Schaaf-Yang syndrome overview: Report of 78 individuals

John McCarthy¹ | Philip J. Lupo² | Erin Kovar² | Megan Rech³,⁴ | Bret Bostwick⁴ | Daryl Scott⁴,⁵ | Katerina Kraft⁶ | Tony Roscioli⁷,⁸ | Joel Charrow⁹,¹⁰ | Samantha A. Schrier Vergano¹¹ | Edward Lose¹² | Robert Smieg⁰¹³ | Yves Lacassie¹⁴ | Christian P. Schaaf¹,³,⁴,¹⁵,¹⁶

¹Institute of Human Genetics, University Hospital Cologne, Köln, Germany
²Department of Pediatrics, Baylor College of Medicine, Houston, Texas
³Jan and Dan Duncan Neurological Research Institute at Texas Children’s Hospital, Houston, Texas
⁴Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas
⁵Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas
⁶Department of Human Molecular Genetics, Max Planck Institute for Molecular Genetics, Berlin, Germany
⁷Department of Clinical Genetics, Sydney Children’s Hospital, Sydney, Australia
⁸Neuroscience Research Australia (NeuRA), University of New South Wales, Sydney, Australia
⁹Division of Genetics, Birth Defects and Metabolism, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, Illinois
¹⁰Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois
¹¹Division of Medical Genetics and Metabolism, Children’s Hospital of The King’s Daughters, Norfolk, Virginia
¹²Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama
¹³Department of Social Pediatrics, Wroclaw Medical University, Poland
¹⁴Department of Pediatrics, LSU Health Sciences Center and Children’s Hospital, New Orleans, Louisiana
¹⁵Center for Molecular Medicine Cologne, University of Cologne, Köln, Germany
¹⁶Center for Rare Diseases, University Hospital Cologne, Köln, Germany

Correspondence
Christian Schaaf, Institute of Human Genetics, University Hospital Cologne, Kerpener Straße 34, 50931, Köln, Germany.
Email: christian.schaaf@uk-koeln.de

Schaaf-Yang Syndrome (SYS) is a genetic disorder caused by truncating pathogenic variants in the paternal allele of the maternally imprinted, paternally expressed gene MAGEL2, located in the Prader-Willi critical region 15q11-15q13. SYS is a neurodevelopmental disorder that has clinical overlap with Prader-Willi Syndrome in the initial stages of life but becomes increasingly distinct throughout childhood and adolescence. Here, we describe the phenotype of an international cohort of 78 patients with nonsense or frameshift mutations in MAGEL2. This cohort includes 43 individuals that have been reported previously, as well as 35 newly identified individuals with confirmed pathogenic genetic variants. We emphasize that intellectual disability/developmental delay, autism spectrum disorder, neonatal hypotonia, infantile feeding problems, and distal joint contractures are the most consistently shared features of patients with SYS. Our results also indicate that there is a marked prevalence of infantile respiratory distress, gastroesophageal reflux, chronic constipation, skeletal abnormalities, sleep apnea, and temperature instability. While there are many shared features, patients with SYS are characterized by a wide phenotypic spectrum, including a variable degree of intellectual disability, language development, and motor milestones. Our results indicate that the variation in phenotypic severity may depend on the specific location of the truncating mutation, suggestive of a genotype-phenotype association. This evidence may be useful in both prenatal and pediatric genetic counseling.

KEYWORDS
autism spectrum disorder, genotype-phenotype association, MAGEL2, neurodevelopment, Schaaf-Yang syndrome

Received: 1 August 2018 Revised: 23 August 2018 Accepted: 7 September 2018
DOI: 10.1002/ajmg.a.40650

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2018 The Authors. American Journal of Medical Genetics Part A published by Wiley Periodicals, Inc.
MAGEL2 has long been recognized as one of the imprinted, protein-coding genes involved in Prader-Willi Syndrome (PWS [OMIM # 176270]), and it has been shown that lack of MAGEL2 plays a critical role in the pathogenesis of PWS (Lee et al., 2000). PWS is characterized by neonatal hypotonia, failure to thrive, developmental delay/intellectual disability (DD/ID), hypogonadism, and hyperphagia leading to excessive weight gain in childhood. In 2013, the first four individuals with truncating mutations in the paternal copy of MAGEL2 were reported (Schaaf et al., 2013). These four patients demonstrated “Prader-Willi-like Syndrome,” as they shared partial phenotypic overlap with PWS, including neonatal hypotonia, feeding problems, and DD/ID. However, as the clinical cohort of individuals with truncating pathogenic variants of MAGEL2 expanded, the distinctive phenotypic profile of these patients became more apparent, leading to the renaming of the disorder from “Prader-Willi-like Syndrome” to Schaaf-Yang Syndrome (SYS [OMIM # 615447]).

In 2017, Fountain et al. reported 28 cases of SYS, and suggested an expanded phenotype that included neonatal hypotonia, feeding difficulties, contractures, and developmental delay, as well as sleep apnea and gastroesophageal reflux (GERD). It was also proposed that individuals affected by SYS are not subject to the later nutritional stages of PWS, and do not typically engage in the characteristic Phase III hyperphagia seen in PWS (Fountain et al., 2017; Miller et al., 2011). Additionally, it was reported that SYS patients displayed a higher prevalence of Autism Spectrum Disorder (ASD) diagnoses than patients with PWS (Bennett, Germani, Haqq, & Zwaigenbaum, 2015; Fountain et al., 2017).

