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CASE REPORT

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Report of two cases of Schaaf-Yang syndrome: Same genotype and different phenotype

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Key Clinical Message

We report two, genotypically identical but phenotypically distinct cases of Schaaf-Yang syndrome and propose the early use of Genome Sequencing in patients with nonspecific presentations to facilitate the early diagnosis of children with rare genetic diseases and improve overall health care outcomes.

KEYWORDS

ICU, MAGEL2, phenotype–genotype association, rapid whole genome sequencing

1 | INTRODUCTION

Rare diseases are defined as any disease or condition that affects less than 200,000 people in the United States.[1] Because of their rarity, these conditions are difficult to diagnose and therefore, the time to diagnosis is prolonged and often involves extensive and expensive work up (i.e., the diagnostic odyssey). With a prevalence of <1/1,000,000,[2] Schaaf-Yang syndrome (SYS, OMIM #615547) caused by pathogenic variants in the MAGEL2 gene is a rare disease with a very unspecific phenotype which overlaps with numerous other more common conditions, hence, defaulting it's diagnosis even further. Nonetheless, with the advent of Next Generation Sequencing (NGS) and with it, broad sequencing techniques, more individuals with SYS have been identified and some phenotypic–genotypic associations have been proposed.[3] However, diagnosis continues to be delayed and achieved only after extensive workup has been done, without significant impact in management once diagnosis has been achieved. The rapid Whole Genome Sequencing (rWGS) protocol was developed at Nicklaus Children's Hospital to facilitate the early diagnosis of children with rare genetic conditions to guide management strategies and improve long-term outcomes. We report two, genotypically identical but phenotypically distinct, cases of SYS diagnosed through the rWGS protocol and propose the early utilization of WGS in patients with poorly specific presentations to facilitate the diagnosis of patients with rare genetic diseases. In turn, this will allow for better understanding of these conditions and guide targeted management approaches that can positively influence health care outcomes in the acute and long-term settings.

2 | METHODOLOGY

Both cases reported were admitted to the Neonatal Intensive Care Unit at Nicklaus Children's Hospital and were enrolled in the The rWGS protocol for whole genome analysis at the Rady Children's Institute for Genomic Medicine (RCIGM). Other genetic testing modalities, including chromosome analysis, chromosome microarray, and Fragile X Syndrome, were performed at the Miami Genetics Laboratories at Nicklaus Children's Hospital.

2.1 | Whole-genome sequencing

Whole genome sequencing was performed on NovaSeq 6000 instruments (Illumina), generating paired 101-nt reads with an average coverage of 55× and 42× for proband 1 and 2, respectively. Alignment and single nucleotide polymorphisms (SNV) calling were performed using the DRAGEN processor (Illumina). Copy number variant (CNV) calling was performed with CNVnator and Manta.[4,5] Variant call format (VCF) files incorporating SNV and CNV calls were annotated and analyzed using Fabric Enterprise version 6.2.8 (Fabric Genomics) according to standard guidelines.[6,7] The Human Phenotype Ontology terms used during analysis are listed below. Parental samples were available for targeted variant analysis and inheritance determination.

Human phenotype ontology terms used for Patient 1: neonatal hypotonia (HP:0001319), feeding difficulties in infancy (HP:0008872), arthrogryposis multiplex congenital (HP:0002804), hip dysplasia (HP:0001385), overlapping fingers and toes (HP:0010557).

Human phenotype ontology terms used for Patient 1: Small for gestational age (HP:0001518), apnea (HP:0002104), arthrogryposis multiplex congenital (HP:0002804), bilateral talipes equinovarus (HP:0001776), and abnormality of limb bone morphology (HP:0002813).

