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MAGEL2-Related Disorders: A study and case series.

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Abstract

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Zoe Powis, Timothy Vo, Sha Tang and Wendy Alcaraz are employed by Ambry Genetics, where whole exome sequencing is commercially available.

Data sharing statement: De-identified patient data, excluding case series presentations, and 'R' scripts are available upon request to the corresponding author.

Pathogenic *MAGEL2* variants result in the phenotypes of Chitayat-Hall (CHS), Schaaf-Yang (SYS) and Prader-Willi (PWS) syndromes. We present five patients with mutations in *MAGEL2*, including the first patient reported with a missense variant, adding to the limited literature. Further, we performed a systematic review of the CHS and SYS literature, assess the overlap between CHS, SYS and PWS, and analyze genotype-phenotype correlations among them. We conclude that there is neither a clinical nor etiological difference between CHS and SYS, and propose that the two syndromes simply be referred to as *MAGEL2*-related disorders.

Keywords

Chitayat-Hall syndrome; Schaaf-Yang syndrome; MAGEL2; MAGEL2-related disorder; Prader-Willi syndrome locus

Introduction

Prader-Willi syndrome (PWS)(OMIM# 176270) is characterized postnatally by profound neonatal hypotonia that can lead to poor suck and asphyxiation. As PWS patients age, most will be noted to have genital hypoplasia, developmental delay, short stature and extreme food-seeking behavior with hyperphagia and obesity.[1, 2] Hypothalamic-pituitary axis dysfunction, including growth hormone deficiency, osteoporosis, hypogonadism, and late menarche are commonly reported.[3]

The PWS locus, located on 15q11–15q13,[4] contains the genes *MKRN3*, *MAGEL2, NDN, PWRN1, NPAP1, SNURF-SNRPN, SNORD, IPW, SNORD115*, and *SNORD109B*.[2] PWS is caused by three separate but related genetic mechanisms, all involving failure of proper paternal gene dosage.[5] While PWS is autosomally inherited, the maternal region is silenced through methylation.[5, 6] Thus, the most common mechanism is paternal deletion of the PW locus, which occurs in 70% of cases.[5] Less common mechanisms are maternal uniparental disomy (20%−30%) and imprinting defects (rare).[5]

The gene *MAGEL2*, which resides in the PWS locus, is a single-exon gene encoding the melanoma-antigen-subfamily-like-2 protein and is part of a large ubiquitination complex that regulates endocytosis, receptor recycling and cell-surface localization. In mouse models, Magel2 regulates the cell cycle, neuronal signal transduction, neurite growth, and muscle function.[16–22] Because the maternal genetic region is silenced through methylation, all classes of mutations in the maternal *MAGEL2* allele are clinically insignificant.[4] However, pathogenic mutations on the paternal allele, which is expressed, are detrimental to neural and muscular development and are responsible for a number of human syndromes.

Chitayat-Hall syndrome (CHS)(OMIM# 208080) is a rare, genetic syndrome first described in male and female siblings three decades ago,[7, 8] and only 11 additional patients have since been described. Its core symptoms have been reported as distal arthrogryposis, hypopituitarism, intellectual disability (ID), and facial dysmorphisms.[7–9] In 2018, CHS was reported to arise from pathogenic variants in *MAGEL2*.[10]

Interestingly, in 2013 Schaaf *et al.* reported a phenotype associated with truncating *MAGEL2* mutations and noted that affected individuals had considerable phenotypic overlap with those affected by PWS, except that they also presented with arthrogryposis, autism spectrum disorder and, in subsequent reports, endocrine dysfunction, such as hypopituitarism.[4, 11–14] Based on its distinct genetic etiology in comparison to PWS, the syndrome was named Schaaf-Yang syndrome (SYS)(OMIM# 615547).[12]

Recently, mutations in *MAGEL2* have been reported to be associated with additional clinical diagnoses. For example, some patients with arthrogryposis multiplex congenita (AMC) (OMIM #208100), which is characterized by limb deformities, craniofacial anomalies, genital abnormalities, growth delay, and respiratory issues, have been shown to harbor truncating *MAGEL2* mutations.[15, 16] Furthermore, a patient previously thought to have Opitz Trigonocephaly C syndrome (OTCS)(OMIM #211750), a rare, high-mortality genetic syndrome characterized by facial dysmorphism, intellectual and developmental delay, hypotonia, and distal arthrogryposis, was also found to carry a truncating mutation in *MAGEL2*.[17]

There is significant phenotypic and etiological overlap between CHS, SYS and PWS. The similarities between SYS and PWS are well established. In fact, SYS is considered a “Prader-Willi-like” syndrome,[11] with overlapping but distinct features.[4, 6] Although Jobling *et al.* (2018) suggested overlap between CHS and SYS, to our knowledge no one has systematically compared the three syndromes.

In the largest case series and review of *MAGEL2*-related disorders to-date, McCarthy *et al.* (2018) found a genotype-phenotype correlation in SYS patients.[18] The authors reported that the most common mutation found in SYS patients, c.1996dupC, results in a more severe phenotype than other pathogenic mutations.[18] The authors also mentioned that deletion of the same nucleotide, c.1996delC, caused *in utero* or perinatal demise, yet no study to date has assessed the potential biological differences between these mutations.

Here, we report five patients with *MAGEL2*-related disorders, including the first patient ever reported to carry a *MAGEL2* missense variant, adding to the limited literature. In addition, we use this opportunity to compare the clinical presentations of CHS, SYS and PWS, with a systematic review of the literature. Furthermore, we determine that the c.1996dupC and delC mutations have different predicted protein-level consequences, potentially accounting for the observed phenotypic differences in patients.

Methods

All patients were counseled on the outcomes of whole exome sequencing and signed a consent form approved by the respective Institutional Review Board and outlined in the Declaration of Helsinki. Genomic DNA from the probands and the parents was harvested from either whole blood or saliva and whole-exome sequencing was performed. In depth methods from each institution is available in the supplemental files.

Literature searches were conducted using the PubMed and Google scholar databases. Search terms included “Schaaf-Yang syndrome”, “Prader-Willi and Schaaf-Yang syndromes”,

"MAGEL2", "MAGEL2-related disorders", "Chitayat-Hall syndrome", "Chitayat-Hall and Schaaf-Yang syndromes".