Interestingly, whole gene deletions of MAGEL2 appear to have milder phenotypic consequences than truncating mutations, and do not cause SYS (Buiting et al., 2014; Kanber et al., 2009). It has been suggested that deletion of the entire paternal copy of the gene and promoter could lead to leaky expression of the maternal copy of MAGEL2, as suggested by studies of mice lacking the paternal MAGEL2 copy (Fountain & Schaaf, 2016).

As of July 2018, 43 total cases of SYS have been reported in the literature (Bayat, Bayat, Lozoya, & Schaaf, 2018; Fountain et al., 2017; Jobling et al., 2018; Matuszewskia et al., 2018; McCarthy et al., 2018; Mejachowicz et al., 2015; Palomares-Bralo et al., 2017; Schaaf et al., 2013; Soden et al., 2014; Takui et al., 2018; Tong et al., 2018; Urreizti et al., 2017). Here, we describe the phenotypic presentation of a total of 78 patients with SYS, the largest cohort reported to date. We also compare the presentation of SYS within two subgroups, based upon the location of the gene mutation, and define genotype–phenotype associations.

2 | SUBJECTS AND METHODS

2.1 | Subjects

To date, 115 individuals with nonsense and frameshift mutations in MAGEL2 have been identified through whole-exome sequencing or single-gene Sanger sequencing, and reported to Baylor College of Medicine in Houston, TX (Dr. Schaaf, personal communication; Figure 1). From this cohort, all families for whom contact information was available were notified of the research study. In addition, the research study was announced in the closed Facebook group for SYS (Web Resources I). Families were sent an IRB-approved consent form, as well as a phenotypic questionnaire, providing a detailed review of their child’s medical history (Supporting Information). Families were given a one-week deadline to complete the necessary forms and return them to investigators. Inclusion criteria was the presence of a nonsense or frameshift mutation in the paternal allele of MAGEL2 based on previous genetic testing. There were no exclusion criteria. We received 44 checklists from families. Of these 44, 35 of these patients had not been reported previously, while 9 of them had been reported upon in the literature. For the 43 total patients that had previously been reported, the investigators gathered phenotypic data using completed questionnaires if possible and supplemented this information with the data provided in the literature.

The average age of the cohort is 8.1 years (range: 1 month–24 years; SD: 5.6 years) and consists of 39 male patients and 39 female patients.

2.2 | Methods

For the 78 individuals in the study, we investigated the cognitive, neurological, developmental, and physical spectrum of phenotypes through the collection of data in the form of a clinical questionnaire (Supporting Information). Height and weight percentiles were calculated using the online World Health Organization growth chart tool (Web Resources II). Phenotypic information collected from the questionnaires was combined with information provided in previous studies of SYS to provide an overview of the clinical presentation of all 78 patients in the cohort.

For assessment of genotype-phenotype associations, two groups of patients were assessed: (1) those with a c.1996dupC (p. Gln666Profs*47) mutation (n = 35) and (2) patients with nonsense or frameshift mutations other than c.1996dupC (n = 38). Patients with c.1996delC mutations (p.Gln666Serfs*36) (n = 5) were not included in this analysis, as all passed away either prenatally or perinatally, and therefore a full clinical phenotype could not be established. Differences between the two groups on categorical variables were evaluated using the Fisher’s exact test. Categorical phenotypic variables included all items provided in the clinical questionnaire, with each variable coded as yes versus no. Differences between the two groups for continuous variables were evaluated using the Student’s t test. Continuous phenotypic variables included IQ score, developmental milestones (measured in months), and speech milestones (measured in months). The p values <.05 indicated a statistically significant difference between the variable being tested and the two patient groups. All analyses were conducted using Stata 14.2.
information has been provided. Feeding problems requiring special feeding technique, neonatal hypotonia, and joint contractures are also present in greater than 85% of the cohort.

A summary of cognitive, neurologic, and physical traits of the 78 individuals is provided in Table 1. All data regarding developmental milestones, speech milestones, and growth parameters is provided in Table 2. A table comparing the clinical phenotype of SYS with that of PWS is provided in Table 3.

The results of analysis comparing the phenotype of patients with c.1996dupC mutations to the phenotype seen with all other mutations are provided in Table S2 in Supporting Information. Specific variables of statistically significant difference between the two groups have been placed in bold text.

### 3.1 Intellectual disability

The level of intellectual disability is widely variable, ranging from mild to profound. Thirteen individuals with SYS diagnoses have undergone formal IQ testing, with a mean score of 38.2 (range: 1–65; SD: 23.4), indicating moderate intellectual disability per both the Wechsler Intelligence Scale for Children and Stanford-Binet Scale. However, there is a wide range of IQ scores, with 7 of 13 patients scoring between 50 and 69, indicating mild intellectual disability, 3 of 13 scoring between 20 and 34, indicating severe disability, and 3 of 13 scoring below 20, indicating profound disability. The highest IQ in our cohort was measured at 65, while the lowest was measured with a functional IQ of 1.

### 3.2 Autism spectrum disorder and seizures

ASD is highly prevalent in SYS patients. Of the individuals in the cohort, 32 have been formally evaluated for ASD using ADOS-2 and ADI-R testing. Of these 32 individuals, 25 have been formally diagnosed with ASD (78%). ADI-R recommendations suggest testing when the child has reached an intellectual age of at least 18 months, which limits the testing of a large proportion of SYS patients (Reaven, Hepburn, & Ross, 2008). However, it should be noted that many of the SYS children who have not undergone formal evaluation have shown characteristic autistic behaviors as noted by their physicians in a clinical setting.

