitayat-Hall syndrome, initially described in 1990, is a rare condition characterised by distal arthrogryposis, intellectual disability, dysmorphic features and hypopituitarism, in particular growth hormone deficiency. The genetic aetiology has not been identified.
Methods and results We identified three unrelated families with a total of six affected patients with the clinical manifestations of Chitayat-Hall syndrome. Through whole exome or whole genome sequencing, pathogenic variants in the *MAGEL2* gene were identified in all affected patients. All disease-causing sequence variants detected are predicted to result in a truncated protein, including one complex variant that comprised a deletion and inversion.
Conclusions Chitayat-Hall syndrome is caused by pathogenic variants in *MAGEL2* and shares a common aetiology with the recently described Schaaf-Yang syndrome. The phenotype of *MAGEL2*-related disorders is expanded to include growth hormone deficiency as an important and treatable complication.

INTRODUCTION

In 1990 Chitayat *et al*[1] reported siblings with distal arthrogryposis, hypopituitarism, intellectual disability and dysmorphisms. This condition is known as Chitayat-Hall syndrome or distal arthrogryposis with hypopituitarism including growth hormone (GH) deficiency, mental retardation and facial anomalies (OMIM #208080). A similar phenotype has been described in other patients, including one case with consanguineous parents. Autosomal recessive inheritance has been suggested based on the history of consanguinity and sibling recurrence.[1–3] Here we report six patients with Chitayat-Hall syndrome from four families, including updated information on the female proband originally reported by Chitayat *et al*.[1] All patients were found to have truncating sequence variants in the *MAGEL2* gene, including the first reported disease-causing complex rearrangement involving *MAGEL2*. Patients with truncating variants in *MAGEL2* have been described to have Schaaf-Yang syndrome (SHFYNG; OMIM #615547), a variable phenotype characterised by intellectual disability, early feeding difficulties followed by excessive weight gain in some patients, hypotonia, and contractures ranging in severity from distal arthrogryposis to severe arthrogryposis multiplex congenita.[4–6] We demonstrate that Chitayat-Hall syndrome has the same aetiology as SHFYNG, and that GH deficiency is an important feature of this condition.

CLINICAL REPORTS

The cohort was recruited from centres across Canada. All patients initially received a clinical diagnosis of Chitayat-Hall syndrome from a medical geneticist, with the exception of patient 4-I, who did not have a clinical diagnosis but was noted to have similar features. Clinical features are summarised in table 1. Pedigrees are shown in figure 1 and patient photographs in figure 2. Full phenotype reports are found in the online supplementary clinical information. Here we provide detailed information regarding GH deficiency in this cohort. Consent to publish clinical information was obtained from all families.

Patient 1-I presented with poor growth velocity. She was treated with somatotropin until age 17. Her final height is on the 10th percentile. In addition to GH deficiency, she has central hypothyroidism and is treated with levothyroxine.[1] She has not been formally investigated for hypogonadism, but has amenorrhoea.

At 4 months of age patient 2-I presented with rhythmic limb movements. At arrival to the emergency room, blood glucose was 2.2 mmol/L. She suffered recurrent hypoglycaemic episodes, with critical samples taken on three occasions and showing low GH levels: 1.04 μg/L, 0.8 μg/L and 2.45 μg/L with blood glucose concentrations of 1.3 mmol/L, 0.8 mmol/L and 2.3 mmol/L, respectively. She was started on somatotropin treatment at 0.17 mg/kg/week and the hypoglycaemic

