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RESEARCH REVIEW

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Comprehensive investigation of the phenotype of *MEF2C*-related disorders in human patients: A systematic review

Jessica A. Cooley Coleman[1,2] | Sara M. Sarasua[1] | Luigi Boccuto[1] | Hannah Warren Moore[2] | Steven A. Skinner[2] | Jane M. DeLuca[1,2]

[1]School of Nursing, Clemson University, Clemson, South Carolina, USA

[2]Greenwood Genetic Center, Greenwood, South Carolina, USA

Correspondence
Jessica A. Cooley Coleman, School of Nursing, Clemson University, Clemson, SC, USA.
Email: cooley8@g.clemson.edu

Abstract

MEF2C-related disorders (aka *MEF2C*-haploinsufficiency) are caused by variations in or involving the *MEF2C* gene and are characterized by intellectual disability, developmental delay, lack of speech, limited walking, and seizures. Despite these findings, the disorder is not easily recognized clinically. We performed a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to assemble the most comprehensive list of patients and their phenotypes. Through searching PubMed, Web of Science, and MEDLINE, 43 articles met the inclusion criteria and were fully reviewed. One hundred and seventeen patients were identified from these publications with most having a phenotype of intellectual disability, developmental delay, seizures, hypotonia, absent speech, inability to walk, stereotypic movements, and MRI abnormalities. Nonclassical findings included one patient with a question mark ear, two patients with a jugular pit, one patient with a unique neuroendocrine finding, and nine patients that did not have *MEF2C* deletions or disruptions but may be affected due to a positional effect on *MEF2C*. This systematic review characterizes the phenotype of *MEF2C*-related disorders, documents the severity of this condition, and will help providers to better diagnose and care for patients and their families. Additionally, this compiled information provides a comprehensive resource for investigators interested in pursuing specific genotype–phenotype correlations.

KEYWORDS
MEF2C, *MEF2C* haploinsufficiency, phenotype, systematic review

1 | INTRODUCTION

The *MEF2C* gene is a member of the myocyte enhancer factor 2 (MEF2) subfamily of the MADS (MCM1-agamous-deficiens-serum response factor) gene family of transcription factors. Transcription factors in the MEF2 family consist of a highly conserved N-terminal MADS-box that is adjacent to a MEF2 domain. These domains facilitate dimerization, interaction with other transcription factors, and DNA binding. *MEF2C* is particularly crucial during embryogenesis as it plays a role in myogenesis, neural crest formation, anterior heart field development, lymphoid development, neurogenesis, and synaptic formation, among other functions (Zweier et al., 2010).

Quite a few microdeletions encompassing chromosome region 5q14.3 have been reported in the literature over the past decade. Initially, some patients with similar phenotypes were reported to have microdeletions that did not include *MEF2C* (Cardoso et al., 2009; Engels et al., 2009). A year later, additional patients with deletions were reported, one of which had *MEF2C* as the only deleted gene (Le Meur et al., 2010). In the same

study, a patient with a nonsense variant in *MEF2C* was reported. A few months later, another study reported two additional patients with deletions in this 5q14.3 region including the *MEF2C* gene, and four patients with point mutations in *MEF2C* (Zweier et al., 2010). This led to the determination that *MEF2C* was likely the causative gene of the phenotype in these 5q14.3 deletions.

Zweier et al. (2010) isolated RNA from blood and performed expression studies by quantitative real-time PCR on their six patients as well as the three patients reported by Engels et al. (2009), one of which had a deletion ending 329 kb upstream of *MEF2C*. Of the total nine patients, seven had *MEF2C* expression levels that were significantly decreased (five patients with microdeletions and two patients with truncating variants), one had levels that were significantly increased (a patient with a missense variant), and one had relatively normal expression levels (another patient with a missense variant). The Engels et al.'s patient that had a microdeletion not encompassing the *MEF2C* gene itself was among those with decreased *MEF2C* expression. It is likely that deletions distal or proximal to the *MEF2C* gene may have a positional effect that disrupts the expression of *MEF2C* (Zweier et al., 2010). However, there have been other reports of downstream deletions (1.1 Mb away from *MEF2C*, Shimojima et al., 2012) and a translocation upstream of *MEF2C* (121.5 kb away from *MEF2C*, Saitsu et al., 2011) that did not affect *MEF2C* gene expression. Saitsu et al. (2011) hypothesized that the expression could be tissue-specific (i.e., the developing brain), which may explain why expression was not altered in lymphoblasts in these two cases. Additional studies will need to be performed to elucidate the exact mechanism of these positional effects.