Additionally, 21 of 64 individuals (33%) in this cohort have experienced seizures, either of focal, generalized, or unknown onset.

### 3.3 Hypotonia, feeding, and respiratory abnormalities

Neonatal hypotonia and feeding problems in early childhood were identified as prominent early phenotypes, with 66 of 68 individuals (97%) exhibiting the former, and 69 of 71 (97%) exhibiting the latter. Of those with a need for special feeding techniques, 45 of 60 patients (75%) require/referred a nasogastric tube for feeding, and 28 of 53 patients (53%) rely/relied on a g-tube for a portion or all of their nutrients. Digestive issues are frequent, with 39 of 55 patients (71%) presenting with chronic constipation and 34 of 60 (57%) presenting with GERD.

Respiratory distress is another common manifestation of SYS, with 32 of 55 patients (58%) requiring intubation during their lifetime, 30 of 55 (55%) requiring the use of mechanical ventilation, and 9 of 50 (18%) requiring a tracheostomy.

### 3.4 Developmental and speech delay

Regarding motor milestones, children typically learn to sit independently by 6 months, crawl by 12 months, and walk independently by 15 months (Dosman, Andrews, & Goulden, 2012). In contrast, children with SYS on average sat independently at 18 months (range: 8–60 months; SD: 13.1 months), crawled at 31 months (range: 12–84 months; SD: 20.8 months), and walked independently at
| Cognitive/Neurologic | Total (n = 78) |
|---------------------|---------------|
|**Fountain** (n = 28) |               |
| Intellectual Disability | 21/21 2/2 1/1/1 1/2/2 3/3 3/3 1/1 2/2 | 34/34 70/70 100% |
| ASD Diagnosis (+) | 14/16 2/2 1/1 | N/A N/A N/A N/A N/A N/A N/A N/A N/A 7/12 25/32 78% |
| Full Scale IQ (avg.) | 30.48 8.00 N/A | N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A N/A 59.60 38.22 |
| Seizures | 7/21 1/2 1/1 | N/A 1/1 2/3 1/1 N/A 1/1 N/A 1/1 N/A 7/34 21/64 33% |
| Sleep Apnea | 12/18 2/2 1/1 | N/A N/A N/A N/A N/A N/A N/A N/A N/A 22/28 38/50 76% |
| Temp. Instability | 9/19 1/2 1/1 | N/A N/A N/A N/A 0/1 1/1 N/A 1/1 27/35 40/60 67% |
| **Respiratory Distress** | 8/12 2/2 1/1 | 1/1 1/1 3/3 N/A 1/1 2/2 22/35 41/58 71% |
| Intubation | 7/11 2/2 1/1 | 1/1 1/1 2/2 N/A 1/1 2/2 15/34 32/55 58% |
| Mechanical Ventilator | 6/10 2/2 0/1 | N/A 1/1 3/3 N/A 1/1 2/2 15/35 30/55 55% |
| Tracheostomy | 1/10 0/1 0/1 | N/A N/A 2/2 N/A 0/1 1/1 5/34 9/50 18% |
| **Feeding Problems** | 22/22 2/2 1/1 | 1/1 1/1 3/3 3/3 1/1 2/2 33/35 69/71 97% |
| Poor Suck in Infancy | 19/19 1/1 1/1 | 1/1 1/1 3/3 N/A 1/1 2/2 33/35 62/64 97% |
| Dysphagia | 12/13 1/1 1/1 | 1/1 N/A 3/3 N/A 1/1 2/2 27/35 48/57 84% |
| Hyperphagia | 7/19 0/1 0/1 | N/A N/A N/A N/A N/A N/A 0/1 7/34 14/56 25% |
| Use of ng Tube | 15/18 1/1 1/1 | N/A 1/1 2/2 N/A 1/1 2/2 22/34 45/60 75% |
| Use of g Tube | 6/12 2/2 1/1 | N/A N/A 2/2 N/A 1/1 2/2 14/33 28/53 53% |
| Excessive Weight Gain | 7/20 0/1 0/1 | N/A N/A N/A N/A N/A N/A N/A N/A N/A 0/1 6/35 13/60 22% |
| Reflux/GERD | 11/18 2/2 1/1 | N/A N/A N/A 3/3 1/1 1/1 15/34 34/60 57% |
| Chronic Constipation | 11/17 1/2 1/1 | N/A N/A N/A N/A N/A 1/1 0/1 25/33 39/55 71% |
| Neonatal Hypotonia | 19/21 2/2 1/1 | 1/1 2/2 3/3 3/3 1/1 2/2 32/32 66/68 97% |
| Scoliosis | 9/20 2/2 N/A | N/A N/A N/A 1/1 3/3 N/A N/A 1/1 10/19 26/46 57% |
| Exaggerated Kyphosis | 6/15 1/1 N/A | N/A N/A N/A 1/1 N/A N/A 0/1 4/19 12/37 32% |
| Contractures | 23/28 2/2 1/1 | 1/1 2/2 3/3 3/3 1/1 2/2 31/35 69/78 88% |
| Hypogonadism | 13/24 0/1 1/1 | 1/1 1/1 1/1 N/A N/A N/A N/A N/A N/A 9/35 26/64 41% |