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Phenotypes

Table 1 Clinical features of patients with Chitayat-Hall syndrome

Patient	1-I	2-I	2-II	3-I	3-II	4-I	Literature* (affected (n)/with information available (n))
Variant	Partial deletion/inversion	c.1762 C>T (p.Gln588Ter)	c.1762 C>T (p.Gln588Ter)	c.2179_2180del (p.Asp727Profs*6)	c.2179_2180del (p.Asp727Profs*6)	c.1996dupC (p.Gln666Profs*47)	
Age at last assessment (years)	35	13	11	10	8	6	
Short stature	+	+	+	+	+	+	14/22
Increased subcutaneous fat	Noted in infancy, current BMI 19.4	NR	NR	+	+	+	9/20
Developmental delay/ intellectual disability	+ (moderate)	+	+	+ (severe)	+ (severe)	+ (severe)	22/22
Eye abnormalities	–	+ (nystagmus, microcornea, glaucoma)	+ (nystagmus, microcornea)	–	–	+ (myopia, hyperopia, exotropia)	16/20†
Dysmorphisms	+	+	+	+	+	+	25/30
Heart defect	–	+ (patent foramen ovale)	–	+(atrial septal defect)	–	–	NR
Feeding problems	+	–	–	+	+	+	22/24
Gastro-oesophageal reflux	+	–	–	+	+	+	8/14
Contractures	+	+	+	+	+	+	25/30
Scoliosis/kyphosis	+	+	+	+	+	+	9/19
Hypoglycaemic episodes	–	+	+	+	+	+	3/3‡
Growth hormone deficiency	+	+	+	+	+	+	1/1§
Hypothyroidism	+	–	–	–	–	–	NR
Hypotonia	+	+	+	+	+	+	15/15
MRI abnormalities	MRI not performed	Early myelination delay, hypothalamic hypoplasia	Hypersignal of pituitary stalk	Frontal volume loss and decreased pituitary size	MRI not performed	Thin pituitary stalk, dilatation of third ventricle possibly due to hypothalamic atrophy, ventriculomegaly	
Previous normal genetic testing	Karyotype, array genomic hybridisation	Karyotype, fragile X,	Array genomic hybridisation, fragile X	Karyotype, array genomic hybridisation	Array genomic hybridisation	Karyotype, array genomic hybridisation	

NR indicates that this information was not reported.

*Refs 4–6, 10–12.

†Esotropia, myopia and strabismus.

‡Hyperinsulinaemic hypoglycaemia[10] and recurrent hypoglycaemia of unknown origin.[11]

§Ref 4.

BMI, body mass index.

episodes decreased. She presented again at 11 months with a further episode of hypoglycaemia. Arginine stimulation testing confirmed GH deficiency with a peak GH level of 1.32 μg/L. Her somatotropin dose was adjusted to 0.18 mg/kg/week and her glycaemic control improved again. At age 2, a brain MRI revealed hypothalamic hypoplasia, with normal sella turcica. Her height increased from the 5th to the 25th percentile after treatment.

Her younger sister, patient 2-II, presented at 2 months with multiple hypoglycaemic episodes, including during an arginine stimulation test. GH was inappropriately low on multiple critical samples: 4.8 μg/L, 4.6 μg/L and 3.3 μg/L with blood glucose concentrations of 2.2 mmol/L, 2.8 mmol/L and 1.8 mmol/L, respectively. The rest of the endocrine and metabolic work-up was normal. She was treated with somatotropin at 0.23 mg/kg/week, since her hypoglycaemia was more severe. Subsequently the dose was reduced to 0.185 mg/kg/week. After treatment her height increased from below the 3rd to the 25th percentile.

Brain MRI at age 6 showed hypersignal of the pituitary stalk and posterior pituitary.

