

## ORIGINAL ARTICLE

# Clinical findings from the landmark *MEF2C*-related disorders natural history study

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## Abstract

**Introduction:** *MEF2C*-related disorders are characterized by developmental and cognitive delay, limited language and walking, hypotonia, and seizures. A recent systematic review identified 117 patients with *MEF2C*-related disorders across 43 studies. Despite these reports, the disorder is not easily recognized and assessments are hampered by small sample sizes. Our objective was to gather developmental and clinical information on a large number of patients.

**Methods:** We developed a survey based on validated instruments and subject area experts to gather information from parents of children with this condition. No personal identifiers were collected. Surveys and data were collected via REDCap and analyzed using Excel and SAS v9.4.

**Results:** Seventy-three parents completed the survey, with 39.7% reporting a *MEF2C* variant and 54.8% reporting a deletion involving *MEF2C*. Limited speech (82.1%), seizures (86.3%), bruxism (87.7%), repetitive movements (94.5%), and high pain tolerance (79.5%) were some of the prominent features. Patients with *MEF2C* variants were similarly affected as those with deletions. Female subjects showed higher verbal abilities.

**Conclusion:** This is the largest natural history study to date and establishes a comprehensive review of developmental and clinical features for *MEF2C*-related disorders. This data can help providers diagnose patients and form the basis for longitudinal or genotype–phenotype studies.

## KEYWORDS

*MEF2C*, *MEF2C*-related disorders, natural history study, neurodevelopmental, parent survey, social media research

## 1 | INTRODUCTION

*MEF2C*-related disorders, also known as *MEF2C* haploinsufficiency syndrome or 5q14.3 microdeletion syndrome (OMIM #613443), are neurodevelopmental disorders characterized by developmental delay, intellectual disability, lack of verbal language, limited walking, hypotonia, and seizures (Paciorkowski et al., 2013). Originally, patients with this phenotype were found to have microdeletions of the 5q14.3 region, with most including the *MEF2C* gene (OMIM\*600662). Eventually, *MEF2C* was identified as the causative gene after patients were reported with microdeletions only encompassing *MEF2C* (Novara et al., 2010; Nowakowska et al., 2010) as well as another patient with a nonsense variant in *MEF2C* (Le Meur et al., 2010). There have also been some cases reported in patients with a similar phenotype that had microdeletions in the proximal or distal region closely surrounding but not including the *MEF2C* gene (Cardoso et al., 2009; Engels et al., 2009). It is hypothesized that these deletions may disrupt the regulation and expression of *MEF2C*, and therefore cause the same phenotype. Interestingly, some patients with *MEF2C* variants and microdeletions not only had diminished *MEF2C* expression, but also diminished *CDKL5* and *MECP2* expression, indicating a shared molecular pathway (Zweier et al., 2010). Although the phenotype has some overlap to Rett syndrome, patients do not typically have regression and would not meet current criteria for the diagnosis of Rett syndrome (Neul et al., 2010).

A recent systematic review of the literature revealed 43 manuscripts describing 117 patients with a *MEF2C*-related disorder reported to date (Cooley Coleman et al., 2021). Most publications report only one or a few patients, with the largest cohort being 17 new patients in one publication (Raviglione et al., 2021). Despite the phenotypic information provided, the disorder is not easily recognized clinically. Additionally, the disorder has only been described for just over a decade, a much shorter time than other similar, but well-characterized, neurodevelopmental disorders, such as Rett syndrome, prompting the need to further characterize the disorder. We conducted a natural history study in the form of a parent survey to gather additional data and improve the clinical description of the disorder. This is the largest cohort to date containing parent-reported phenotype information about *MEF2C*-related disorders. The information revealed by the survey further characterizes the disorder, aids providers in recognizing, diagnosing, and treating patients, and illuminates features not previously reported.

## 2 | METHODS

### 2.1 | Ethical compliance

The study was approved by the Self Regional Healthcare IRB (Pro00091979). No personally identifiable information was collected. IRB approval was shared with the Clemson University IRB. No additional IRB approval was required by Clemson University.

### 2.2 | Survey development

Survey development commenced in January 2019. The Rett Syndrome Natural History Study (Percy, 2017, 2021) and the Fragile X Online Registry with Accessible Research Database (FORWARD) (Sherman et al., 2017) surveys were used as guides to help develop appropriate survey questions. The draft of the survey was piloted by four parents of children with *MEF2C*-related disorder. These parents were asked for feedback and any additional question suggestions. The final survey contains 81 questions on demographic information, developmental history, medical issues, and symptoms. The survey questions were vetted by a team of clinical and research experts from the Greenwood Genetic Center (GGC), Clemson University, and the Medical University of South Carolina (MUSC). The final version was then loaded into REDCap (Research Electronic Data Capture) (Harris et al., 2009) for online survey distribution. The questionnaire may be made available upon request.