N/A, Information not provided or otherwise unavailable.
TABLE 2  Developmental/speech milestones and growth parameters of patients with SYS

| Developmental Milestones | Fountain (n = 28) | McCarthy (n = 2) | Palomares-Bralo (n = 1) | Urelizt (n = 1) | Tong (n = 2) | Takiji (n = 3) | Jobling (n = 3) | Bayat (n = 1) | Matuszewska (n = 2) | New (n = 35) | Average | n | Not achieved |
|--------------------------|------------------|-----------------|------------------------|----------------|------------|--------------|-------------|--------------|-------------------|------------|---------|---|-------------|
| Sitting (months)          | 19               | 10              | 60                     | N/A            | N/A        | N/A          | N/A         | 16           | NY                | 18         | 16      | 41 | 7/48        |
| Crawling (months)         | 34               | 84              | NY                     | N/A            | N/A        | N/A          | N/A         | NY           | N/A               | 27         | 31      | 25 | 22/47       |
| Walking (months)          | 49               | NY              | NY                     | 132            | N/A        | N/A          | N/A         | NY           | 48                | 46         | 50      | 35 | 19/54       |
| Speech Milestones         |                  |                 |                        |                |            |              |             |              |                   |            |         |    |            |
| First Word (months)       | 52               | 66              | 60                     | NY             | N/A        | N/A          | N/A         | NY           | 36                | 29         | 36      | 30 | 23/53       |
| First Two-Word Sentence   | 42               | NY              | NY                     | 42             | N/A        | N/A          | N/A         | NY           | NY                | 39         | 40      | 10 | 39/50       |
| Growth Parameters         |                  |                 |                        |                |            |              |             |              |                   |            |         |    |            |
| Height Centile            | 18%              | N/A             | 1%                     | 3%             | N/A        | N/A          | N/A         | 18%          | 1%                | 24%        | 22%     | 48 |            |
| Weight Centile            | 41%              | N/A             | 15%                    | 3%             | N/A        | N/A          | N/A         | 41%          | 50%               | 47%        | 45%     | 48 |            |

N/A, Information not provided or otherwise unavailable. NY, Milestone not yet achieved.

3.6 Sleep apnea, temperature regulation, and hypogonadism
Of the 50 patients that have undergone sleep studies, 38 have been diagnosed with central and/or obstructive sleep apnea (76%). Additionally, 40 of 60 patients (67%) experience temperature instability, either manifesting as excessive sensitivity to the cold or as excessive sweating. Hypogonadism is found in 21 of 36 males (58%) and 5 of 28 females (18%).

3.7 Genotype-phenotype association
In this report, we also compare the phenotypes of two groups of patients. One group consists of the 38 patients with any truncating mutation other than c.1996dupC (n = 38), and the other group consists of patients with the c.1996dupC mutation (n = 35). When compared to the rest of the cohort, patients with the c.1996dupC mutation show a higher prevalence of joint contractures, feeding difficulties, and intellectual disability/developmental delay.

Among those with a c.1996dupC mutation, 34 of 35 individuals (97%) display joint contractures, while 5 of 28 individuals with any truncating mutation other than c.1996dupC (n = 38) show a higher prevalence of joint contractures, feeding difficulties, and intellectual disability/developmental delay. Supporting information Table S1.

Joint contractures are present in 69 of 78 individuals (88%), while further skeletal phenotypes include scoliosis in 26 of 46 patients (57%), and exaggerated kyphosis in 12 of 37 (32%).

3.8 Hypothyroidism
Hypothyroidism is found in 21 of 36 males (58%) and 5 of 28 females (18%).

3.9 Growth parameters and skeletal abnormalities
Short stature is defined clinically as manifesting a height that is less than the third centile for one's age and gender. According to these parameters, 35 of 63 patients (56%) present with short stature. Among the entire cohort, the average height of individuals measures in the 22nd centile (SD: 0.3), while the average weight measures in the 45th centile (SD: 0.3).

Joint contractures are present in 69 of 78 individuals (88%), while further skeletal phenotypes include scoliosis in 26 of 46 patients (57%), and exaggerated kyphosis in 12 of 37 (32%).

TABLE 2  Developmental/speech milestones and growth parameters of patients with SYS

| Totals (N = 78) |
|-----------------|

N/A, Information not provided or otherwise unavailable. NY, Milestone not yet achieved.

3.5 | Growth parameters and Skeletal abnormalities
Short stature is defined clinically as manifesting a height that is less than the third centile for one's age and gender. Among the entire cohort, the average height of individuals measures in the 22nd centile (SD: 0.3), while the average weight measures in the 45th centile (SD: 0.3). Supporting information Table S1.

Joint contractures are present in 69 of 78 individuals (88%), while further skeletal phenotypes include scoliosis in 26 of 46 patients (57%), and exaggerated kyphosis in 12 of 37 (32%).
technique, as 30 of 32 (94%) within this cohort require/required a nasogastric feeding tube compared to 15 of 28 (54%) of those with mutations other than c.1996dupC (p-value: 0.001). Additionally, 19 of 26 (73%) patients with c.1996dupC mutations require/required a g-tube for feeding compared to 9 of 27 (33%) patients with mutations other than c.1996dupC (p-value: 0.006).

Regarding respiratory dysfunction, 21 of 28 patients (75%) in the c.1996dupC cohort required intubation, versus 11 of 27 individuals (41%) in the other cohort (p-value: 0.014). Furthermore, 20 of 28 (71%) with a c.1996dupC mutation required mechanical ventilation compared to 10 of 27 (37%) without c.1996dupC mutations (p-value: 0.015).

We also observed differences in IQ between the two groups for those who were formally evaluated. Specifically, the mean IQ for those with a c.1996dupC mutation (n = 5) was 14.2 (SD: 12.1) compared to 53.2 (SD: 13.5) in those without a c.1996dupC mutation (n = 8) (p-value: 0.0003). This suggests that, on average, those with a c.1996dupC mutation had profound intellectual disability compared to those with a different mutation, who demonstrated mild intellectual disability.