3 | CASE PRESENTATION

3.1 | Patient 1

Full-term male transferred to Nicklaus Children's Hospital's neonatal intensive care unit (NICU) at 1 week of age for concerns of an underlying genetic etiology given dysmorphic features, respiratory insufficiency, and feeding difficulties. He was born via C-section from a pregnancy complicated by intrauterine growth restriction (IUGR) and clubfeet identified on second trimester ultrasound. No other complications during pregnancy and delivery. Family history was noncontributory. At birth, he was noted to be small for gestational age (SGA) (birth weight near 2nd percentile); to have a wide posterior fontanelle, down slanting palpebral fissures, micrognathia with limited mouth opening; bilateral cryptorchidism; arthrogryposis multiplex congenita (AMC) (flexion deformity of wrists and proximal metacarpophalangeal joints and bilateral talipes equinovarus); bilateral club feet; Mongolian spot on the right buttock; hypertonia of upper and lower extremities with normal central tone and tendon reflexes (2+); weak suck and gag reflexes and; absent rooting and Moro reflexes. Perinatal course was complicated by feeding difficulties with nasogastric tube (NG tube) dependence, respiratory distress requiring invasive respiratory support, apneic episodes and hypoglycemia requiring treatment with dioxide.

Chest and abdominal x-rays, abdominal ultrasound, and echocardiogram were reported as normal. Bone survey demonstrated findings consistent with arthrogryposis, bilateral clubfeet, and 11 ribs. CT scan of the face revealed a hypoplastic mandible, flattening of the condylar heads, and bilaterally shallow temporomandibular joint glenoid fossa.

Botox injection was performed to help manage oral secretions at 1 month of age. Subperiosteal release of the mouth floor was performed at 1 month of age to help with oral feeding and respiration. The patient failed extubation after the release of the mouth floor. Due to high risk for aspiration and continued respiratory issues, gastrostomy tube (G-tube) with fundoplication and tracheostomy were performed at 6 weeks of life.

In addition to the feeding and respiratory issues, there was suspicion of partial diabetes insipidus due to persistent hypernatremia and low urine osmolarityand specific gravity. Brain MRI showed suspicion of ectopic neurohypophysis but was otherwise normal. The patient also had episodes of hypoglycemia requiring continuous feeds and treatment with diazoxide. Insulin, growth hormone, free fatty acids, cortisol, and β-hydroxybutyrate random levels were unremarkable, although a critical sample was unable to be collected during hypoglycemic events.

Initial genetic work-up included normal chromosome analysis, chromosome microarray, spinal muscular atrophy analysis, and Fragile X testing. The patient and both of his parents were then enrolled in the protocol for rapid whole genome sequencing (rWGS).

3.2 | Patient 2

Patient 2 is a full-term appropriate for gestational age (AGA) male born via repeat C-section at a local hospital after an uncomplicated pregnancy. Upon delivery, he presented as floppy and apneic with respiratory distress

requiring intubation and transfer to Nicklaus Children's Hospital. Prior to transfer, he was placed on a nasal cannula after self-extubating. His family history was only significant for a maternal second cousin with developmental delays and intellectual disability of unknown etiology.

Physical exam was significant for frontal bossing, bitemporal narrowing, hypertelorism, deep set eyes, wide and depressed nasal bridge, right cup ear, micrognathia, bilateral cryptorchidism, clenched hands with overlapping fingers and toes, arthrogryposis multiplex congenita (proximal and distal contractures of bilateral upper and lower extremities), and sacral dimple; peripheral hypertonia of upper and lower extremities with central hypotonia, and absent Moro reflex.

Evaluations during admission included normal chest x-ray, spine/hip/head ultrasounds, brain MRI, CT skull, electroencephalogram (EEG), and ophthalmologic evaluation. Abdominal ultrasound showed mild left pelviectasis. Testicular ultrasound revealed left undescended testicle and left inguinal hernia. Echocardiogram revealed a small atrial septal defect. Early polysomnograms demonstrated central apnea.

Clinical course was complicated by gastroesophageal reflux disease (GERD), respiratory distress requiring nasal cannula, apneic episodes requiring caffeine administration, and poor feeding (NG tube dependency). G-tube tube placement was performed at 6 weeks of age after the videofluoroscopy swallow study showed silent aspiration of thin liquids and significant pooling within the vallecula and piriform sinuses.

Initial genetic work-up included normal newborn screen, chromosome analysis, microarray, and a non-diagnostic Neuromuscular Disorders Panel at GeneDx Laboratory (80 genes). At 7 weeks of age, the patient and his mother were enrolled for rapid whole genome sequencing (rWGS).