### 2.3 | Recruitment

The survey was opened for online data collection in January 2020. Any patient with a previously reported *MEF2C* alteration (variant, deletion, and duplication) met the criteria for this study. The research team had a goal of 50 survey responses. Parents, relatives, and guardians or caregivers of a child with a *MEF2C*-related disorder were made aware of the survey via an IRB-approved advertising script posted to the Facebook support group “MEF2C Medical Personnel and Families”. As of 04 August 2021, the Facebook group had over 350 worldwide members, including medical personnel, parents, and family. A reminder post was put on the Facebook support group twice, each about 2 months apart from the last post, for a total of three advertising posts. Additionally, two parents shared the advertising script and survey link to the parents-only Facebook group “MEF2C Parent Support Group” on behalf of the research team. Although the survey remained

anonymous, informed consent was obtained electronically by each parent prior to starting the survey. The survey was closed in June 2020.

## 2.4 | Data analysis

Survey results were exported from REDCap into an Excel file. Descriptive statistical analysis, including percentages, means, and standard deviations (*SDs*) were performed using both Excel and SAS v9.4. Categorical analyses (between alteration type or gender, and anxiety, hyperactivity, seizures, abnormal MRI, use of words for communication, and walking) were assessed with chi-square tests or, when cell counts were small, Fisher's Exact test. Ordinal analyses (between age group and anxiety, hyperactivity, seizures, abnormal MRI, use of words for communication, and walking) were assessed using the Cochran–Armitage trend test. For tests of association, alteration type was divided into two categories of variant (SNV/point mutation/INDEL) or deletion (large deletion/CNV). There were no participants reporting a large duplication. Patients with an uncertain type of pathogenic alteration were excluded from the analysis. Gender was male or female, and age group consisted of infant (9 months to <24 months), preschool (2 years to <6 years), child (6 years to <13 years), adolescent (13 years to <19 years), and adult (19 years to <45 years). The dichotomous choice for the use of words for communication, anxiety, hyperactivity, seizures, abnormal MRI, and walking was either yes or no. Missing data were omitted from the analysis. Chi-square test, Fisher's Exact test, and Cochran–Armitage trend test were carried out using SAS v9.4. A *p*-value < .05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Study population

A total of 108 survey records were available in REDCap. There were 35 incomplete records of which the majority had only answered one question before closing the survey. Only three of the incomplete records were at least 50% completed. These incomplete records were excluded and data analysis proceeded only on the 73 complete survey responses. All 73 completed responses (100%) were submitted by a parent who had a child with a *MEF2C*-related disorder (vs. relative or guardian/caregiver).

Of the 73 parent-completed survey results, 35 reported having a female child (48%) and 38 reported having a male child (52%) with a *MEF2C*-related disorder. The majority of children (91.7%) were reported to be

of White race and not of Hispanic, Latino, or Spanish ethnicity. Mother's age at the child's birth ranged from 20 to 41 years of age (mean 31.8 years, *SD* = 5.12). The children's current age at the time of the survey ranged from 9 months to 38 years (mean 8.12 years, *SD* = 7.21). BMI was calculated based on parent-reported height and weight, and 46.6% fell within the normal/healthy weight category (Table 1). Nearly 33% (22/67) had short stature, with a height falling below the third percentile compared to individuals of the same sex and age in the general population.

Of the 73 patients, 29 (39.7%) reported a *MEF2C* variant (point mutation or INDEL), 40 (54.8%) reported a deletion involving the *MEF2C* gene, and four (5.5%) were uncertain of the pathogenic alteration at the time of taking the survey. There were no reported large duplications and only one small duplication (six base pairs) in the INDEL category. About 33% of parents provided the specific variant nomenclature or deletion coordinates (16 variant and 8 deletion). Of the variants reported, seven fell within the MADS domain, one was in the MEF2 domain, and the remaining eight variants were downstream of these two domains. Reported deletions ranged in size from 217 KB to 8 MB, including anywhere from one or a few exons to the entire gene being deleted. Other parents gave a description of what they remembered, such as “location of stop codon is halfway, not at the end of the gene” or “217k deletion of 5q14.3”.

### 3.2 | Maternal pregnancy history

Twenty-five parents (34.2%) reported pregnancy exposures, which included tobacco (8.2%), secondhand smoke (8.2%), alcohol (5.5%), chemicals (1.4%), prescription medicines (12.3%), and other (9.6%; Table S1). Of these exposures, only tobacco use was higher, albeit only slightly, as compared to the 7.2% in the general population that reported smoking during pregnancy (Drake et al., 2018). Thirty parents (41.1%) reported pregnancy complications, including premature labor (8.2%), preeclampsia (5.5%), low amniotic fluid (1.4%), gestational diabetes (4.1%), illness (5.5%), and other (26.0%; Table S1). These percentages were less than or in range with percentages seen in the general population. Thirty-five parents (47.9%) reported birth complications, including breech position (8.2%), failure to progress (11.0%), fetal meconium aspiration (5.5%), fetal distress (19.2%), and other (21.9%; Table S1). Of note, the percentage of breech position and fetal distress were higher in our cohort as compared to the general population (3–4% and about 4%, respectively, in the general population) (Gray & Shanahan, 2021; Hoque, 2011). Fifty-five (75.3%) mothers carried their child to full term (delivery

**TABLE 1** Demographic, physical, and genetic information reported by parents regarding their child with *MEF2C*-related disorder