There are also statistically significant differences between the two cohorts regarding motor and speech development. On average, patients with c.1996dupC mutations learn to sit at 23 months (SD: 16.1), while patients with other mutations learn to sit at 12 months (SD: 5.4) (p-value: 0.0087). Those in the c.1996dupC cohort learn to crawl at 45 months (SD: 28.6), while those with other mutations learn to crawl at 23 months (SD: 9.0) (p-value: 0.0106). Additionally, patients with c.1996dupC mutations learn to walk at 62 months (SD: 19.6), while patients with other mutations learn to walk at 43 months (SD: 27.0) (p-value: 0.0364).

Speech milestones in the c.1996dupC cohort are also more significantly delayed, as they learn their first word at an average of 49 months (SD: 30.1), compared to those with alternative mutations, who learn their first word at 25 months (SD: 20.1) (p-value: 0.0161).

**TABLE 3  Phenotype comparison between SYS and PWS**

|                        | SYS | PWS | Reference                  |
|------------------------|-----|-----|----------------------------|
| **Cognitive/Neurologic** |     |     |                            |
| ASD Diagnosis (+)      | 25/32 78% | 210/786 27% | Bennett et al., 2015 |
| Full Scale IQ (avg.)   | 38 60-70 | 60-70 | Cassidy et al., 2012 |
| Seizures               | 21/64 33% | 13/126 10% | Gilboa & Gross-Sur, 2013 |
| Sleep Apnea            | 38/50 76% | 68/90 76% | Gunay-Aygun et al., 2001 |
| Temp. Instability      | 40/60 67% | 8/118 6.8% | Williams, Rooney, Williams, Josephson, & Pauli, 1994 |
| **Respiratory Distress** |     |     |                            |
| Intubation             | 41/58 71% | 20/49 41% | Bar et al., 2017 |
| Mechanical Ventilator  | 32/55 58% | 6/49 12% | Bar et al., 2017 |
| Feeding Problems       | 30/55 55% | 14/42 33% | Bar et al., 2017 |
| Excessive Weight Gain  | 69/71 97% | 70/90 78% | Gunay-Aygun et al., 2001 |
| **Developmental Milestones** |     |     |                            |
| Sitting (months)       | 66/68 97% | 79/90 88% | Gunay-Aygun et al., 2001 |
| Mechanical Ventilator  | 26/46 57% | N/A 40%–80% | Cassidy et al., 2012 |
| **Speech Milestones**  |     |     |                            |
| First Word (months)    | 39/55 71% | 8/20 40% | Kuhlmann, Moeller-Joennson, Broendum Froekjaer, Krogh, & Farholt, 2014 |
| First Two-Word Sentence (months) | 34/60 57% | 15/29 52% | Saeves, Strom, Sandvik, & Nordgarden, 2018 |
| Feeding Problems       | 39/55 71% | 8/20 40% | Kuhlmann, Moeller-Joennson, Broendum Froekjaer, Krogh, & Farholt, 2014 |
| Hypogonadism in Males  | 26/46 57% | N/A 80%–100% | Cassidy et al., 2012 |
| Hypogonadism in Females | 5/28 18% | N/A 76% | Cassidy et al., 2012 |
| **Growth Parameters**  |     |     |                            |
| Height Centile         | 18 12 | 12 12 | Cassidy et al., 2012 |
| Weight Centile         | 31 14 | 14 14 | Cassidy et al., 2012 |
| **Growth Parameters**  |     |     |                            |
| Height Centile         | 50 24 | 24 24 | Cassidy et al., 2012 |
| Weight Centile         | 40 18 | 18 18 | Butler et al., 2006 |
| **Growth Parameters**  |     |     |                            |
| Height Centile         | 50 24 | 24 24 | Cassidy et al., 2012 |
| Weight Centile         | 40 18 | 18 18 | Butler et al., 2006 |
| N/A, Information not provided or otherwise unavailable. | | | |

**DISCUSSION**

In this report, we present 78 individuals with molecularly confirmed truncating mutations in MAGEL2 and aim to elucidate the complex phenotype of SYS. The complexity can be attributed to the multitude of symptoms that SYS patients can manifest, as well as the variable expressivity of the phenotype. Here, we also highlight the significant, but incomplete overlap between SYS and PWS phenotypes, to

MCCARTHY ET AL.
facilitate more specific diagnostic criteria for SYS and allow for more tailored patient care. The syndromes share common features, primarily during infancy, including neonatal hypotonia, feeding difficulties/failure to thrive, respiratory distress, and DD/ID. However, distinctions between the syndromes begin prenatally and increase throughout development. The earliest distinctive feature of SYS is the presence of joint contractures, which are frequently seen in SYS, while not typically described in the PWS phenotype. However, it should be noted that four publications regarding PWS have reported fetal hypokinesia resulting in distal arthrogryposis (Bigi et al., 2008; Denizot, Boscher, Le Vaillant, Roze, & Gras Le Guen, 2004; Fong & de Vries, 2003; Haugen, Ronnestad, & Kroken, 2009). Our results also indicate that individuals with SYS tend to experience a higher prevalence of respiratory distress in the first 2 months of life than do those with PWS.