MEF2C-related disorders and haploinsufficiency are reported to have a clinical presentation of intellectual disability, developmental delay, lack of speech, limited walking, and seizures (Paciorkowski et al., 2013). *MEF2C*-related disorders are rare, not fully characterized, and hard to distinguish clinically. Many manuscripts report one or only a few patients. Our aim was to conduct a systematic review to assemble the most comprehensive list of patients with a *MEF2C*-related disorder and thoroughly investigate their phenotypes. This review will further characterize the disorder, highlight the defining features, and assist healthcare providers in diagnosing and delivering the best clinical care for patients and their families.

2 | METHODS

2.1 | Editorial policies and ethical considerations

Ethical approval was not required as data included in this systematic review comes from peer-reviewed, published literature.

2.2 | Systematic review protocol

We conducted a systematic literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). The search strategy and inclusion and exclusion criteria were developed by the first author and are described below. A protocol was developed for registration to PROSPERO (supplementary document 1). The screening was performed in two stages: first on titles and abstracts and second on the full text. The PRISMA flow diagram map and Zotero Citation Manager (Version 5.0.90; Roy Rosenzweig Center for History and New Media, 2020) were used to manage the screening process and articles. Necessary data were extracted from the articles allowing final conclusions to be produced.

2.3 | Systematic review research question

We used the CoCoPop approach to frame our research question. The abbreviation CoCoPop stands for condition, context, and population (Munn et al., 2018). Our research question for this systematic review was: What is the comprehensive phenotype of all human patients reported with a *MEF2C*-related disorder? The condition would be *MEF2C*-related disorders, the context would be the phenotype, and the population is human patients. This format lends itself to systematic reviews on the prevalence and/or incidence of a certain condition. Although prevalence and incidence were not addressed directly, gathering a comprehensive list of patients and their phenotypes elucidated how rare the disorder truly is.

2.4 | Search strategy

The following electronic databases were searched: Web of Science, PubMed, and MEDLINE. The search strategy included terms relating to the research question from the CoCoPop framework. Search terms were adapted for database-specific filters. Database searches were conducted using the keywords, MeSH terms, and combinations of each with specific Boolean operators as shown in Table 1. Other articles were selected after screening the bibliography of articles meeting the inclusion criteria.

2.5 | Inclusion and exclusion criteria

Only peer-reviewed publications in the English language were considered for inclusion. All scientific journals and article types were considered. Gray literature and dissertation material were not included. There was no restriction to publication dates: articles reviewed included those from the very first publication on the search criteria up until the search date of May 9, 2021. Article title and abstracts were scanned for mention of phenotype information on a human patient case having a *MEF2C*-related disorder. Only articles that included phenotypic information on a human patient were considered for inclusion. Studies available in meeting abstract format only were excluded due to lack of information. Articles focusing solely on animal or cell culture studies and lacking a human case report were