4 | RESULTS

Patients 1 and 2 were each found to have a heterozygous, pathogenic frameshift variant, c.1996dupC; p. Gln666ProfsTer47 in the *MAGEL2* gene (Table 1. rWGS Results of Patient 1 and 2). This is also referred to as the c.187dupC; p.Gln63ProfsTer47 (NM_019066.4) in the literature based on the transcript used. This variant is expected to create a frameshift in the protein-coding sequence, leading to a truncated protein. This variant has been previously reported in individuals with Schaaf-Yang syndrome and has been classified as pathogenic in ClinVar (Variation ID: 190122). The variant was found to be de novo in Patient 1 and not reported in the mother of Patient 2.

TABLE 1 rWGS Results of Patient 1 and 2.

Gene	HGVS cDNA	HGVS protein	Zygosity	Parent of origin	Variant interpretation	Age of testing/Age of return of results
Patient 1						
MAGEL2	c.1996dupC	p. Gln666ProfsTer47	Heterozygous	De Novo	Pathogenic	6 weeks/10 weeks
ABCC8	c.3130_3149del ACCCCTGC...	p.Thr1044LeufsTer63	Heterozygous	Maternally inherited	Pathogenic	
Patient 2						
MAGEL2	c.187dupC	p. Gln666ProfsTer47	Heterozygous	De Novo	Pathogenic	7 weeks/10 weeks

Patient 1 also had a heterozygous, maternally inherited, pathogenic variant, c.3130_3149delACCCCTGC; p.Thr1044LeufsTer63, in the *ABCC8* gene. This variant is expected to create a frameshift in the protein sequence, leading to a truncated protein. This variant has been classified as pathogenic in ClinVar and *Human Gene Mutation Database* (HGMD). Pathogenic variation in the *ABCC8* gene has been associated with autosomal dominant/recessive familial hyperinsulinemic hypoglycemia-1 (HHF1, MIM: #256450). Mother did not report any signs or symptoms associated with this condition.

5 | LONG-TERM CLINICAL OUTCOMES AFTER DIAGNOSIS

5.1 | Patient 1

Patient 1 was discharged from NICU at 12 weeks of age with a G-tube and tracheostomy. Dioxide was discontinued prior to discharge with no further episodes of hypoglycemia. The family moved back to his country of origin but return periodically to continue care with various specialties at Nicklaus Children's.

Patient 1 is currently 4 years old, has global developmental delay, short stature, is nonambulatory and continues to be G-tube and tracheostomy dependent. He is currently undergoing endocrine evaluation for concerns of micropenis and persistent cryptorchidism (pending surgery). However, care has been complicated and delayed because of barriers to accessing care.

The patient underwent bilateral Ponseti casting for his bilateral clubfeet with residual equinus and cavus for which he later required bilateral open Achilles lengthenings (2019). However, he was noted to have mild recurrence of bilateral cavus and equinus deformities during his last orthopedic evaluation, for which he is uses full time orthoses. Furthermore, he has reduced range of motion of knees and hips secondary to arthrogryposis and is unable to stand.

5.2 | Patient 2

Patient 2 was discharged from the NICU on nasal cannula to be used during sleep. Soon after discharge, he was readmitted several times for breath holding spells and unusual rigid movements but had normal repeat EEG and negative work up.

Currently, he is 4 years of age, has global developmental delay, is nonambulatory, nonverbal, and G-tube dependent. Since NICU discharge, he is no longer having apneic episodes during sleep and oxygen was discontinued. Ophthalmology has since noted esotropia, bilateral myopia, and astigmatism. He is also being followed for short stature, obesity, GERD, and he has undergone strabismus surgery, tonsillectomy adenoidectomy, and bilateral orchiopexy.

Patient 2 continues to have mild torticollis and mild knee flexion contractures bilaterally managed with custom solid orthoses and physical therapy. He also receives occupational and feeding therapies and has nursing at home.