During childhood development, the phenotypic profile of SYS becomes increasingly unique. It has been noted previously that patients with SYS do not typically manifest the hyperphagia and severe obesity seen in children with PWS, and that SYS patients demonstrate a higher prevalence of ASD (Fountain et al., 2017). Due to the size of our patient cohort, we can provide further evidence to bolster these early findings. Our results also reveal additional distinctions, as SYS patients tend to have a more severe form of developmental delay and a more profound level of intellectual disability (Table 3). In addition to excessive weight gain and hyperphagia, there are other features of PWS that are not commonly seen in SYS. For example, 73% of patients with PWS display hypopigmentation (Gunay-Aygun, Schwartz, Miller, & Driscoll, 2012). Those facial features are the cause of oculocutaneous albinism type 2 (OMIM #203200). As the OCA2 gene is not affected in SYS, individuals with SYS do not typically manifest hypopigmentation. Individuals with PWS manifest characteristic facial features, including narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, and thin upper vermilion with down-turned corners of the mouth (Cassidy, Schwartz, Miller, & Driscoll, 2012). Those facial features are not consistently seen in SYS, and may be, at least in part, due to genes within the PWS locus on chromosome 15q11q13, other than MAGEL2. There are other features prevalent in PWS that have not been studied systematically in SYS, including small hands/feet, narrow hands/straight ulnar borders, thick viscous saliva, articulation defects, and skin picking/behavioral abnormalities. Further studies should explore the prevalence of these features in SYS and investigate whether the features found in PWS and not in SYS are caused by the deletion or maternal disomy of other genes in the PWS locus.

In addition to refining the clinical phenotypic spectrum of SYS, the results of this investigation also indicate important genotype-phenotype associations for SYS. While all individuals in our cohort harbor pathogenic truncating mutations in MAGEL2, it appears that individuals with the c.1996dupC mutation display a more severe phenotype than individuals with other truncating mutations.

As the use of molecular genetic testing increases worldwide, it is becoming apparent that several different conditions originally described based upon clinical presentation may be caused by truncating mutations in MAGEL2. Truncating mutations in MAGEL2 have been identified in individuals originally diagnosed with Optiz Trigonocephaly C syndrome (OTCS [OMIM #211750]), Chitayat-Hall syndrome (OMIM #208080), and arthrogryposis multiplex congenita (AMC [OMIM #208100]) (Jobling et al., 2018; Mejlachowicz et al., 2015; Takuji et al., 2018; Urreizti et al., 2017).

OTCS is a rare genetic disorder characterized by craniofacial abnormalities, variable intellectual and psychomotor disability, arthrogryposis, hypotonia, and cardiac defects with a high mortality rate. In 2017, Urreizti et al. reported on 10 patients initially diagnosed with OTCS that underwent whole exome and genome sequencing and found that one of the 10 harbored a truncating mutation in MAGEL2. Due to the similarities between SYS and OTCS, it has been suggested that the 60+ individuals with OTCS should be tested for variants in MAGEL2 (Urreizti et al., 2017). Chitayat-Hall syndrome was first described in 1990, and manifests as distal arthrogryposis with hypotuitarism including growth hormone deficiency, intellectual disability, and facial anomalies. In 2018, Jobling et al. reported on three patients originally diagnosed with Chitayat-Hall syndrome who harbor truncating mutations in MAGEL2, and possess features common to the SYS phenotype, including joint contractures, hypotonia, DD/ID, feeding difficulties, scoliosis, and GERD (Jobling et al., 2018). It has also become apparent that truncating mutations in MAGEL2 can lead to the classic AMC phenotype, often seen in conjunction with other SYS features such as generalized hypotonia, respiratory difficulties, poor feeding, DD/ID, and endocrinological abnormalities. Individuals with c.1996delC mutations tend to express particularly severe AMC, leading to fatalities in utero or perinatally (Fountain et al., 2017; Mejlachowicz et al., 2015; Takuji et al., 2018).

In the following paragraphs, we present the emerging phenotype and natural course of SYS and present the genotype-phenotype associations related to the specific location of the MAGEL2 mutation.

4.1 | Infantile phenotype: Hypotonia, feeding difficulties, and joint contracture

Neonatal hypotonia is a nearly universal finding amongst patients with SYS (97%) and contributes to many of the clinical manifestations of the disorder, including feeding difficulties, motor/speech delays, respiratory dysfunction, and skeletal abnormalities.

In the first 2 months of life, most SYS patients are unable to suck an adequate quantity of milk from the bottle or breast, and require a special feeding technique, such as nasogastric tube feeding or the use of a special nipple. While these special feeding techniques are particularly critical in the first few months of life, 53% of SYS patients also require g-tube placement to supplement feeding throughout childhood, suggesting that the feeding difficulties of SYS extend beyond infancy. The hypotonia seen in SYS may also have a deleterious effect on gastric motility, and therefore may play a role in chronic constipation, which is seen in 71% of patients (Chumpatizai & Nurko, 2008).

In our cohort, 88% of individuals are affected by joint contractures, which range in severity from mild contractures of the distal phalanges to severe AMC, such as those seen in the cases reported by Takuji et al. (2018) and Mejlachowicz et al. (2015). Joint contractures
and AMC are considered a result of fetal akinesia or hypokinesia, which may be related to the abnormal expression of MAGEL2 in the nervous system during development and to the resulting hypotonia (Mejlachowicz et al., 2015). Due to their high prevalence, SYS should be considered in the differential diagnosis of any neonate presenting with joint contractures, hypotonia, and feeding difficulties.