	Totals (N = 73)
Child's gender	
Female	35 (47.9%)
Male	38 (52.1%)
Ethnicity	
Hispanic, Latino, or Spanish origin	6 (8.2%)
Not Hispanic, Latino, or Spanish origin	63 (86.3%)
Unknown	4 (5.5%)
Race	
White or Caucasian	67 (91.7%)
Black or African American	3 (4.1%)
Asian	1 (1.4%)
American Indian or Alaskan Native	1 (1.4%)
Unknown	1 (1.4%)
Mother's age when child was born	
Average	31.8 yr ( <i>SD</i> 5.12 yr)
Range	20–41 yr
Father's age when child was born	
Average	33.6 yr ( <i>SD</i> 7.07 yr)
Range	21–57 yr
Child's birth weight	
Extremely low birth weight (less than 0.992 kg)	1 (1.4%)
Very low birth weight (between 0.993 kg and 1.616 kg)	0 (0%)
Low birth weight (between 1.617 kg and 2.495 kg)	13 (17.8%)
Normal birth weight (between 2.496 kg and 3.997 kg)	57 (78.1%)
High birth weight (greater than 3.997 kg)	2 (2.7%)
Child's current age	
Infant (9 months to <24 months)	8 (11.0%)
Preschool (2 years to <6 years)	36 (49.3%)
Child (6 years to <13 years)	11 (15.1%)
Adolescent (13 years to <19 years)	10 (13.7%)
Adult (19 years to <45 years)	8 (11.0%)
Average	8.12 yr ( <i>SD</i> 7.21 yr)
Range	9 mo – 38 yr
Child's current BMI	N = 58
Underweight	
(Child and Teen: less than 5th percentile; Adult: BMI below 18.5)	18 (31.0%)

**TABLE 1** (Continued)

	Totals (N = 73)
Normal/Healthy Weight	
(Child and Teen: 5th to less than 85th percentile; Adult: BMI of 18.5 to 24.9)	27 (46.6%)
Overweight	
(Child and Teen: 85th to less than 95th percentile; Adult: BMI of 25.0 to 29.9)	6 (10.3%)
Obese	
(Child and Teen: 95th percentile or greater; Adult: BMI of 30.0 or greater)	7 (12.1%)
Genetic alteration	
<i>MEF2C</i> variant (point mutation/INDEL)	29 (39.7%)
Deletion involving the <i>MEF2C</i> gene	40 (54.8%)
Uncertain	4 (5.5%)

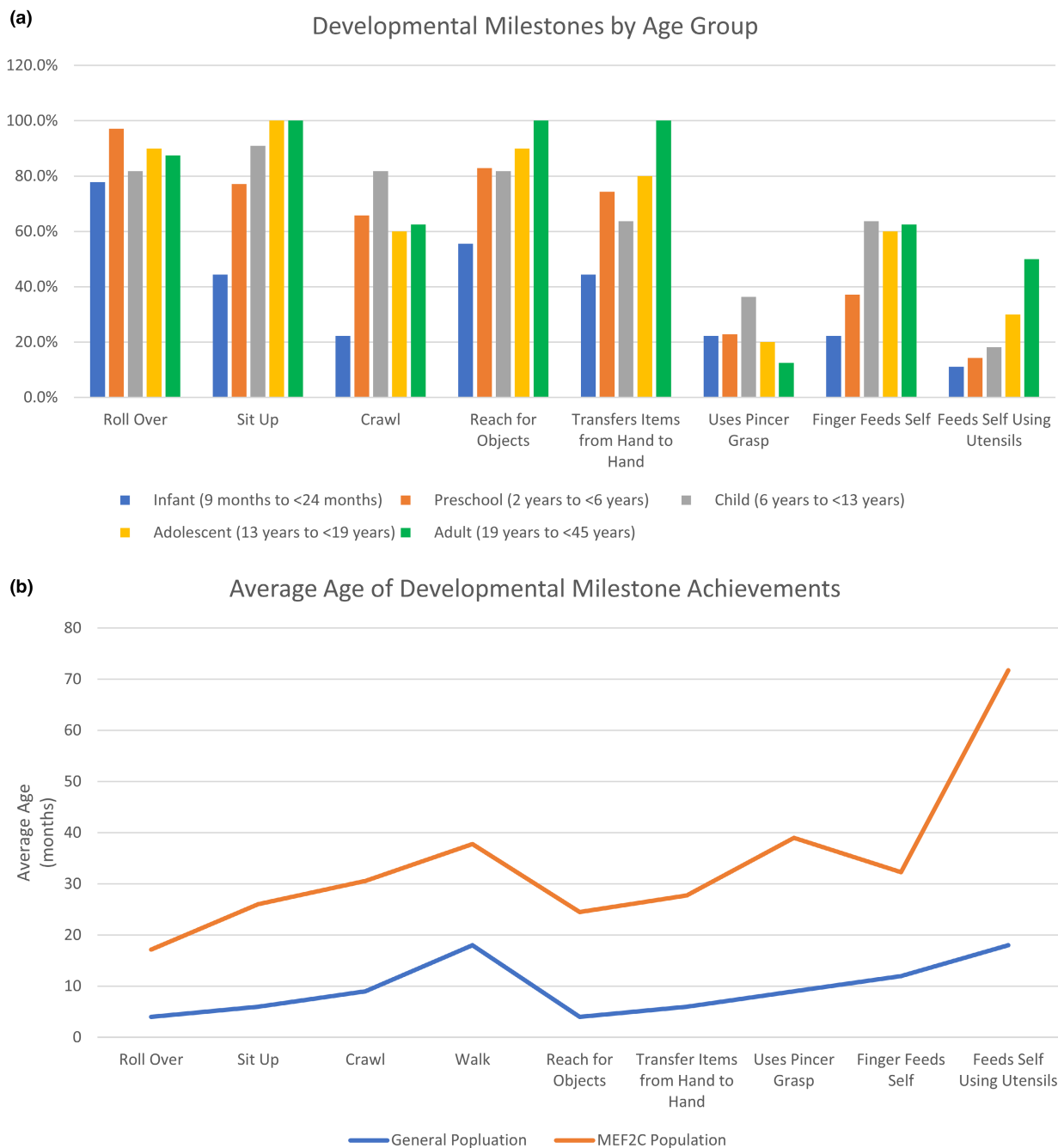
Abbreviation: *SD*, standard deviation.