6 | DISCUSSION

MAGEL2 is a paternally expressed, maternally imprinted, protein-coding gene located on chromosome 15. *MAGEL2* is one of the genes that falls into the paternally expressed region of chromosome 15 (15q11-q13) known to result in Prader-Willi Syndrome (PWS, MIM: #176270).[8] Prader-Willi Syndrome is characterized by hypotonia, feeding difficulties followed by hyperphagia later, failure to thrive, developmental delay, and hypogonadism in males.[9] Schaaf-Yang syndrome (SYS) has a great deal of clinical overlap with PWS in that affected individuals often have hypotonia, feeding difficulties, failure to thrive, developmental delay/intellectual disabilities, and hypogonadism.[8] However, individuals with Schaaf Yang are more likely to have congenital contractures ranging from mild to severe, autistic spectrum disorder, and hypopituitarism.[10-12] Hyperphagia which is common in PWS is not a common feature of SYS. Truncating mutations in *MAGEL2* appear to be more consistent with classic SYS phenotype, whereas whole gene deletions including the promoter region in *MAGEL2* have been found to have milder phenotypic consequences.[13-15] This may be due to a dominant negative effect of the truncated protein or due to "leaky" expression of the maternal copy of *MAGEL2* in whole gene deletion cases which has been suggested in mice studies.[9,12]

6.1 | Comparing patient one and patient two

Both our patients had many of the characteristic features reported in SYS such as short stature, dysmorphic facial features, hypogonadism, arthrogryposis multiplex congenital, hypotonia, respiratory depression with apneic episodes, feeding difficulties requiring G-tube placement, and delayed psychomotor development[3,16] (Table 2. Comparative table of clinical features presented by Patient 1 and Patient 2). Nonetheless, there were some notable differences between both patients. Patient 1 had IUGR

TABLE 2 Comparative table of clinical features presented by Patient 1 and Patient 2.

Feature	Shared Features	Case 1	Case 2
Prenatal			
Growth		IUGR	
US findings		Club foot	
Postnatal			
Birth weight		SGA	AGA
Exam findings			
Head		Wide posterior fontanelle	Frontal bossing Bitemporal narrowing
Ears			Right cup ear
Eyes		Downslanting palpebral fissures	Hypertelorism Deep set eyes
Nasal bridge			Wide and depressed
Chin	Micrognathia		
GU/Pelvic	Cryptorchidism	Micropenis	Inguinal hernia
Extremities	ACM	Club feet	
Skeletal		11 ribs	Hip dysplasia
Skin		Mongolian spot	
Neurologic	Central hypotonia Peripheral hypertonia Absent Moro reflex	Weak suck Weak gag reflex Absent rooting reflex	Head lag
Perinatal complications/interventions			
Respiratory	Invasive respiratory support Apneic events		
Metabolic	Feeding difficulties	Hypoglycemia	
G-Tube	GT+		
Tracheostomy		+	
Long-term outcomes			
Growth	Short Stature		Obesity
Development	GDD		
Ophthalmology			Esotropia Myopia Astigmatism
Surgeries		Achilles lengthening's	Tonsillectomy Adenoidectomy Strabismus surgery Orchiopexy

Abbreviations: ACM, arthrogryposis multiplex congenita; AGA, appropriate for gestational age; GDD, global developmental delay; IUGR, intrauterine growth retardation; SGA, small for gestational age; US: ultrasound.

and a birth weight in the 5th percentile while Patient 2 had a birth weight in the 75th percentile. Patient 1 is tracheostomy dependent and had more severe congenital contractures while patient 2 only required invasive respiratory support for a short period and had milder contractures primarily involving the hands. Patient 1 also had unexplained hypernatremia and persistent hypoglycemia. However, it is unknown whether these endocrine abnormalities were associated to the MAGEL2 variant or whether the ABCC8 variant, found as an incidental finding, may have contributed to these clinical features.