4.2 | Infantile phenotype: Respiratory distress and sleep apnea

The infantile phenotype of SYS is also notable for severe respiratory distress, as 58% of our cohort required intubation and 55% required mechanical ventilation in the first 2 months of life. In a recent study in France, only 12% of infants with PWS required intubation, and 33% required mechanical ventilation, suggesting a relatively higher prevalence of respiratory distress in SYS (Bar et al., 2017).

Respiratory issues can be particularly hazardous in early childhood and should be monitored carefully. Three individuals with SYS have passed away within the first year of life due to apnea or respiratory failure, with deaths occurring at 2 days, 2 months, and 9 months postnataally (Mejlachowicz et al., 2015; Tong et al., 2018).

Overall, 10 deaths have been reported in individuals with SYS, all of whom are included in our cohort of 78. Five individuals with c.1996delC mutations died prenatally or perinatally due to severe AMC and fetal akinesia (Fountain et al., 2017; Mejlachowicz et al., 2015). It has also been reported that one child with SYS passed away due to cardiovascular failure at 11 months of age (Tong et al., 2018). Additionally, one patient with SYS passed away at 8 years of age, following a pancreatic cyst rupture.

The respiratory complications of SYS stem from multiple possible causes. First, while primarily expressed in the hypothalamus, murine models have shown moderate Magel2 expression in the diaphragm and abdominal wall muscles, indicating that loss-of-function could result in decreased respiratory effort and hypoventilation (Kamaludin et al., 2016). The hypotonia in the abdominal wall and diaphragm may also result in a lessened cough reflex, increasing the risk for aspiration/aspiration pneumonia. The risk of aspiration pneumonia is further increased if the patient is affected by GERD, which has been diagnosed in 57% of our patient cohort, thus prompting further caution.

Respiratory issues may also extend later into childhood and into adulthood, as both central and obstructive sleep apnea are commonly reported problems that must be managed over one’s lifetime. As 76% of the SYS cohort has been diagnosed with sleep apnea, we recommend that all patients with SYS undergo a sleep study once per year until the age of 8 years, and then continue to have sleep studies performed every other year after this age.

4.3 | Childhood development: Developmental delay/ intellectual disability and autism spectrum disorder

Our results indicate that individuals with SYS display more profound delays in motor and speech development and tend to manifest a more severe form of intellectual disability than those with PWS.

Children with PWS tend to reach milestones of motor development at about double the normal age (Cassidy et al., 2012). Therefore, they tend to sit independently around 12 months and walk independently around 24 months. In our SYS cohort, these milestones were significantly delayed beyond those of PWS patients, measuring at 18 months and 50 months, respectively. Notably, a sizable portion of SYS patients fails to reach developmental milestones at any age, while those with PWS do reach these milestones, albeit at a delayed rate. In our cohort, 47% of individuals with SYS have not yet learned to crawl, and 35% have not yet learned to walk independently, with many relying on the assistance of walkers and/or wheelchairs.

Speech delays are quite severe in patients with SYS, as they average 36 months before using their first word, and 40 months before using their first two-word phrase. In contrast, patients with PWS tend to reach both speech milestones around 18 months (Butler, Lee, Whitman, & Lewis, 2006). Like the pattern seen in motor milestones, patients with SYS often miss speech milestones altogether, as 43% of our cohort have not used their first word, and 78% have not used a two-word phrase.

While developmental milestones are often delayed, it should be noted that SYS patients have not shown any regression in skills, that is, learned motor or mental skills, and are in this way distinguishable from those affected by many neurometabolic disorders.

On average, patients with SYS display a more profound level of intellectual disability than those with PWS, as the mean IQ of SYS patients falls within the moderate disability range, whereas the mean IQ of patients with PWS falls within the mild disability range (Cassidy et al., 2012).

One of the defining features of the SYS behavioral phenotype is the prevalence of ASD. Of the patients with MAGEL2 mutations that have undergone formal evaluation, 78% have been diagnosed with ASD, compared to 27% of patients with PWS that receive an ASD diagnosis (Bennett et al., 2015). The extremely high prevalence of ASD in SYS patients suggests that MAGEL2 influences the development of social behavior. Variants of MAGEL2 may play a role in ASD beyond SYS, such that variants in MAGEL2 other than nonsense and truncating may cause "hypomorphic" phenotypes that are also ASD-related.

4.4 | Physical phenotype and skeletal abnormalities

Patients with SYS tend to express a combination of short stature, elevated fat mass, and low IGF-1 levels, suggesting a growth hormone deficiency similar to PWS (McCarthy et al., 2018). In the cohort of 78, the average height measures in the 22nd centile, while the average weight measures in the 45th centile, suggesting increased adiposity relative to height. However, despite the relative adiposity, only 22% of SYS patients have reported excessive weight gain, which is a defining feature of PWS. While increased adiposity without excessive weight gain may appear incongruous, a similar pattern has been recapitulated in mouse models, as Bischof et al. demonstrated that Magel2-null mice demonstrated an elevated percentage fat mass compared to their wild-type littermates, but showed no significant difference in body weight (Bischof, Stewart, & Wegrzyn, 2007).

SYS also differs from PWS regarding eating behaviors. While hyperphagia is a distinguishing clinical feature of PWS, beginning around the age of 8 years and persisting throughout adulthood, this
behavior is only seen in 14 of 56 patients (25%) with SYS (Miller et al., 2011).