between 38 and 42 weeks), whereas the remaining 18 (24.7%) reported a gestational age of before 38 weeks.

### 3.3 | Early development

Most children learned to roll over (90.4%), with this activity first occurring between 3 months of age and 10 years (mean 1.43 years, *SD* 1.57 years). Most children also learned to sit up (80.8%), with the first occurrence ranging between 6 months and 12 years (mean of 2.17 years, *SD* 2.15 years), 61.6% learned to crawl, ranging between 1 year and 16 years (mean of 2.55 years, *SD* 2.50 years), 50.7% of the children over 18 months of age had learned to walk, with first occurrence ranging between 1.33 and 6 years (mean of 3.15 years, *SD* 1.27 years).

By the time of the survey, most children learned some useful hand functions; 82.2% learned to reach for objects with first occurrence ranging between 2 months and 14 years (mean 2.04 years of age, *SD* 2.37 years), 72.6% learned to transfer items from hand to hand with first occurrence between 6 months and 11 years (mean 2.31 years, *SD* 2.13 years), 23.3% developed a pincer grasp with first occurrence between 9 months and 6 years of age (mean 3.25 years, *SD* 1.70 years), and 45.2% were able to finger feed themselves with first occurrence between 1 and 8 years of age (mean 2.69 years, *SD* 1.70 years). Lastly, 21.7% of the children over 18 months of age were able to feed themselves with utensils with first occurrence between 20 months and 14 years of age (mean 5.98 years, *SD* 4.31 years) (Table S2; Figure 1).



**FIGURE 1** Developmental milestones. (a) Percentages by age group. (b) Average age the milestone was achieved in this patient cohort with *MEF2C*-related disorders as compared to the general population (Hagan et al., 2017)

Only one child (1.4%) was reported to be both bowel and urine trained, and seven participants (9.6%) were time trained. The remaining 65 (89.0%) were not toilet trained.

### 3.4 | Communication skills

Of 29 children aged 6 years and older, 26 (89.7%) were reported to have intellectual disability. In addition, most were reported to have limited language, with 89.2% of children over 2 years of age lacking any spoken words

(Table 2). When assessing children over 5 years of age, the majority (82.1%) lacked any spoken words. Overall, only eight children were reported to use at least a small number of words for communication, one of whom was able to use a series of single words or two-word combinations meaningfully, and one was able to use phrases or sentences of three words or more.

There was not a significant difference between alteration types ( $p = .1194$ ), while there was a significant difference between gender ( $p = .0033$ ) and age groups ( $p = .0416$ ) showing that females and older subjects were

**TABLE 2** Child's developmental, language, and motor milestones as reported in the survey

Most recent milestone	Totals No. (%)
<b>Developmental</b>	<i>N</i> = 73
Roll over	66 (90.4%)
Sit up	59 (80.8%)
Crawl	45 (61.6%)
Reach for objects	60 (82.2%)
Transfer items from hand to hand	53 (72.6%)
Pincer grasp	17 (23.3%)
Finger feed self	33 (45.2%)
Feed self using utensils (>18 months of age)	15 (21.7%)
<b>Toileting</b>	<i>N</i> = 73
Both bowel and urine trained	1 (1.4%)
Bowel or urine trained only	0 (0.0%)
Time trained	7 (9.6%)
Not toilet trained	65 (89.0%)
<b>Language</b>	<i>N</i> = 73
Nonverbal/no signs	26 (35.6%)
Nonverbal but using signing in a meaningful way	6 (8.2%)
Babbling/vocalizations	33 (45.2%)
A small number of words or signs for minimal communication	6 (8.2%)
Series of single words or two-word combinations used meaningfully	1 (1.4%)
Phrases/sentences of three words or more	1 (1.4%)
<b>Alternate communication methods</b>	<i>N</i> = 71 <sup>a</sup>
Signing	14 (19.2%)
Picture exchange communication system (PECS) or equivalent	19 (26.0%)
Apps on an iPad/iPhone, smart phone, or tablet	9 (12.3%)
Augmentative communication device	12 (16.4%)
Other (hand leading, singing nursery rhymes, and vocalizations for agreement, annoyance, and attention)	4 (5.5%)
None of the above	36 (49.3%)
<b>Motor abilities</b>	<i>N</i> = 73
Unable to roll	1 (1.4%)
Rolls	4 (5.5%)
Sits with support	8 (11.0%)
Sits unaided	9 (12.3%)
Crawls	4 (5.5%)
Stands with support	7 (9.6%)
Stands unaided	0 (0.0%)
Walks with support	12 (16.4%)
Walks unaided	22 (30.1%)
Runs unaided	6 (8.2%)