The GeneMatcher (genematcher.org) and matchbox nodes of the Matchmaker exchange database were used to obtain collaborations and additional patient profiles, using the search term MAGEL2.[19], [20, 21]

ExPASy database was used to predict the protein translation from the mRNA sequences of *MAGEL2* and the protein translations were subjected to basic local alignment search tool (BLAST) searches.[22, 23]

The R statistical environment was used for all mutational analysis computing.[24]

Results

Case Reports

Patient one: The male proband was born to a 21-year-old G2, P0010 mother of Irish and Italian descent and a 24-year-old father of Native American and mixed European descent. The couple was healthy, not consanguineous and the family history was non-contributory. A prenatal ultrasound revealed macrocephaly. The pregnancy was conceived naturally and there was no known exposures to teratogens. Delivery was at 38 weeks gestation by Cesarean section due to a poor biophysical profile (2/10). The APGAR scores were 3 at one minute, 4 at five minutes and 7 at ten minutes. The proband's anthropomorphic measurements were weight: 3950 g (75–90th percentile), length: 48.8 cm (25–50th percentile), and head circumference: 38.8 cm (97th percentile). Postnatal examination showed facial dysmorphism including hypertelorism, down-slanting palpebral fissures and micrognathia. The external genitalia was hypoplastic and the patient had tapering digits (Figure 2B). The patient spent the first 12 months of life in the neonatal intensive care unit. He had respiratory insufficiency in the neonatal period that required ventilation. Over time the child displayed autism spectrum disorder, global developmental delay, and scoliosis. Brain MRI showed dysplastic corpus callosum, hypoplastic vermis, decreased myelination and generalized brain atrophy. At 3 years 9 months of age, his weight was 20,800 g (98th percentile), length 97.0 cm (18th percentile), head circumference 54.0 cm (98rd percentile) and body mass index (BMI) 22.13kg/m2 (98th percentile). The patient is still non-verbal. He can stand independently but cannot walk. He breathes room air, but still occasionally uses his ventilator for sleep apnea. Prior to genetic testing, Prader-Willi-like syndrome was considered in the differential diagnosis.

Patient two: The female proband was born to a G2, P0010, 37-year-old mother of American Caucasian decent and a 32 year-old father of American Caucasian decent. The couple was healthy and nonconsanguineous. The family history was non-contributory. The pregnancy was complicated with exposure to cigarette smoking for the duration and by eclampsia in the last month of gestation. Fetal movements and prenatal ultrasounds were normal. The birth weight was 2865g (20th percentile), length 51.5 cm (75th percentile), and head circumference was not documented. Examination in the newborn period revealed atrial septal defect, tracheomalacia, cleft palate and jaundice. On follow-up, the patient was noted

to have developmental delay. She first smiled at 6 months, sat at 2 years, and walked at 6 years of age. Currently, at 18 years she has been diagnosed with autism spectrum disorder and intellectual and motor disabilities. Reportedly, she is self-injurious and has aggressive behavior. On examination at age 3 years, she was noted to have multiple congenital anomalies including macrocephaly (58.8 cm; >97th percentile), down-slanting palpebral fissures, prominent epicanthic folds, telecanthi, hypertelorism, prominent nasal bridge, short philtrum, thick vermillion upper and lower lip, cleft palate, low set ears (Figure 2B). She also had bilateral single transverse palmar creases, hirsutism, and scoliosis. She had bilateral knee contractures but no camptodactyly. Brain MRI showed agenesis of the corpus callosum. The initial diagnosis was Toriello-Carey syndrome (OMIM #217980).

Patient three: The male patient was born to a 26-year-old G2, P2 mother of Caucasian descent and a 27-year-old father of Caucasian descent. The couple was healthy and non-consanguineous. The couple's family histories were non-contributory. The pregnancy was uncomplicated, and delivery was by Cesarean section at term, for breech presentation. The birth weight was 2830g (5–10th percentile); length and head circumference were not available. At birth he was noted to be hypotonic with poor suck and scarce spontaneous movements. He required ventilator support for ten days. He had growth and developmental delay and at 6 years of age his weight was 12.2kg (−2.6 SD); height 95cm (−4.9SD). His OFC at 8 years was 50 (−2SD). He had dry skin and abnormal hair growth pattern, dolichocephaly, low set ears, broad nasal root, deep philtrum, widely spaced teeth, mild contractures of both knees, tapering digits with camptodactyly of fingers 2 to 5, and poorly developed palmar creases. His penis and scrotum were hypoplastic and he had bilateral cryptorchidism, which were surgically corrected. At age 3 he not walking and had only a few words and receptive language. He had two episodes of seizures and his MRI and EEG were normal. He had chronic constipation, and recurrent hypoglycemia (low IGB1 and BP3). A formal diagnosis of autism spectrum disorder was made at age 5. At 8 years of age the patient's hypoglycemia had improved spontaneously. He had almost absent speech and limited communication skills. He had growth delay with accelerated bone age. He was also being investigated for sleep apnea. No initial diagnosis was made prior to genetic testing.

Patient four: The female patient was born to a 38-year-old G2, P2 mother of Caucasian descent and a 44-year-old father of Caucasian descent. The couple was healthy, non-consanguineous. The pregnancy was complicated with polyhydramnios and decreased fetal movements. Delivery was by cesarean section for polyhydramnios. The birth weight was 3090g (25th percentile), length was 46.5cm and the head circumference was 34cm. The baby developed respiratory distress requiring ventilation during the first 36 hours of life and oxygen supplementation until day 13. She had hypotonia and scarce spontaneous movements. Facial dysmorphia included prominent forehead, bitemporal narrowing, deep-set eyes and a wide nasal bridge. She also presented with distal contractures with tapering fingers. Investigation at age 10 months showed hypoglycemia and hypothyroidism (low TSH), and a brain MRI showed a small hypophysis. At age 7 she receives hormone replacement treatment for GH and TSH deficiency. She has global developmental delay and some self-injurious behavior. A formal diagnosis of autism spectrum disorder was made. She

has growth delay with accelerated bone age. No initial diagnosis was made prior to genetic testing.

Patient five: The female patient was born to a 37-year-old G2 P2 mother and a 38-year-old father. The mother of the proband had a history of seizures beginning in her third decade of life, but otherwise the parents of the proband were healthy and non-consanguineous. Family history revealed that a paternal aunt was born with bilateral clubfoot, and a paternal cousin had high-functioning autism spectrum disorder. The maternal grandmother's family had multiple individuals of both sexes who were short (under 5'). Additionally, a male second cousin on the maternal side was diagnosed with ptosis of unknown etiology. The pregnancy was complicated with hyperemesis gravidarum and diabetes. The mother was treated with escitalopram oxalate and anti-nausea medication during the first trimester. She developed gestational diabetes and was treated with Glyburide. She also developed polyhydramnios and pruritus. Fetal ultrasound showed left clubfoot but otherwise no anomalies were detected.

Although the records for indication could not be recovered, delivery was at term via Cesarean section. The patient had a birth weight of 3.8kg (79^{th} percentile), length of 53cm (90^{th} percentile), and head circumference of 34.5cm (42^{nd} percentile). At birth, the patient did not cry or move her body, face, or eyes, and was transferred to the neonatal intensive care unit, where she remained for 3.5 months. She had facial dysmorphism including a high forehead, frontal bossing, micrognathia and a high but intact palate. Her chest appeared long and narrow, and she had a left-sided supranumerary nipple. She had hand and wrist contractures and left clubfoot. She had severe hypotonia, could not suck or swallow and developed respiratory acidosis. She was noted to sleep with her eyes open and had xerophthalmia. EKG, MRI, and routine blood work were normal. Skeletal X-rays showed mesomelic shortening of the long bones, probable tiny cervical ribs bilaterally, and bilateral clubfoot. She required a tracheostomy for acidosis, and gastrostomy tube insertion for nutrition. Her left clubfoot was treated surgically.

Assessment at five years of age noted full ocular movements with left eye exotropia, episodic nystagmus, and preference for moving her head rather than her eyes. She had myopathic face and could not make facial movements until three years of age. She had prominent tongue and altered facial sensation She had velopharyngeal insufficiency, difficulties swallowing and inability to chew or drink from a cup. She had severe GERD with eosinophilic esophagitis, multiple food allergies, and excessive drooling. She had short stature, small hands and feet, camptodactyly and "sandal gap".