Skeletal analysis of SYS patients shows that 57% have been diagnosed with scoliosis, while 32% have been diagnosed with exaggerated kyphosis. In PWS, it is estimated that scoliosis is present in 30% of children and 80% of adults, suggesting that it is a progressive disorder (Cassidy et al., 2012). It has been hypothesized previously that MAGEL2 is the scoliosis-determining gene of PWS, as MAGEL2 loss-of-function leads to hypotonia and muscle atrophy, and Magel2-null mice exhibit scoliosis (Kamaludin et al., 2016). Due to these findings and the progressive nature of scoliosis, we suggest continued monitoring of skeletal growth throughout development for all patients with SYS.

4.5 | Hypogonadism and temperature instability

Hypogonadism is a consistent finding in both males and females with PWS and is often thought to be of hypothalamic etiology. Up to 80% of males with PWS are diagnosed with hypogonadism, evident at birth as cryptorchidism (Emerick & Vogt, 2013). Due to the commonalities between disorders and the hypothalamic expression of MAGEL2 in adult tissues, the prevalence of hypogonadism was analyzed in patients with SYS. Our findings show that 41% of patients have been diagnosed with hypogonadism, with a prevalence of 21 of 36 males and 5 of 28 females. The lower relative prevalence of hypogonadism in SYS patients suggests that the hypogonadism seen in PWS may only in part be the result of MAGEL2 deficiency.

As the hypothalamus serves as the primary CNS component of thermoregulation, we also analyzed temperature instability in SYS patients, finding that 67% of patients experience feelings of excessive cold or excessive sweating.

4.6 | Mutational hotspot and genotype–phenotype associations

Nucleotides c.1990–1996 represents a sequence of seven cytosines and function as a mutational hotspot in SYS. Of the 78 reported cases, 42 harbor mutations within this region. The most common mutation is the c.1996dupC mutation, which occurs when an additional cytosine is included within this hotspot by error and is found in 35 of 78 patients. While c.1996dupC mutations represent the most prevalent mutation, the most severe phenotype occurs in individuals with a missing cytosine in this region. To date, five individuals with c.1996delC mutations have been reported, all of whom passed away during gestation or within hours following their birth (Fountain et al., 2017; Mejlachowicz et al., 2015).

By comparing clinical characteristics between mutation groups, we demonstrate further genotype–phenotype associations found in SYS. Our results indicate that syndromic severity may depend on the specific location of the truncating mutation, as individuals with c.1996dupC mutations show a more severe phenotype compared to all other truncating mutations (excluding c.1996delC mutations). Specifically, individuals with this duplication show a higher prevalence of joint contractures, more severe feeding difficulties, more severe respiratory difficulties, and more significant intellectual disability/developmental delay (Supporting Information Table S2).

Although the pathomechanism of these differences is not well understood, it is important to note that MAGEL2 is a single exon gene, and mutations leading to a premature stop codon are predicted not to cause nonsense-mediated mRNA decay. Instead, it is expected that such mutations will result in a truncated protein product. Therefore, one could speculate that the pathogenic effect may differ depending on the precise location of the mutation on MAGEL2, as it would result in a different truncated protein product. Further studies will be necessary to clarify the underlying pathomechanics behind the variable expressivity of phenotypes seen in SYS.

5 | CONCLUSION

SYS leads to a complex phenotype, characterized by profound ID/DD, ASD, respiratory dysfunction, feeding difficulties, digestive complications, skeletal abnormalities, sleep dysfunction, hypogonadism, and temperature instability. However, the severity of the SYS phenotype is highly variable, and may depend on the precise location of the mutation in MAGEL2.

Additional studies will be necessary to continue monitoring the expanding cohort of individuals with truncating mutations in MAGEL2, as well as to examine individuals with missense mutations, which have not been reported. Through the continued analysis of these patients, we hope to provide updated recommendations for physicians and families, to provide the best care for those affected by SYS.

ACKNOWLEDGMENTS

The authors thank the individuals and the families with Schaaf-Yang syndrome, who have provided clinical data and overwhelming support for our efforts. The authors also thank the referring clinical physicians and genetic counselors, who have helped us connect with patients around the world. The authors also thank Felix Marbach for his helpful feedback.

DECLARATION OF INTERESTS

The authors declare no competing interests.

WEB RESOURCES

I. (www.facebook.com/groups/SchaafYangFamilyGroup/)
II. (https://www.infantchart.com/child/childrenstatureage.php).

ORCID

Samantha A. Schrier Vergano https://orcid.org/0000-0001-9194-0644
Yves Lacassie https://orcid.org/0000-0002-6231-4967
Christian P. Schaaf https://orcid.org/0000-0002-2148-7490
children with neurodevelopmental delay accompanied unexplained dyspnea. Scientific Reports, 8(1), 5214. https://doi.org/10.1038/s41598-018-23503-2

Urreizti, R., Cueto-Gonzalez, A. M., Franco-Valls, H., Mort-Farre, S., Roca-Ayats, N., Ponomarenko, J., ... Balcells, S. (2017). A de novo nonsense mutation in MAGEL2 in a patient initially diagnosed as Opitz-C: Similarities between Schaaf-Yang and Opitz-C syndromes. Scientific Reports, 7, 44138. https://doi.org/10.1038/srep44138

Williams, M. S., Rooney, B. L., Williams, J., Josephson, K., & Pauli, R. (1994). Investigation of thermoregulatory characteristics in patients with Prader-Willi syndrome. American Journal of Medical Genetics Part A, 49(3), 302–307. https://doi.org/10.1002/ajmg.1320490312

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: McCarthy J, Lupo PJ, Kovar E, et al. Schaaf-Yang syndrome overview: Report of 78 individuals. Am J Med Genet Part A. 2018;176A:2564–2574. https://doi.org/10.1002/ajmg.a.40650