<sup>a</sup>A total of 71 parents answered this question with 18 using more than one type of alternate speech method; therefore, the total counts and percentages look to exceed 71/100%.

more likely to use words to communicate (Figure 2, Table S3). Interestingly, all eight patients able to use words to communicate were female with their current ages ranging from infancy (<24 months) to adulthood. Alternate speech methods used included signing (19.2%), picture exchange communication system (PECS) or equivalent (26.0%), apps on an iPad/iPhone, smartphone, or tablet (12.3%), and augmentative communication device (16.4%), with some patients (18 of 71, or 25.4%) using more than one type. Nearly 18% pointed, 30.1% used gestures or waves, and 38.4% were reported to follow one-step or simple commands. Of those over 2 years of age, 25 (39.1%) were non-verbal and not using signs. Additionally, 16 of these 25 did not report using any alternate communication methods.

### 3.5 | Motor milestones

Assessing the highest motor milestone obtained, 40.5% of children over 18 months of age were able to run or walk without support, 17.4% were able to walk with support, and the remaining 42.0% were unable to walk (Table 2). A higher percentage of females (57.1%) compared to males (39.5%) had learned to walk; however, the difference between males and females learning to walk was not significant ( $p = .0867$ ). Similarly, a higher percentage of patients with variants (58.6%) compared to those with large deletions (42.5%) had learned to walk but the difference was also not significant ( $p = .2083$ ). There was a significant association between being able to walk and age group ( $p = .0483$ ) (Table S4). This is expected, as walking is a milestone met with increasing age. With each age group, the percentage of those able to walk generally increased, with 75% of those in the adult group being able to walk (Figure 2).

Of those six who were able to run unaided, 50% were unsteady when walking. Of the 22 who were able to walk unaided, 95.5% were reported to be unsteady when walking. Of the 12 who were able to walk with support, 100% were reported to be unsteady when walking. Most had seemingly low muscle tone (72.6%), whereas 19.2% reported normal muscle tone, and 8.2% reported increased muscle tone.

### 3.6 | Social characteristics

Fifty of the children (68.5%) were reported to like giving affection, and 58 liked receiving affection (79.5%). The majority (71.2%) could recognize family members. Forty of the children (54.8%) reported to typically resist holding someone's hand. Fifty-three (79.1%) were reported to have a reduced concern with an environmental threat