Her hypotonia has improved over time but remained substantial over the left lower limb. She was able to roll over and walk short distances without support and was unable to pull herself from a supine to a sitting position. She had gross and fine motor delay as well as speech and language delay. By age ten she used a walker routinely and felt to have good receptive language skills. She was learning American Sign Language, was able to use over 800 signs, and was becoming verbal with 10–15 words. The tracheostomy remained in place, but supplemental oxygen was minimal and suctioning was needed just once a day. There were

no concerns about hyperphagia or obesity. She was diagnosed with anxiety and attention-deficit/hyperactivity disorder.

Molecular data

Patient one: Karyotype analysis with FISH for 15q11.2 was normal, and SNP microarray was uninformative. WES revealed a *de novo*, truncating variant of paternal origin in the *MAGEL2* gene (c.3122delT, p.Val1041Alafs*7).

Patient two: Karyotype, CGH array, FISH, Angelman methylation studies and *MECP2* sequence and CNV analyses were uninformative. WES revealed three *de novo* missense variants, only one of which is pathological: 1) GRIK4 (c.1858T>C, p.C620R); 2) SPG7 (c.2205G>C, p.K735N), which is associated with spastic paraplegia but only recessively (OMIM# 602783) and this patient contains only a single allelic variant; 3) *MAGEL2* (c.1613C>A, p.Ala538Glu), a paternally inherited variant, which was determined by trios next-generation sequencing with single-nucleotide polymorphism comparison (NM_019066.4). This variant was predicted to be deleterious (SIFT) and disease causing (MutationTaster).[25, 26] Thus, matching the ACMG classification of “pathogenic, strong (PS2)”. The variant was absent from ExAC v0.3, and gnomAD r2.0.2 population databases.

Patient three: Targeted panel sequencing revealed a heterozygous truncating variant in *MAGEL2* c.1996_1997dup; (p.Gln666Hisfs*37). The same variant was detected in 50 reads of the paternal sequencing and was estimated at 4% mosaicism.

Patient four: Targeted panel sequencing revealed a *de novo* heterozygous truncating variant of paternal origin in *MAGEL2* c.3169G>T; (p.Glu1057*).

Patient five: BAC array, SNP array, and karyotype testing were uninformative. Whole Genome Sequencing (WGS) analysis revealed a heterozygous *de novo* truncating variant in *MAGEL2* (c.1996dupC, RefSeq transcript NM_019066.4; p.Gln666ProfsTer47, RefSeq NP_061939.3). This variant has a CADD Phred score of 24.2,[27] had been previously associated with Schaaf-Yang Syndrome (MIM 615547; www.omim.org), and had been classified as pathogenic by five independent submitters in ClinVar (variation ID 190122; entries SCV000329409.5, SCV000703044.1, SCV000740854.1, SCV000746657.1, and SCV000222765.3. Date of access: 9/30/2018.).[28] The variant was absent from the 1000 Genomes, GnomAD genomes, and TOPMed databases and has minor allele frequencies of 0.00029 and 0.000047 in the ExAC and gnomAD exome databases, respectively. The presence of the variant at low frequency in the general population may be explained by the imprinted nature of *MAGEL2*. Bidirectional Sanger sequencing of a 492 bp fragment containing the *MAGEL2* variant in the proband and her parents confirmed its *de novo* status.

Clinical overlap among the five probands: All patients presented with intellectual disability, developmental delay, eye abnormalities and facial dysmorphia. Four of our patients had contractures, autism spectrum disorders, hypotonia/neonatal hypotonia, respiratory difficulties, and structural brain anomalies by MRI. There were, however, only two patient comparisons that showed significance for overlap; namely, patient one (c.

3122delT, p.Val1041Alafs*7) compared with patient four (c.3169G>T; p.Glu1057*), and patient three (c.1996_1997dup; p.Gln666Hisfs*37) compared with patient four (c.3169G>T; p.Glu1057*). Interestingly, patient two, who harbored the missense variant, had the least overlap with the others (Figure 2).

Literature review

Literature review yielded 23 articles and one letter to the editor pertaining to these syndromes, which are summarized in the PRISMA diagram (Figure 1).[4, 7, 8, 10–18, 29–38] We include a simplified summary of the patients' symptoms (Table 1) and further summaries of all CHS and SYS patients to date (Supplemental Table 1). In addition, tissue-specific symptomatic breakdowns for CHS, SYS and PWS are also included (Supplemental Table 2). Based on these data, we conclude that CHS and SYS are not clinically different (Figure 3) and we concur with Jobling *et al.* that they should be considered the same syndrome.

Mutational analysis

Previously reported mutations in *MAGEL2* reveal that there may be a mutational hotspot in the cytosine stretch in positions 1990–1996 in the cDNA.[4, 11] We confirm the 1990–1996 mutational hotspot and summarize all reported mutations for both CHS and SYS, both at the gene and protein level (Figure 4A, B).

Comparing the predicted protein products of c.1996dupC and 1996delC revealed that the dupC variant results in a truncated protein lacking the MAGE domain. By contrast, the predicted translation of the delC variant contains 11 fewer amino acids than the dupC-MAGEL2 and only contains the DNA Pol3-gamma domain, instead of the PAT1 domain associated with this region of the protein in both the full-length and dupC version (Figure 4C–E).

Based on hierarchical clustering of patient symptoms (Figure 5), there was a disproportionate clustering of patients with 1996dupC mutation in cluster 1 (83.3%). We found a significant enrichment of five symptoms in patients that harbor 1996dupC mutations in comparison with patients that harbor any other mutation (NG tube requirement ($p = 0.0017$); G tube ($p = 0.011$); intubation ($p = 0.035$); time to development of 1st word ($p = 0.038$); and mechanical ventilator requirement ($p = 0.049$)). In addition, there was a significant effect of symptom number with 1996dupC mutation, in comparison with the other mutations (mean number of symptoms 1996DupC = 14.81, SE = 0.82; mean number of symptoms non 1996dupC = 11.15, SE = 0.73; $p = 0.0001346$) (Figure 6).

Discussion

Case series summary

The five patients in our case series all harbor *MAGEL2* mutations and have overlapping clinical presentations, including multiple congenital anomalies, autism, intellectual disability, neurological findings (e.g. hypotonia, nystagmus, seizures, etc.), endocrinological

perturbations (e.g. hypoglycemia, growth hormone deficiency, hypopituitarism, etc.), contractures, and respiratory dysfunction.

This is a challenging diagnosis due to the rarity and intra-syndrome variability, as evidenced by a failure of experienced geneticists to correctly diagnose any of the patients in our cohort on a clinical basis. These five patients fit the clinical paradigms for both CHS and SYS. However, as they all carry pathogenic *MAGEL2* variants, they have a diagnosis of SYS.

Syndrome comparisons

The clinical findings of SYS, CHS and PWS as reported in the literature are very similar. In the largest published case series of SYS (35 new affected individuals), McCarthy *et al.* summarized the clinical features of the syndrome and compared it to PWS, suggesting that the primary differences were that SYS patients present with autism and contractures.[18] Here, we compare all reported patients with SYS and CHS. We find that there is significant overlap of features attributed to SYS and CHS, something that was recently suggested in a different case series.[3]

We did not find any CHS patients that report “temperature instability” as a symptom, while SYS patients commonly report that as a feature (67%). However, unless this is a defined lack of central core temperature maintenance, the clinical aspects of this symptom are challenging to interpret. We also found no CHS patients that used an NG tube, while 75% of SYS patients have reported using this intervention. That being said, there were other specialized feeding techniques, such as gastronomy tubes, that were used in CHS patients. Thus, the significance of this finding is negligible. Hyperphagia was also not reported in CHS, although, it is also present in a minority of SYS patients (25%).