MacArthy et al. 2018, reported an association between the phenotypic severity and the location of the truncating mutation and, described a genotype–phenotype association comparing individuals with the p.Gln666ProfsTer47 *MAGEL2* variant with other mutations. According to their prediction, this variant can be associated with severe phenotypes, including a higher

prevalence of joint contractures; more severe feeding difficulties likely to require a nasogastric feeding tube; more severe respiratory difficulties likely to require mechanical ventilation and; more likely to have profound intellectual disability/significant developmental delay.[3] Both patient 1 and patient 2 carry the p.Gln666ProfsTer47 variant in *MAGEL2*. Both had congenital contractures, required NG/G-tube placement, invasive respiratory support, and had significant developmental delays supporting the phenotype–genotype association described by MacArthy et al. 2018.

It is important to note that hypopituitarism is reported as typically present in patients with SYS but neither of the two patients have presented with it. Likewise, hyperphagia has been reported to be present in 22% of reported cases[3] and, although patient 2 has been noted to be overweight, it is unclear if hyperphagia is present or not.

6.2 | Current needs in the SYS research world

The current knowledge available about the natural presentation and course of SYS is limited. In January 2019, the SYS/*MAGEL2* Advisory Group outlined the needs of SYS research, which include identifying the full phenotypic spectrum of SYS, establishing standards of care for individuals with SYS, and understanding the SYS patient's perspective to improve outcomes.[17]

While patient 1 and patient 2 presented close in time with similar clinical presentation, enough differences existed to keep the patients distinct. It was the utilization of rapid whole genome sequencing that found the commonality between these two patients, which might have not been achieved based on clinical criteria only. McCarthy et al, 2018 noted that based on clinical presentation, several different conditions may be caused by truncating mutations in *MAGEL2*. In fact, individuals initially diagnosed with Opitz trigonocephaly C syndrome, Chitayat–Hall syndrome, and arthrogryposis multiplex complex diagnoses were found to have truncating mutations in MAGEL2.[18-21] Thus, many more cases of SYS may exist that can add to the variable phenotypic picture that exists today. Nevertheless, this wide phenotypic spectrum that is characteristic of SYS represents an obstacle for reaching a diagnosis as patients typically undergo extensive workup prior to achieving the diagnosis of SYS. This is especially important considering that the *MAGEL2* gene is not included in many gene panels and is, therefore, typically only identified through broad testing options (i.e., expanded panels, whole exome sequencing (WES), and WGS). For both of our patients, early diagnosis was achieved through the rWGS protocol, which allowed for rapid turnaround of results in the acute setting.

With whole genome sequencing becoming more accessible,[22] this diagnostic odyssey can be shortened, saving both time and other valuable resources for families and the community. An earlier diagnosis can also have a significant impact in care outcomes by guiding decision-making in the acute care setting, especially now with some available knowledge about certain phenotype–genotype associations that could influence those decisions. An example of this would be earlier tracheostomy placement based on the expected prognosis associated with the p.Gln666ProfsTer47 *MAGEL2* variant, as multiple studies (in both children and adults) have reported improved medical outcomes associated with earlier tracheostomy in critically ill patients.[23-25]

7 | CONCLUSIONS

Our patients exemplify the broad phenotypic spectrum that is characteristic of SYS while at the same time support the previously described phenotype–genotype association suggested by MacArthy et al. 2018, in which they associate the p.Gln666ProfsTer47 *MAGEL2* variant with more severe clinical outcomes. This report supports the early utilization of whole genome sequencing, especially in critical settings, to facilitate early diagnosis of rare conditions like SYS, which, in turn, could help save time and resources and help to improve clinical outcomes of patients.

AUTHOR CONTRIBUTIONS

Ana Maria Rodriguez Barreto: Conceptualization; investigation; visualization; writing – original draft. **Katherine Schain:** Conceptualization; investigation; writing – original draft. **Parul Jayakar:** Conceptualization; investigation; project administration; supervision; visualization; writing – original draft. **Meredith S. Wright:** Formal analysis; investigation; resources; writing – original draft. **Shimul Chowdhury:** Formal analysis; investigation; resources; writing – original draft. **Daria Salyakina:** Project administration; supervision; visualization; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

We know of no conflicts of interests associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. As Corresponding Author, I confirm that the

manuscript has been read and approved for submission by all the named authors

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by The Institutional Review Board (or Ethics Committee) of Nicklaus Children's Hospital Pediatric Specialists.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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