Patient 3-II developed seizures at 12 months, thought to have been precipitated by hypoglycaemia (glucose 2.4 mmol/L). At 14 months of age her Insulin-like growth factor 1 (IGF-1) was 27 μg/L (reference value 49–342 μg/L). Arginine stimulation testing revealed GH deficiency (GH peak value 4.1 μg/L). Her blood glucose was monitored leading to a decision not to start somatotropin treatment. At 3 years of age she presented again with hypoglycaemic seizures. A critical sample showed an insulin level of 26 pmol/L, GH was low at 0.08 μg/L, beta-hydroxybutyrate was 0.020 mmol/L (normal, 0.02–0.29 mmol/L) and free fatty acids was 263 μmol/L (normal, 100–900 μmol/L) for a glucose of 1.7 mmol/L. However, a second critical sample showed a fully suppressed insulin of <7 pmol/L and GH of 0.2 μg/L, for a glucose of 2.5 mmol/L. Her blood glucose was monitored regularly and the hypoglycaemic episodes have improved over time. She has not been treated with somatotropin.
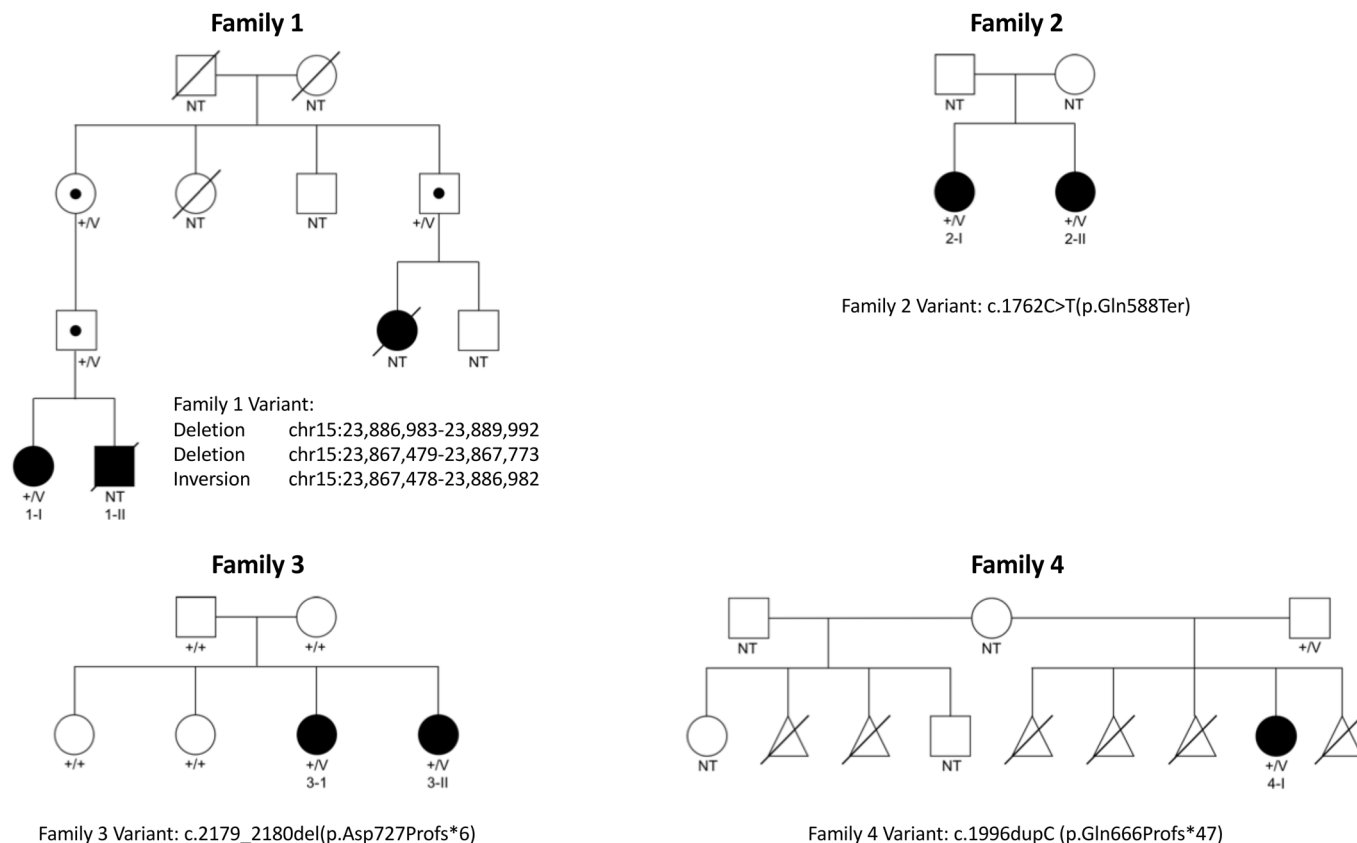
Figure 1 Pedigrees and *MAGEL2* variants identified in patients with Chitayat-Hall syndrome. Filled black squares and circles indicate clinically affected individuals, black dots indicate carriers, V indicates that the familial variant was found in an individual, + indicates the reference sequence and NT indicates that the individual was not tested.

Following the diagnosis of GH deficiency in her younger sister, patient 3-I was investigated. Her IGF-1 was low at <25 µg/L at 3 years and 10 months and 28 µg/L at 6 years 1 month (reference value 49–342 µg/L). Arginine stimulation testing revealed a peak value of 2.7 µg/L. Her blood glucose was monitored, but the decision was made not to start somatotropin treatment. Brain MRI at 4 years showed a small pituitary gland.