Using an unbiased clustering analysis, we could not separate the patients into their diagnostic classifications based on clinical presentation. This analysis, combined with our symptoms-based overlap comparison, strongly suggests that there is no difference between CHS and SYS on a clinical basis. Albeit, our analysis is limited by the number of patients that have been characterized with CHS.

Based on the evidence of our systematic review, we suggest that there is not a significant clinical difference between the two disorders. Also, any apparent clinical variations or differences in symptom frequency between the two syndromes can be explained by the much larger number of patients that has been reported with SYS. Furthermore, CHS was defined before awareness of some of the defining signs, such as autism. However, based on recent findings, the etiology of the two syndromes appears to overlap and to be identical in some cases; meaning, they are both caused by truncating and terminating mutations in *MAGEL2* and patients of both disorders, CHS and SYS, have been reported with the same mutations, i.e. 1996dupC.[12]

SYS was defined largely as a Prader-Willi-like syndrome due to mutations in *MAGEL2*, with a proposed mutational hotspot in one region, c.1990–1996.[4–6] Strikingly, the etiology of CHS also is mutation in the *MAGEL2* gene, including mutations in the c.1990–1996

hotspot, among others.[11–13, 23, 24] It should be noted, that patients with lethal AMC were also found to carry previously characterized *MAGEL2* mutations, such as the 1996delC.[16]

Mutational Analysis

Our mutational analysis, although limited in scope, shows that 1) there are predicted protein differences in two similar mutations that have distinct phenotypes, 2) based on symptom type and number, certain genotypes have more severe phenotypes than others, and 3) there is high intra-syndrome variability.

1996dupC mutations in *MAGEL2* were reported to cause SYS, and 1996delC mutations to cause death *in utero* or soon after birth.[11, 15, 16] Since the two mutations are similar in that they both cause frameshifts in the same place, it is peculiar that they would result in such drastically different phenotypes. Based on our comparison of the translated versions of the 1996dupC and 1996delC we find that there is a protein-level difference of both amino acid number and, possibly, the resulting domains contained in the protein product. The functional significance of this finding is difficult to interpret and would benefit from biochemical analysis of the protein products, which is outside the scope of this study. We suggest that at least a portion of the high degree of intra-syndrome variability could also be a manifestation of genotype-phenotype correlations such as this.

Although there are reports of intron-less nonsense mediated decay (NMD),([39] consensus suggests that the mechanism of NMD relies on exon-exon junctions to initiate the decay program for degradation of mRNA transcripts that contain premature stop codons.[40–43] Since *MAGEL2* is a single-exon gene, frameshift mutations may not cause nonsense-mediated decay, but instead a variety of truncated or elongated protein products. We hypothesize that this could also be driving the high degree of intra-syndrome variability and the observation of both dominant negative and less severe haploinsufficiency as mechanisms of disease. [5, 6, 10] However, this is insufficient to explain all of the intra-syndrome variability, as even patients carrying the same mutation can have a high degree of variability in their presentations.

Our report describes the first potentially disease-associated *MAGEL2* missense variant; all other pathogenic variants reported to-date arises are frameshifting or terminating. Analysis of our cohort shows that there is less overlap in both number and type of symptoms between the patient that harbors the missense variant versus the other four patients. Caution is warranted here, as although the patient with the missense variant had fewer symptoms overall, she also presented with certain severe symptoms, autism spectrum disorder, dysmorphia and developmental delay.

Our findings confirm many of the findings reported in McCarthy *et al.* 2018, even with the inclusion of our cohort of patients. However, the only genotype-phenotype resolved for both studies was an increase in syndromic severity in patients that harbor 1996dupC mutations when compared with others. Admittedly both studies lack sufficient power for robust conclusions on this issue, and it may hold true that as patient reports increase, this effect is simply due to the inflated number of patients that have been reported with 1996 mutations to-date.

Conclusion

CHS was clinically defined before SYS, but there were no genetic etiologies associated with the disorder. Later, Schaaf *et al.* found a similar syndrome associated with *MAGEL2* mutations and characterized it as such without describing the phenotypic overlap with CHS. We find that there is no discernable difference between CHS and SYS in clinical presentation or in genetic etiology. We propose that it would benefit patients, physicians and researchers to consider these disorders to be the same entity, and assimilate the patients into one phenotypic spectrum with a common etiology.

Based on the evidence provided here, the clinical differences between Chitayat-Hall and Schaaf-Yang syndromes reflect intra-syndrome variability. With regard to nomenclature, although Chitayat-Hall does have historical priority over Schaaf-Yang, as the clinical syndrome was reported two decades prior to the genetic associations of Schaaf and Yang, we agree with previous reports and propose the nomenclature become “MAGEL2-related disorders”, moving forward.[12] Importantly, our proposal does not abolish either designation, but allows for the incorporation and expansion of the clinical presentations of MAGEL2-mutations, thus allowing for the assimilation of future data if CHS and SYS truly have subtle clinical variations that were not observed in this analysis.