TABLE 1 Search terms and strategy

Concept (CoCoPop)	Keywords	MeSH terms
Co: Condition *MEF2C*-related disorder	"*MEF2C*" OR "*MEF2C*-related disorder" OR "*MEF2C* haploinsufficiency"	Haploinsufficiency (MeSH term to only be used in conjunction with "AND *MEF2C*")
Co: Context Phenotype	"phenotype" OR "present*" OR "presentation" OR "clinical presentation" OR "feature*" OR "character*"	Phenotype
Pop: Population Human Patients	"human" OR "patient" OR "male" OR "female"	Humans OR Patients OR Male or Female
Overall search		
PubMed : (((((MEF2C[Title/Abstract] OR MEF2C-related disorder[Title/Abstract] OR MEF2C haploinsufficiency[Title/Abstract] OR (MEF2C[Title/Abstract] AND Haploinsufficiency[MeSH Terms])) AND (phenotype OR present* OR presentation OR clinical presentation OR feature* OR character* OR phenotype[MeSH Terms])) AND (human OR patient OR male OR female OR Humans[MeSH Terms] OR Patients [MeSH Terms] OR Male[MeSH Terms] OR Female[MeSH Terms]))))		
MEDLINE : AB (MEF2C OR "MEF2C-related disorder" OR "MEF2C haploinsufficiency" OR [MH haploinsufficiency AND MEF2C]) AND (phenotype OR present* OR presentation OR "clinical presentation" OR feature* OR character* OR MH Phenotype) AND (human OR patient OR male OR female OR MH humans OR MH patients OR MH Male OR MH Female)		
Web of Science: TOPIC: (MEF2C OR "MEF2C-related disorder" OR "MEF2C haploinsufficiency") AND TOPIC: (phenotype OR present* OR presentation OR clinical presentation OR feature* OR character*) AND TOPIC: (human OR patient OR male OR female)		

excluded. Articles that met the inclusion criteria by title and abstract review were then subjected to full-text review.

2.6 | Data extraction

The first author extracted data from the articles under full-text review. A summary table was created for data extraction with the following column headers: study type, authors, year published, location published, verification of human case, number of patients, patient sex, patient age, phenotype, and clinical information reported, how phenotype was reported, variation reported, inheritance pattern, methods used to detect variation, and article citation in APA format (supplementary document 2). Special focus was given to extract all phenotype information reported. The summary table was then used to create a phenotype table (supplementary document 3).

3 | RESULTS

The systematic review identified 917 records using the search terms previously described. There were 542 duplicates across the three databases. An additional 13 articles were found after reviewing the bibliographies of articles meeting the inclusion criteria. After duplicates were removed, 375 records remained. The title and abstract of these articles were scanned for relevance considering the inclusion criteria. A total of 317 articles were excluded because they did not meet the inclusion criteria. After reading the remaining 58 articles, 15 were excluded. Five of these excluded records were actually meeting abstracts only. Two articles were not in the English language, one article could not be obtained, two articles did not thoroughly describe the patient phenotype and instead focused on another subject, two articles were review articles without mention of new patients, and finally, three articles described patients previously reported. A full summary of the PRISMA process is included in Figure 1. Most of the studies were case reports (67.4%). Additionally, the majority were conducted in either the US or Europe (Table 2).

3.1 | Demographic information and variant types

A total of 117 patients with a *MEF2C*-related disorder were identified in our systematic literature search (supplementary document 3). There were 59 females (50.4%), 56 males (47.9%), and 2 (1.7%) patients with an unknown gender in the cohort. The average age was 8.52 years (*SD* 9.33 years). Two fetuses were terminated at 20 weeks gestation after considering ultrasound and magnetic resonance imagining abnormalities. The youngest living patient was 5 months old and the oldest 52 years old (Table 3).

Over half of the patients (59.8%) presented with deletions encompassing part or the entire *MEF2C* gene, or with a deleted region near *MEF2C* that may cause a positional regulatory effect disrupting expression of *MEF2C*. The second most common group of variants were point mutations, including missense, nonsense, splicing, and frameshift variants. Insertions, duplications, and translocations were also reported, although not as often. The alteration types for reported patients can be found in Table 3. Variant locations can be found in Figure 2.

3.2 | Common symptoms

The majority of patients presented with features typically described for *MEF2C*-related disorders. For articles reporting the following information, patients presented with intellectual disability (97.6%), developmental delay (99.0%), hypotonia (98.3%), absent speech (92.9%), and seizures and spasms (87.3%) (Table 4). Of patients 3 years of age and older, only five were able to speak several words (7.1%); however, their language skills were severely delayed. Speech was absent in the remaining patients over 3 years of age, but some patients did know a few words, or were able to babble, have vocalizations, mimic sounds,