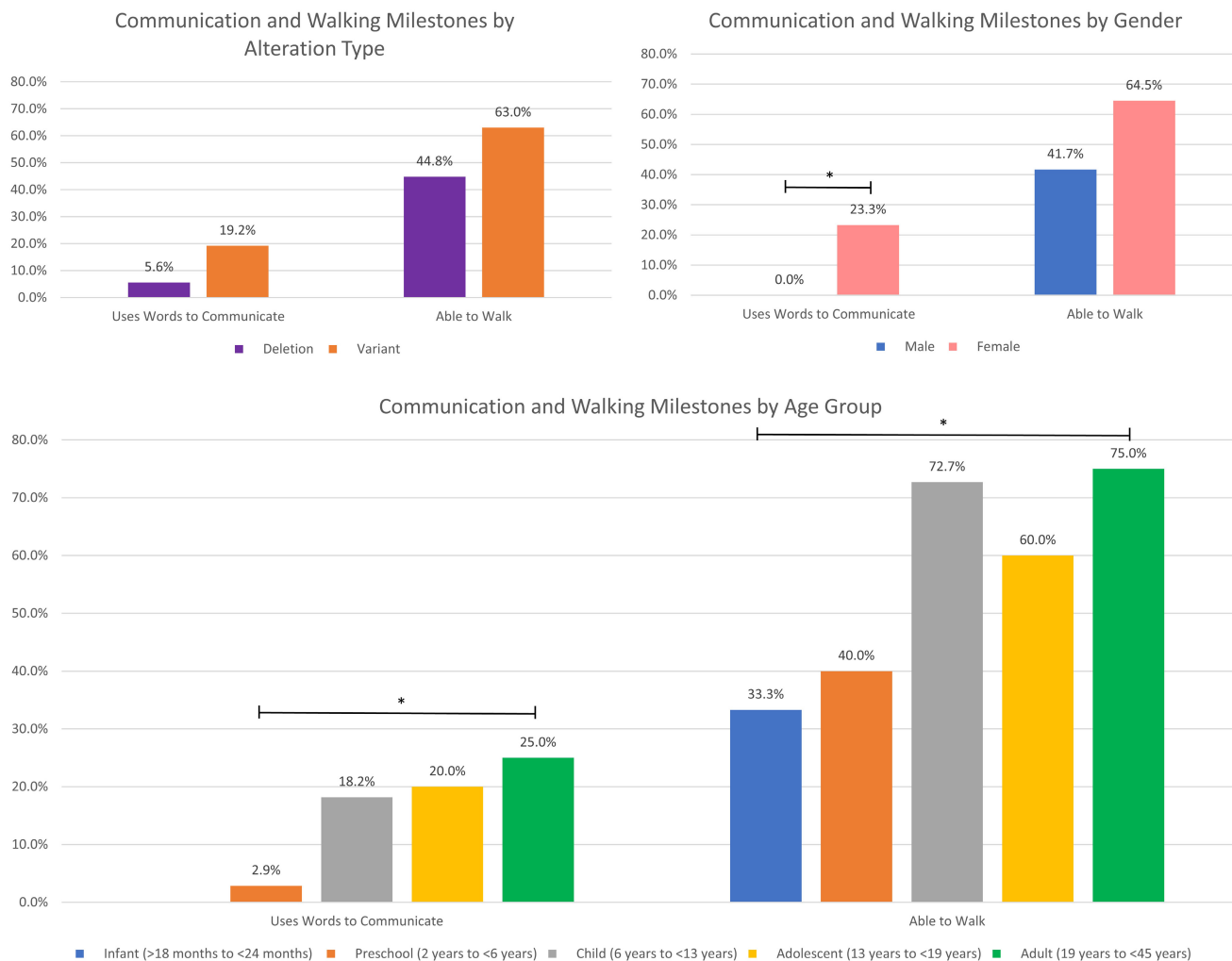


FIGURE 2 Communication and walking milestones by alteration type, gender, and age group. \*Significant at  $p < .05$

(i.e.: walks off, explores, lack of “stranger danger”) and 34 (46.6%) actively sought social interaction. Poor eye contact and attention problems were reported in over half (60.3% and 70.4%, respectively); however, hyperactivity and anxiety were not as common (37.5% and 17.1%, respectively). For hyperactivity and anxiety, there was not a significant difference in gender ( $p = .9515$ ;  $p = .3936$ ), alteration type ( $p = .0807$ ;  $p = .3936$ ), or age group ( $p = .5971$ ;  $p = .6655$ ) (Table S5). Nearly one-fourth (25.7%) reported that their child had been diagnosed with autism spectrum disorder.

### 3.7 | Sensory systems

Forty-four (61.1%) reported vision impairments, which included myopia (27.3%), hyperopia (29.5%), problems with depth perception (38.6%), cortical visual impairment (38.6%), strabismus (47.7%), and other issues (15.9%: esotropia, nystagmus, astigmatism). Hearing impairments were less common (8.3%), and included bilateral

sensorineural hearing loss, deafness in one ear, mild to moderate loss of certain tones, and moderate mixed hearing loss. Additionally, 61.6% reported sensitivity to loud noises. Few reported sensitivity to clothing textures (6.8%). Food textures sensitivities were slightly more common (36.1%). The parents also noted their child had issues with chewing and swallowing, and therefore preferred soft or pureed foods. Many reported sensitivity to heat (27.4%), cold (4.1%), or both (23.3%). Lastly, 58 (79.5%) reported a high pain tolerance.

### 3.8 | Other system symptoms

Many parents reported their child has trouble falling asleep (42.5%) and staying asleep (49.3%). Sleep medications were reported by 38.4% and included melatonin, Zonergan, Cicardin, clonidine, gabapentin, trazadone, cyproheptadine, in addition to essential oils and CBD and CBN oil. Medical conditions, digestion issues,

**TABLE 3** Symptoms (including medical, digestive, immunological, and neuropsychological) as reported by the parents about their child with *MEF2C*-related disorder

Symptoms reported	Totals (N = 73) No. (%)
Sleep issues	
Trouble falling asleep	31 (42.5%)
Trouble staying asleep	36 (49.3%)
Medical conditions	
Diabetes	0 (0.0%)
Congenital heart defect	5 (6.8%)
Asthma or other respiratory issues	8 (11.0%)
Thyroid problems	1 (1.4%)
Sleep apnea	4 (5.5%)
Other	24 (32.9%)
None	41 (56.2%)
Digestion issues	
Diarrhea	10 (13.7%)
Constipation	52 (71.2%)
Reflux	30 (41.1%)
Gall bladder dysfunction	0 (0.0%)
Abdominal distention/bloating	10 (13.7%)
Other	9 (12.3%)
None	11 (15.1%)
Recurrent immune-related problems or frequent illness	31 (42.5%)
Frequent illnesses	26/31 (83.9%)
Frequent fevers	13/31 (41.9%)
Severe allergic reactions	3/31 (9.7%)
Joint inflammation	0/31 (0.0%)
Skin issues (such as eczema)	9/31 (29.0%)
Other	6/31 (19.4%)
Seizures	63 (86.3%)
Generalized	16/63 (25.4%)
Partial	5/63 (7.9%)
Febrile	21/63 (33.3%)
Other	17/63 (27.0%)
Unknown	3/63 (4.8%)
Not answered	1/63 (1.6%)
Puberty	19 (26.0%)
Scoliosis	9 (12.3%)
Hyper-flexibility of fingers, hips, joints, etc.	52 (71.2%)
Regressions in development	25 (34.2%)
Neuropsychological	
Tremors	22 (30.1%)
Hyperventilation	22 (30.1%)

**TABLE 3** (Continued)

Symptoms reported	Totals (N = 73) No. (%)
Breath holding	25/72 (34.7%)
Aerophagia	19/72 (26.4%)
Food pocketing	27/72 (37.5%)
Chewing or swallowing problems	48 (65.8%)
Bruxism	64 (87.7%)
Repetitive hand movements	69 (94.5%)
Obsessive fascination with water	50/72 (69.4%)

immunological, and neuropsychological issues are reported in [Table 3](#) and [Table S1](#). Two parents reported that their children are 100% fed via gastrostomy tube.