Based on the findings of McCarthy *et al.* and our mutational analysis, it seems likely that there are genotype-phenotype correlations in MAGEL2-related disorders, which could also contribute to the high intra-syndrome variability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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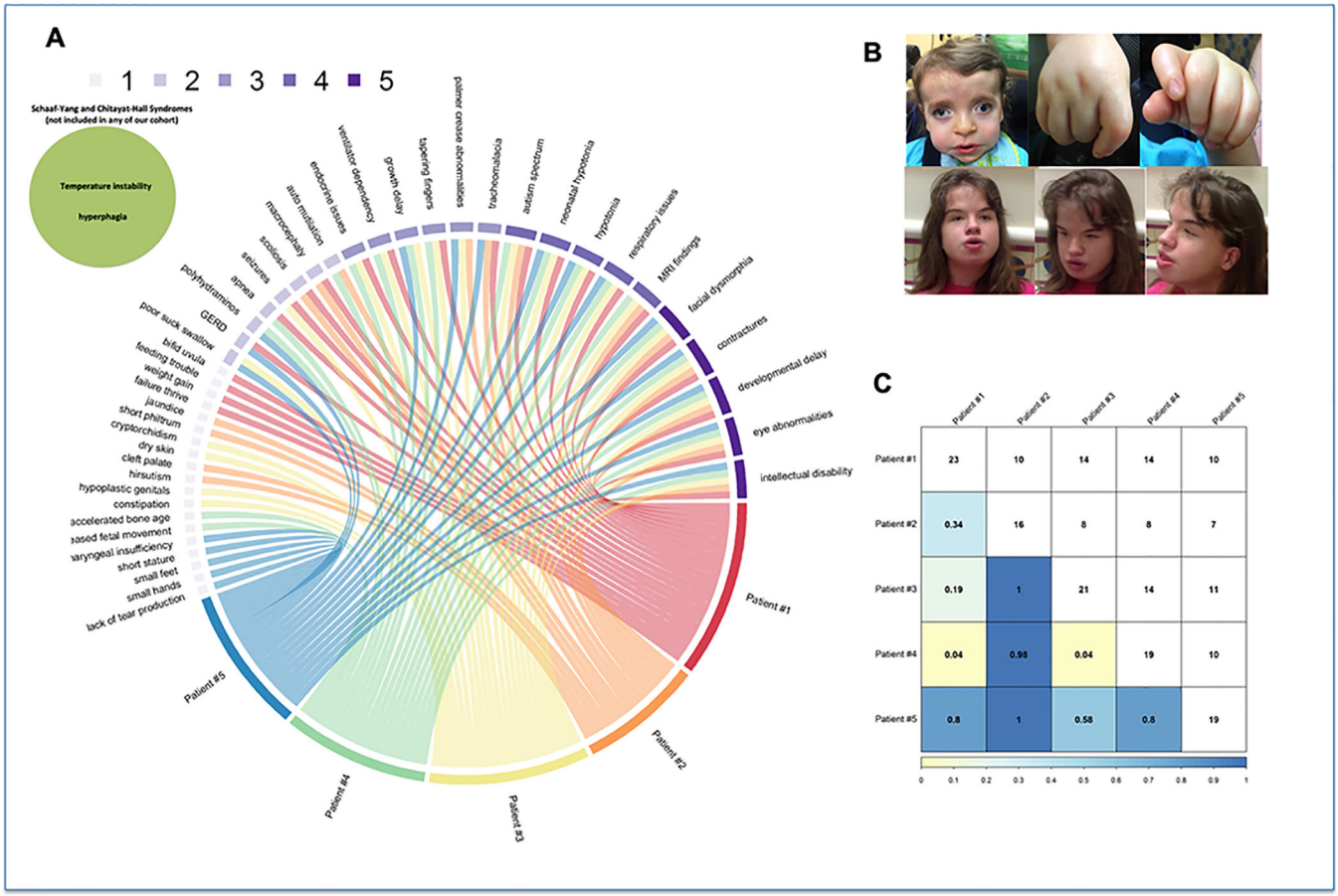

Figure 1.

Physical examination findings. A, Circos plot depicting the overlap between all the new patients in the cohort of this study. The lower hemisphere of the plot shows the patients' umbers and representative, arbitrarily assigned colors. The upper hemisphere has a list of the all symptoms summarized in these patients. The purple heat map under the symptoms represents the number of patients in this cohort with that respective symptom, with five being dark purple and representing all the patients, while one is white and representing a unique symptom. The separate green circle contains the clinical signs that have been previously documented for Schaaf-Yang syndrome and Chitayat-Hall syndrome that were not present in our cohort. B, The image panel with Patient 1 and 2 facial dysmorphia and Patient 1 camptodactyly. C, Panel comparing the symptom overlaps of our cohort. The upper, white panels are the number of symptoms shared by the respective patients; thus, the diagonal panels represent the number of symptoms present in each patient. The lower colored panels are the P-values for the comparison between the respective patients. Due to the low sample size, it is not surprising that there is minimal significance. However, it does show that there is a high degree of intrasyndromic variability in our patients [Correction added on 29 August 2019, after first online publication: Figures 1 and 2 were previously switched and have been corrected in this current version.]

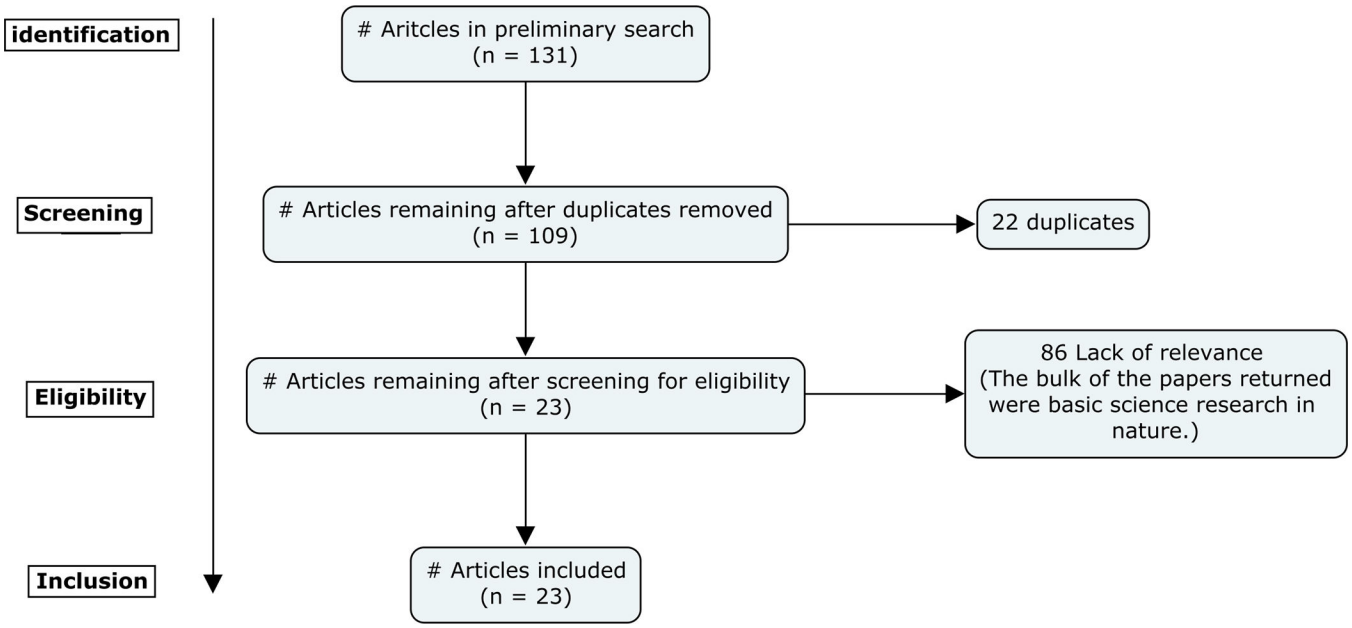

Figure 2.

PRISMA diagram for systematic review. A, Systematic review of the literature was undertaken to summarize the published case reports regarding Chitayat-Hall syndrome and Schaaf- Yang syndrome. This PRISMA diagram summarizes the findings from our systematic searches and how we filtered the results of those searches [Correction added on 29 August 2019, after first online publication: Figures 1 and 2 were previously switched and have been corrected in this current version.]