Patient 4-I had hypoglycaemic episodes requiring hospitalisation at 6 months. GH deficiency was first suspected at 11 months and confirmed at 19 months. The GH measured during two hypoglycaemic episodes was low and a clonidine GH stimulation test showed a deficiency (GH peak value 4.42 µg/L). The arginine GH stimulation test was also abnormal (4.435 mg intravenously ×1: GH peak value 3.53 µg/L). She was successfully treated with somatotropin. With treatment her height increased from below the 3rd to the 10th percentile. Brain MRI done at 3 months and repeated at 3 years and 7 months revealed a thin pituitary stalk and slight dilation of the third ventricle, possibly secondary to hypothalamic atrophy.

Detailed results of GH stimulation testing can be found in online supplementary clinical information, tables 1–3.

METHODS

For all families, genetic analysis was performed by either whole genome sequencing (WGS) or whole exome sequencing (WES) with pathogenic variants confirmed by Sanger sequencing. For family 1, WGS of the proband and her father was performed. WES was performed on samples from affected patients in family 2, and the probands in families 3 and 4 (online supplementary methods).

Analysis of WES and WGS data prioritised variants based on allele frequency, presence in databases of medically relevant variants including ClinVar[7] and the Human Gene Mutation Database,[8] predicted impact on coding sequence, phenotype in the OMIM database, zygosity, and mode of inheritance. In family 2, where both affected individuals were sequenced, shared variants were examined. In family 1 variants shared between the proband and her unaffected father were prioritised due to the paternal family history of similarly affected individuals (figure 1, online supplementary figure 5).

Since *MAGEL2* is expressed exclusively from the paternal allele, only pathogenic variants located on the paternal allele will cause disease.[9] To determine the parental origin of the c.2179_2180del variant identified in family 3, long-range PCR of *MAGEL2* followed by Sanger sequencing was performed on genomic DNA after methylation-sensitive digestion, as described previously[4] (online supplementary methods).

SEQUENCING RESULTS

All affected individuals were found to carry truncating variants in *MAGEL2*. Patient 1-I was found to have a complex rearrangement interrupting the *MAGEL2* gene, consisting of a 22 kb inversion and 3 kb deletion that removes the last 852 bp and the 3' end of the gene (online supplementary figures 1–3). The variant was paternally inherited and segregation analysis for several additional family members was performed (figure 1). Siblings 2-I and 2-II have a nonsense variant (NM_019066; c.1762 C>T(p.Gln588Ter)) in *MAGEL2*. Parental samples were not available for testing. Patients 3-I and 3-II carry a frameshift variant (c.2179_2180del(p.Asp727Profs*6)) in *MAGEL2*. The

Figure 2 Features of affected patients. (A) Patient I-1—myopathic faces with droopy eyelids and open mouth. (B,C) Patients 2-I and 2-II, respectively—both sisters had minor facial dysmorphism with a high forehead, a flat forehead in patient 2-I (B) and frontal bossing in patient 2-II (C) with a ridge over the metopic suture, deep set eyes, depressed nasal bridge with a broad nasal root and tip, and a 'square' chin with a horizontal groove over the chin. In patient 2-II (C) note the low-set ears with the right ear being lower than the left. (D) Patient 3-I—high forehead with a ridge over the metopic suture, hypoplastic supraorbital ridges, deep set eyes, a broad nasal root and tip and a long philtrum, full cheeks, thin upper lip and retrognathia with a square chin and a horizontal groove over the chin. (E) Hand of patient 3-II—'Puffy' hand with proximally inserted thumb, tapering fingers and camptodactyly with absent distal flexion creases. (F) Patient 3-II—deep set eyes, a broad nasal root and tip, long philtrum, thin upper lip, retrognathia, a 'square' chin with a horizontal groove over the chin and low-set ears. (G) Patient 4-I—ridge over the metopic suture, deep set eyes, a broad nasal root and tip, thin upper lip, retrognathia with a square chin, a horizontal groove over the chin and low-set ears. (H) Hand of patient 4-I—adducted thumb with the second and fifth fingers overlapping the third and fourth.

variant was not present in parents or unaffected siblings, and was determined to be on the paternal allele (online supplementary figure 4). Patient 4-I has a previously reported frameshift insertion (c.1996dupC(p.Gln666Profs*47))[6] in *MAGEL2*, inherited from her unaffected father.