Puberty typically occurs between 11 and 14 years of age (Hagan et al., 2017). Nineteen (26.0%) parents reported their child had gone through puberty; seven (36.8%) started puberty before 11 years of age, 10 (52.6%) started puberty between the typical ages of 11–14 years of age, and 1 (5.3%) started puberty after the age of 14. Of those who had not yet started puberty, the majority (96.3%) were under the age of 11, one patient (1.85%) was within the 11–14-year range, and one patient (1.85%) was over the 11–14-year.

Immunological issues are reported in [Table 3](#). “Other” frequent illnesses that the parents described included respiratory infections, tonsillitis, frequent colds and pneumonia, and chronic ear infections. Interestingly, a few parents reported some improvements in developmental skills when the child has a fever (16.4%).

Seizures were reported by 63 parents (86.3%); there was not a significant difference between alteration type ( $p = .3928$ ), gender ( $p = .4114$ ), or age group ( $p = .8165$ ) for having seizures ([Table S6](#)). Seizure types included generalized (25.8%), partial (8.1%), febrile (33.9%), and other (27.4%; multiple seizure types, absence, atonic, myoclonic seizures, atypical complex febrile, infantile spasms, and generalized tonic-clonic). The onset of seizures ranged from the postnatal period up to 9 years of age. The average onset age of seizures was 1.08 years old ( $SD$  1.28 years). Many parents reported that their child’s seizures were under control, and they were no longer having seizures occurring regularly as of the time of the survey (44.4%). For those having seizures currently, 10 (16.4%) reported their child has more than one seizure a day, seven (11.5%) reported daily seizures, one (1.6%) reported weekly seizures, two (3.3%) reported monthly seizures, and 13 (21.3%) reported seizures less than monthly. Thirty-eight parents (61.3%) reported their child takes medication for seizures and 37 of these parents (97.4%) reported the medications helped. Nineteen of the 38 (50%) reported the



use of multiple seizure medications. Many (20/38, 52.6%) reported using Keppra (levetiracetam). Other commonly used seizure medications are reported in Table S1. Two parents noted that the ketogenic diet has helped with their child's seizures. Types and frequencies of certain neuropsychological issues are reported in Table 3.

### 3.9 | Previous imaging reported

Most patients (69/72) previously had a brain MRI (95.8%) with 40 (58.8%) having abnormal results. These abnormal results included thinning of the corpus callosum, partial agenesis of the corpus callosum, enlarged ventricles, cerebral atrophy, suggestive Chiari malformation, dysmorphic basal ganglia, flattening of the pons, myelination delay, white matter atrophy, Blake's Pouch cyst, gray matter heterotopia, right amygdala lesion, cortical dysplasia, asymmetrical hippocampi, and excess fluid in the frontal lobe. There was not a significant difference in gender ( $p = .5411$ ), alteration type ( $p = .5951$ ), or age group ( $p = .0669$ ) for having an abnormal MRI (Table S7). Interestingly, 36 of 40 reported both abnormal MRI results and seizures.

## 4 | DISCUSSION

We presented phenotypic data collected from the parents of 73 patients with a *MEF2C*-related disorder, making this the largest study to date. Both children and adults were represented in the cohort. The most prominent features were limited speech (82.1% of children over the age of five not using words for communication), seizures (86.3%), bruxism (87.7%), repetitive hand movements (94.5%), and high pain tolerance (79.5%). Only eight patients (11.0%) were reported to use a small number of words, or a combination of words or phrases, to communicate, all of whom were female. Additionally, we found communication to be significantly associated with gender ( $p = .0033$ ) and age group ( $p = .0416$ ), with females and older subjects more likely to use words to communicate. Nearly 51% of children over 18 months of age were able to walk; the percentage generally increased with age, with a significant correlation between age group and the ability to walk ( $p = .0483$ ). Most patients were able to reach for objects and transfer them from hand to hand, but more fine motor skills (such as pincer grasping and using utensils to feed oneself) were less common.

Many of these features were also the most prevalent found in a systematic review that compiled information on 117 patients reported in the literature (Cooley Coleman et al., 2021). Similar to the results of our survey,

phenotypic information on these 117 patients in the literature included limited speech in 92.9%, seizures in 87.3%, and stereotypic movements in 83.6% of patients. Our survey revealed an abnormal MRI in 54.8% of patients, while the systematic review revealed this feature in 67.4%. For a final comparison, our survey revealed 59.4% of children over 18 months of age were unable to walk without support, while the systematic review revealed 56.4% over the age of 18 months were unable to walk.