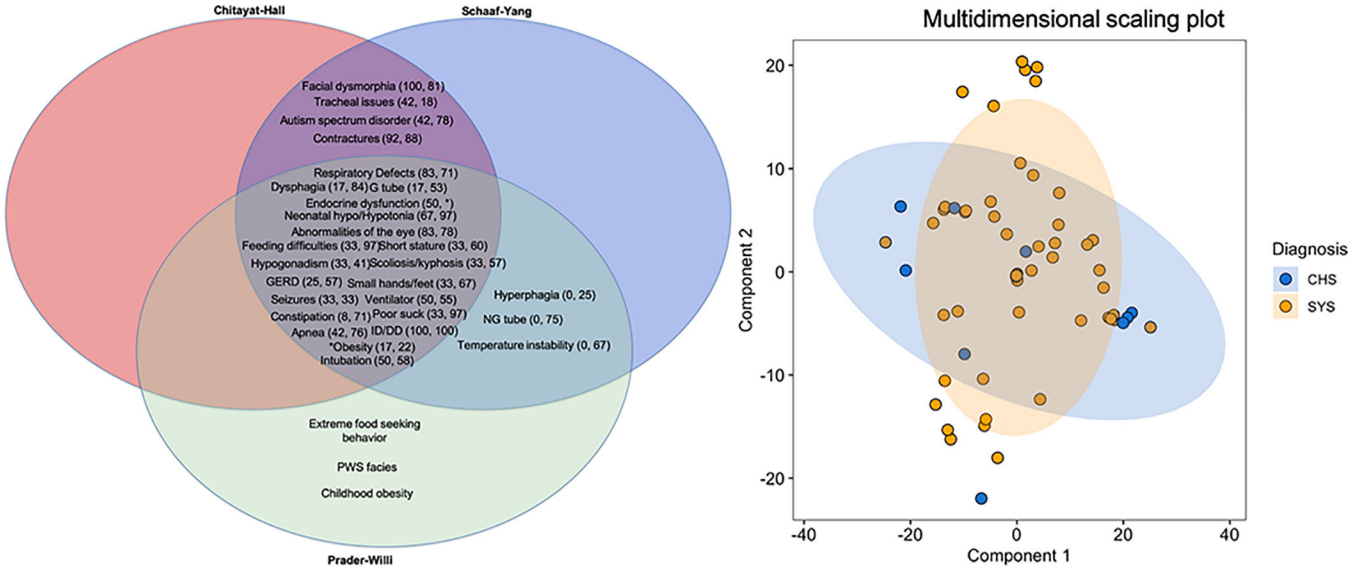

Figure 3.

Venn diagram and multidimensional scaling (MDS) plot comparing the clinical presentations of Chitayat-Hall syndrome (CHS), Schaaf-Yang syndrome (SYS) and Prader-Willi syndrome (PWS). All reported patients with CHS and SYS are summarized here. Within the parentheses indicates the percentages of patients with CHS and SYS, respectively, reported with the listed symptom. All the syndromes share many clinical features, which underlines their shared genetic etiology. There are a number of features that separate CHS and SYS from PWS, although the clinical differentiation can still be challenging for professionals. CHS and SYS seem to have most clinical features in common. Temperature instability remains underreported in CHS patients, to our knowledge, although the scoring principles for this specific presentation should be better defined. Hyperphagia is not typically reported for either CHS or SYS, but is present in the SYS population at low levels. Use of nasogastric (NG) tube has not been reported in CHS, to our knowledge, but other specialized techniques, such as gastronomy tubes, have been. Note: two reports of severe gastrointestinal malfunction have been reported for SYS. *Although it is now highly associated, endocrine dysfunction was underreported in SYS and a systematic review with respect to endocrine function in SYS patients is needed. The MDS plot shows that there is no segregation between CHS and SYS when unbiasedly comparing the symptoms of all patients and predicting the diagnosis. The x and y axes are the first two components derived from an MDS analysis of pairwise Euclidean distances between patients based on symptom data (CHS, n = 12; SYS, n = 67). Ellipses represent the 95% confidence intervals of the MDS scores for each diagnostic group

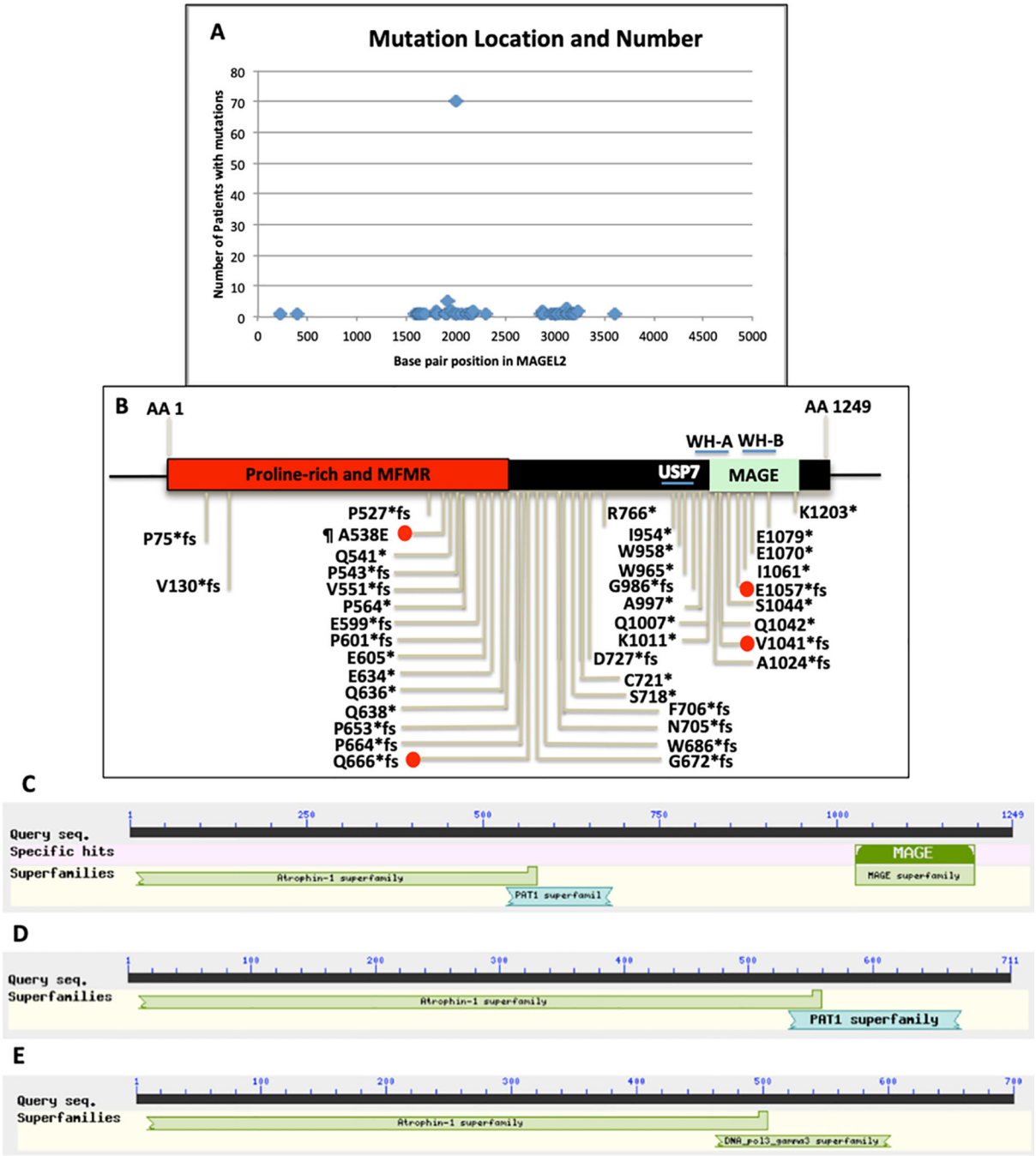

Figure 4.