DISCUSSION

Multiple features first reported in Chitayat-Hall syndrome overlap with those described in the majority of individuals with SHFYNG, including contractures, hypotonia, developmental delay/intellectual disability, feeding difficulties, dysmorphisms, small hands and feet, and tapering fingers.[1 4–6 10–12] Our cohort also has other features reported in a minority of individuals, including scoliosis, gastro-oesophageal reflux, increased subcutaneous fat and prominent ridge over the metopic suture. While eye abnormalities are described, this is the first report of microcornea in patients with an *MAGEL2*-related disorder.[6]

The most common pathogenic sequence variant identified to date in *MAGEL2*, c.1996dupC(p.Gln666Profs*47), has been reported in 14 individuals from nine families diagnosed with SHFYNG.[6 10 11] These individuals present with the features most commonly described in association with SHFYNG, including contractures, developmental delay/intellectual disability, dysmorphism, hypotonia and feeding difficulties. Short stature was reported in 6/14 cases. Our patient 4-I, with the c.1996dupC

variant, has a very similar phenotype to the 14 reported patients, apart from her GH deficiency. Unfortunately, there is no information available regarding GH levels in these 14 individuals.

Deficiency of hormones produced by the anterior pituitary is a prominent feature of Chitayat-Hall syndrome. All patients reported here demonstrated biochemical abnormalities related to GH deficiency on more than one occasion, with either low IGF-1, low GH peak after arginine stimulation, low GH in the context of hypoglycaemia, or all of the above. One patient with SHFYNG has been previously reported to have GH deficiency, presenting with poor linear growth and treated from 2 years of age.[4] However, short stature is common in these patients, and is likely caused by undiagnosed GH deficiency in some cases.[4 6 11] Four patients in our study presented with hypoglycaemia, another manifestation of GH deficiency. Hypoglycaemic episodes have not been reported in the majority of patients with SHFYNG, although may go undiagnosed if not leading to convulsions or loss of consciousness.

The pathophysiology of GH deficiency in patients with *MAGEL2* variants requires further investigation. MRI findings in our patients were not consistent, although it is notable that imaging for patients 2-I and 4-I demonstrated possible hypothalamic hypoplasia. *Magel2* is expressed in both fetal and adult brain,[9 13] and mouse studies have demonstrated robust expression in the fetal hypothalamus. In adult mice *Magel2* is mainly

expressed in the hypothalamus, including the arcuate nucleus where GH-releasing hormone (GHRH) is produced.[14][15] There is evidence of GH deficiency related to hypothalamic dysfunction in the *Magel2*-null mouse. Tennese and Wevrick[16] found low levels of IGF-1 in female *Magel2*-null mice compared with controls. The mice demonstrated a blunted response to hypothalamic stimulation of the GH pathway with ghrelin compared with wild-type littermates, while their response to GHRH was equivalent, indicating a possible hypothalamic origin for the deficiency.[16]

Family 1 carries a complex rearrangement and partial deletion. To our knowledge this is the first report of such a change causing an *MAGEL2*-related disorder. The first 2.9 kb of the coding and the 5' region are apparently intact, and it is possible that a truncated protein product is produced. It has been suggested that frameshift and nonsense variants in *MAGEL2* escape nonsense-mediated decay and have a neomorphic or dominant negative effect, explaining the milder phenotype seen in full gene deletions.[6][17][18] Functional studies are required to investigate this possibility, but are difficult to pursue given that the expression of *MAGEL2* in adult tissues is very limited.[9][13] This case illustrates the benefits of WGS as a diagnostic test, as this complex variant would not have been detected using exome, microarray or targeted sequencing methodologies.

In family 3 we demonstrated that the variant identified in the two affected sisters was on the paternal allele. It was not detectable in paternal blood by Sanger sequencing. This does not rule out the possibility of low level mosaicism in blood or other tissues. This is the third reported case of apparent mosaicism in an unaffected father in *MAGEL2*-related disorder.[10][11] In this situation, the recurrence risk could be up to 50%.

The phenotype of *MAGEL2*-related disorder continues to evolve, now including Chitayat-Hall syndrome. With the exception of the endocrinological findings we describe, our patients' phenotypes are very similar to those observed in patients with SHFYNG, and one of our patients carries the most common recurrent variant c.1996dupC reported in SHFYNG. This suggests that SHFYNG and Chitayat-Hall syndromes are likely the same disorder. A systematic investigation of endocrinological abnormalities in patients with *MAGEL2*-related disorder is needed and GH deficiency should always be considered in the context of poor growth and/or hypoglycaemia.

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