Early studies revealed that *MEF2C* is highly expressed in neurons and plays a role in neuronal differentiation (Leifer et al., 1993; Mao et al., 1999). Correlating to the neuron expression, many symptoms in patients are neurological, including abnormal MRI findings, seizures, speech and motor impairments, high pain tolerance, and hand stereotypies. Additionally, *MEF2C* is also expressed in muscle (Chen et al., 2000), which may relate to the phenotypes of hypotonia, gastrointestinal issues such as constipation, and walking. Of note, *Mef2c* heterozygous mice serve as a valid animal model for *MEF2C*-related disorders as the mice display phenotypic similarities to patients including social and communication impairments, repetitive behaviors, and increased pain tolerance (Harrington et al., 2020). In an RNA-seq experiment on cortical tissue, Harrington et al. (2020) found that hundreds of genes were dysregulated in the *Mef2c* heterozygous mice as compared to wildtype. Many of the upregulated genes were microglial genes, while a large portion of downregulated genes were autism risk-linked genes. *MECP2*, the gene responsible for Rett syndrome, was previously found to be downregulated in patients with *MEF2C* deletions, truncating mutations, and missense variants, indicating a common pathway between the two genes (Zweier et al., 2010). This may also explain the phenotypic similarities between Rett syndrome and *MEF2C*-related disorders, including seizures, intellectual disability, developmental delay, and stereotypic movements. However, regression of skills is a requirement for the diagnosis of Rett syndrome (Neul et al., 2010), whereas regression is not seen in all patients with *MEF2C*-related disorders (34.2% of parents reported developmental regression).

We developed a survey to further characterize *MEF2C*-related disorders. Our survey was based upon well-regarded, validated instruments for Rett syndrome (a condition in the differential diagnosis for *MEF2C*-related disorders) and fragile X syndrome. The survey was vetted by experienced clinical geneticists and other genetics providers and pilot tested by families who have a child with a *MEF2C*-related disorder. This study is responsive to the requests of families and the research community. This survey was made available to two Facebook groups, reaching large numbers of families with multiple reminders. There was an exceptional response rate, exceeding the

goal of 50 with a total of 73 complete responses. This study provided parents the opportunity to participate across the world without requiring onerous travel and was successful in obtaining comprehensive information on the largest group of patients to date. The use of Facebook to conduct research has been established as a time- and cost-effective means of recruiting hard-to-reach populations (Amon et al., 2014; Nebeker et al., 2020). Additionally, using Facebook for recruitment has facilitated research for our team and others (Green et al., 2021) in the era of COVID-19 when in-person evaluations were not feasible.

There are limitations to our study. First, the prevalence of *MEF2C*-related disorders is yet to be determined. Although the Facebook group where our study was advertised contains hundreds of members, it consists of family members and medical professionals. There is another *MEF2C* Facebook group in which only parents have membership and access. Therefore, our study may have missed potential participants by not being able to routinely advertise in the parents-only group as often as we did in the family members and medical professionals group. Second, by advertising the survey through Facebook, participants from across the world were given the opportunity to respond; however, the survey was in English and required Internet access. It may have been difficult for participants to translate, if English was not their first language. At least one parent responded in a different language for the open-ended questions responses, which had to be translated back to English for analysis. Third, the participants may have given certain information from memory (such as variant type and nomenclature as well as early developmental milestones). Future studies may benefit from including instructions prompting the participants to gather their genetic reports for reference prior to beginning the study. Lastly, the recent systematic literature review (Cooley Coleman et al., 2021) illuminated cardiac issues that have not typically been associated with *MEF2C*-related disorders, and of note, *Mef2c* total knockout mice are embryonic lethal due to heart formation defects (Lin et al., 1998). The parent survey was developed prior to the publication of the systematic review; therefore, detailed cardiac-related questions were not considered for inclusion in the survey.

The information collected during this study is a valuable resource to many. Healthcare providers can use the results to learn more about *MEF2C*-related disorders, allowing better diagnosis and care for the patients and families. Families can use this data to obtain answers and see how their child compares or falls within the 73-patient cohort. Lastly, researchers may be able to use this data to pursue specific genotype–phenotype relationships, use it as baseline data for comparison for treatment trials, and for the development of future patient-centered studies.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

*Conceptualization:* Jessica A. Cooley Coleman, Sara M. Sarasua, Hannah Warren Moore, Christopher W. Cowan, Steven A. Skinner, and Jane M. DeLuca. *Data Curation:* Jessica A. Cooley Coleman. *Formal analysis:* Jessica A. Cooley Coleman, Sara M. Sarasua, Hannah Warren Moore, Christopher W. Cowan, Steven A. Skinner, and Jane M. DeLuca. *Supervision:* Sara M. Sarasua and Jane M. DeLuca. *Writing—original draft:* Jessica A. Cooley Coleman. *Writing—review & editing:* Sara M. Sarasua, Hannah Warren Moore, Luigi Boccuto, Christopher W. Cowan, Steven A. Skinner, and Jane M. DeLuca.

## ETHICS STATEMENT

The study was approved by the Self Regional Healthcare IRB (Pro00091979). No personally identifiable information was collected.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available within the article and in the supplementary material. Raw data and the survey instrument may be available upon request.

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## SUPPORTING INFORMATION

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