Mutations in MAGEL2. A, This graph depicts all of the reported mutations in MAGEL2 summarized in the gene location. The highest peak represents the c.1996 region, which was predicted to contain a “mutational hotspot” and contains 70 patients. B, Image of the MAGEL2 protein and the representative locations of all the reported pathogenic mutations. The red dots indicate the mutations presented in this study. Note: there are four red dots, because two of our patients carried mutations in the 1996 base pair. C, Basic local alignment search tool (BLAST) results for native protein sequence for MAGEL2, which depicts the

predicted protein domains. D, BLAST results for the predicted protein product from MAGEL2 containing DupC frameshift mutation. The results suggest that the protein product would miss the MAGE homology domain, but retain the other domains, such as the Atrophin-1 and PAT1 domains. Note: this mutation results in a SYS phenotype. E, BLAST results for the predicted protein product of the MAGEL2 containing DelC mutation. The resulting protein product not only lacks the MAGE domain, but also has a change in PAT1 domain, resulting in a new DNA Pol3 gamma domain. Note: this mutation is not compatible with life. ¶Indicates the position of the first missense mutation ever reported. *Mutations that result in termination of protein translation

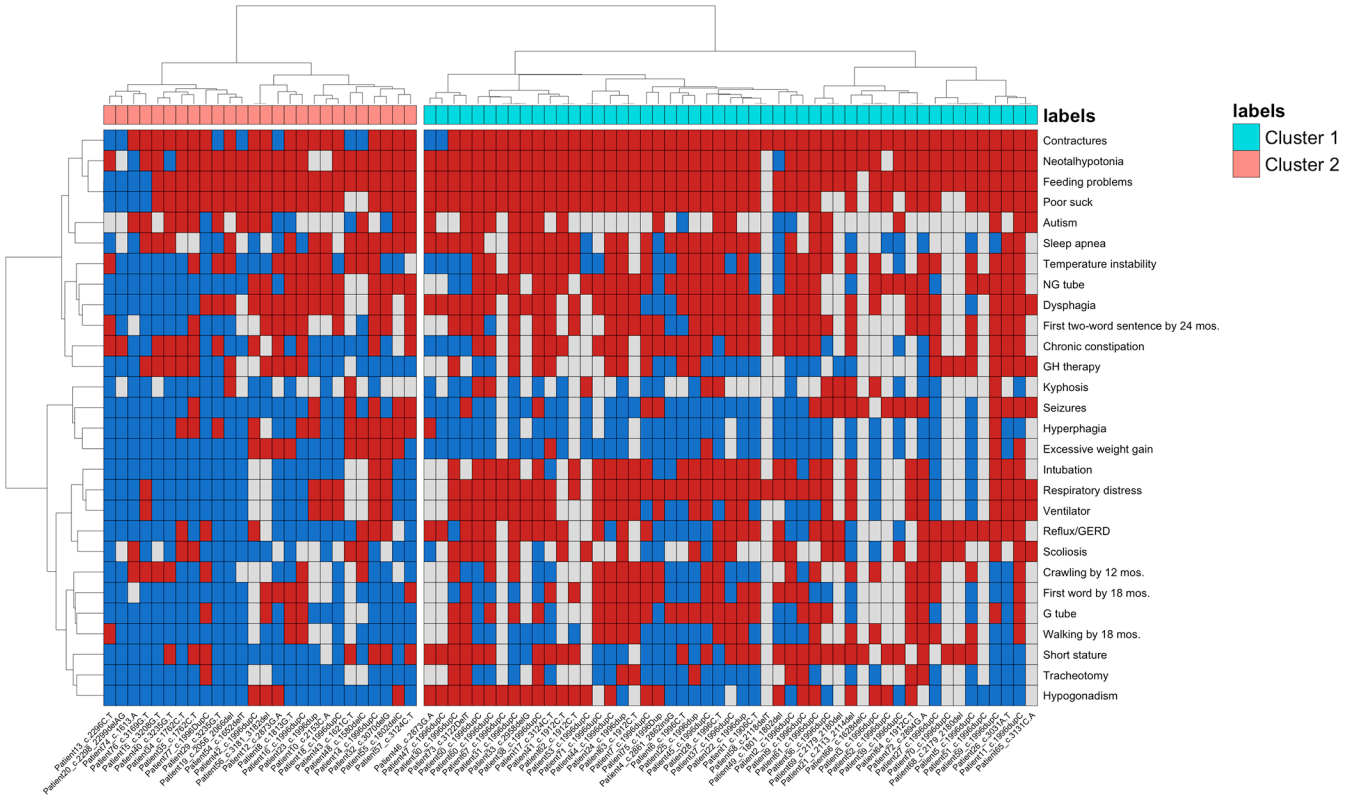

Figure 5.

Dendrogram of hierarchical clustering of symptoms. We modeled the patient symptom data from McCarthy et al9 and added our cohort, using hierarchical clustering and a two-cluster system based on the above dendrogram to predict patient genotype. Thus, this dataset includes all SYS patients and all CHS patients with confirmed MAGEL2 mutations. The 1996DupC is the only mutation that disproportionately clusters (Cluster 1, 83.3%). The symptoms were unable to decipher between frameshift or termination mutations using this same two-cluster methodology. No other solutions were attempted. The data were based on a questionnaire, and red blocks indicate reported symptoms, while blue blocks indicate symptoms not present. White blocks indicate missing data. The columns represent de-identified patients assigned a number and tagged with their respective mutation (bottom label). The patient's symptoms are the rows. Cluster 1 patients are on the right side of the graph, indicated by the teal demarcating blocks across the top of the graph; while Cluster 2 patients are found on the left side and indicated by the pink blocks

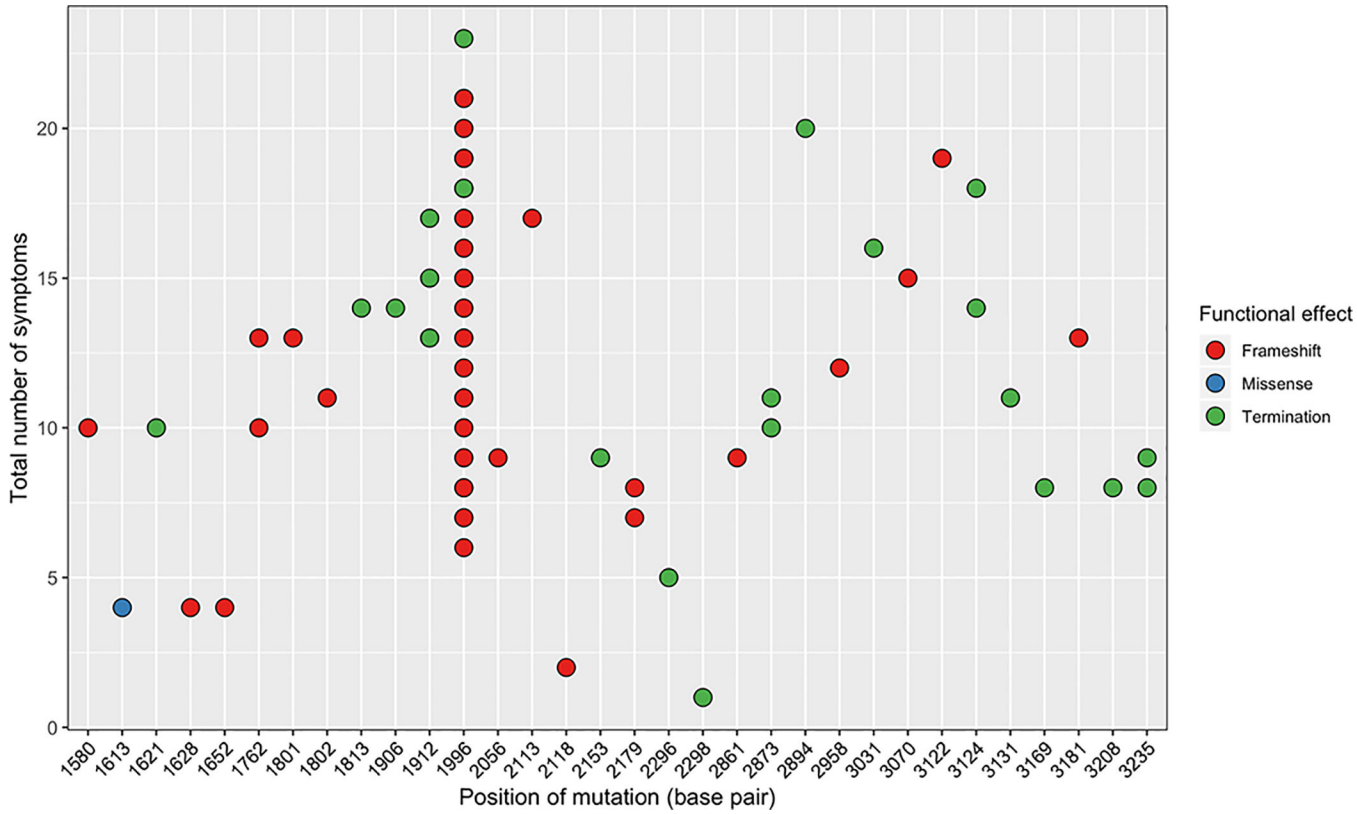

Figure 6.

Number of symptoms based on mutation location. The cDNA position of each mutation and the number of symptoms reported for that respective mutation is reported in McCarthy et al9 dataset and our patient cohort. Similar to McCarthy et al,[9] we report a significant increase in severity for patients that carry a 1996DupC mutation, based on the number of symptoms reported

Table 1.

Patient-Symptom Summary.

Symptom	Patients and source publication							
	1–78 (McCarthy, 2018) n/N*	79 (Hidalgo-Santos, 2018)**	80, 81 (Chitayat, 1990)	82, 83 (Chitayat, 1991)	84 (Wortmann, 2007)	85 (Smigiel, 2010)	86 (Rao, 2013)	87–91 (New)
Intellectual Disability/ Developmental delay	70/70 (100%)	X	2/2	2/2	X	X	X	5/5
ASD Diagnosis	25/32 (78%)	X	N/A	N/A	N/A	X	N/A	4/5
Seizures	21/64 (33%)	N/A	1/2	N/A	X	***AbnormEEG	N/A	2/5
Apnea	38/50 (76%)	N/A	N/A	2/2	N/A	X	N/A	2/5
Temperature Instability	40/60 (67%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Respiratory Distress/Defects	41/58 (71%)	N/A	2/2	2/2	X	X	X	4/5
Intubation	32/55 (58%)	N/A	2/2	1/2	N/A	N/A	N/A	3/5
Mechanical Ventilator	30/55 (55%)	N/A	2/2	1/2	N/A	N/A	N/A	3/5
Tracheostomy/ Tracheal Issues	9/50 (18%)	N/A	1/2	N/A	N/A	X	N/A	3/5
Feeding Issues	69/71 (97%)	X	1/2	N/A	N/A	N/A	X	1/5
Poor Suck in Infancy	62/64 (97%)	N/A	1/2	N/A	N/A	N/A	X	2/5
Dysphagia	48/57 (84%)	X	N/A	N/A	N/A	N/A	X	1/5
Hyperphagia	14/56 (25%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Use of NG tube	45/60 (75%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Use of G tube	28/53 (53%)	N/A	N/A	N/A	N/A	N/A	N/A	2/5
Excessive Weight Gain	13/60 (22%)	N/A	N/A	1/2	N/A	N/A	N/A	1/5
Reflux/GERD	34/60 (57%)	X	N/A	N/A	N/A	N/A	N/A	2/5
Chronic Constipation	39/55 (71%)	N/A	N/A	N/A	N/A	N/A	N/A	1/5
Neonatal Hypotonia/ hypotonia	66/68 (97%)	X	2/2	N/A	X	N/A	X	4/5
Scoliosis	26/46 (57%)	N/A	N/A	1/2	N/A	X	N/A	2/5
Kyphosis	12/37 (32%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Contractures	69/78 (88%)	N/A	2/2	2/2	X	X	X	4/5
Hypogonadism	26/64 (41%)	N/A	1/2	1/2	N/A	X	N/A	1/5
Eye Abnormalities	11/14 (78%)	X	2/2	N/A	X	X	X	5/5
Dysmorphia	16/18 (81%)	X	2/2	2/2	X	X	X	5/5
Hypopituitarism	N/A	N/A	2/2	N/A	N/A	X	X	1/5

Symptom	Patients and source publication							
	1–78 (McCarthy, 2018) n/N*	**79 (Hidalgo-Santos, 2018)****	**80, 81 (Chitayat, 1990)**	**82, 83 (Chitayat, 1991)**	**84 (Wortmann, 2007)**	**85 (Smigiel, 2010)**	**86 (Rao, 2013)**	**87–91 (New)**
Growth Hormone Deficiency	N/A	X	2/2	N/A	N/A	N/A	N/A	1/5
Small Hands	12/14 (72%)	N/A	1/2	1/2	N/A	X	N/A	1/5
Small Feet	8/15 (61%)	N/A	2/2	1/2	N/A	N/A	N/A	1/5
Short Stature	10/16 (60%)	X	1/2	1/2	X	N/A	N/A	1/5
Endocrine Issues	N/A	X	1/2	N/A	N/A	X	X	3/5
Brain MRI findings	N/A	N/A	1/2	1/2	X	X	N/A	4/5
Increased Fatty Tissue	N/A	N/A	2/2	2/2	X	N/A	N/A	N/A
Cortical Blindness	N/A	N/A	1/2	N/A	N/A	N/A	N/A	N/A
Self-Injurious Behavior	7/12 (56%)	N/A	N/A	1/2	N/A	N/A	N/A	1/2
Decreased Fetal Movement	6/15 (60%)	N/A	N/A	1/2	N/A	N/A	X	1/5
Hirsutism	N/A	N/A	N/A	N/A	X	N/A	N/A	1/5

If McCarthy et al. did not report a symptom, Fountain et al, the largest case series on SYS next to McCarthy et al., was used as a surrogate.

*McCarthy *et al.* is a review article that summarizes all the reported patients with SYS, as of early 2018. If a citation was missing from the review, i.e. was published after, we included it in our review. Some symptoms were not reported in McCarthy *et al.* that were reported in Fountain *et al.* (the second largest case series of SYS. When a symptom was not present in McCarthy, the number of patients for that symptom was taken from Fountain *et al.* n = number of reported; N = total number in that cohort.

**Hildalgo-Santos, 2018 was a report of a patient with Schaaf-Yang syndrome that was not reported previously.

***Although no seizures were reported for this patient, they did report an abnormal EEG.