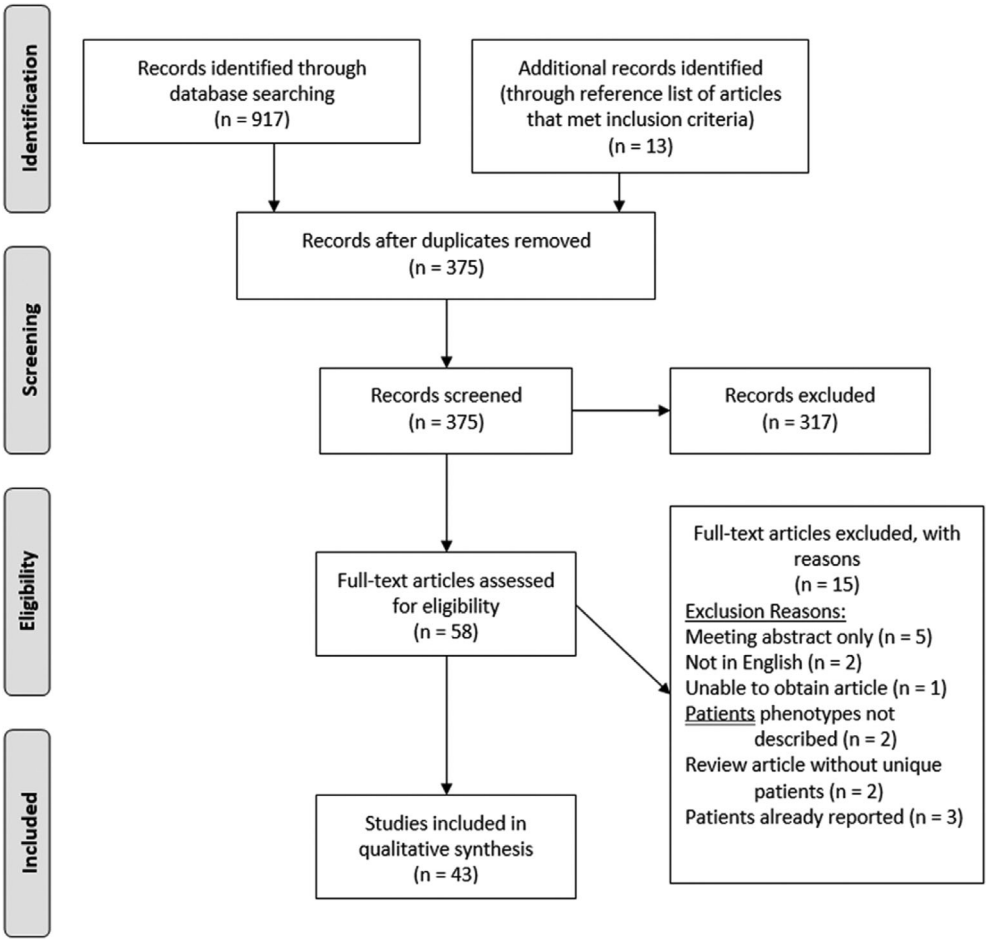

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

and use body language. Seizure types included fever-induced (or febrile), infantile spasms, generalized tonic–clonic, myoclonic, and focal. Thirty-nine patients presented with multiple seizure types. The two most common seizure types reported were febrile (31/89, 34.8%) and myoclonic (30/89, 33.7%). Tonic–clonic and spasms were both present in 17 of 89 patients (19.1%), followed by focal seizures in 14 patients (15.7%). Less prevalent were absence (5.6%), afebrile (3.4%), and atonic (2.2%). Seizure type was broadly characterized as "epilepsy" or "generalized" in 13 patients (14.6%), and "unspecified" in 5 patients (5.6%). Seizures typically had an infantile onset of less than 1 year of age (61.6%), and 87.7% had an onset under 2 years of age. Many patients were not able to walk independently ($N = 31$, 56.4%). These 31 patients were all over 18 months of age, with the youngest being 20 months and the oldest 46 years. Additionally, two patients were reported to have spastic quadriplegia, one of which had hypotonia during the early infantile period (Saitsu et al., 2011; Shimojima et al., 2012). Stereotypic movements, including hand flapping, hand mouthing, hand clapping, hand biting, hand washing, grasping the midline, and head banging, were reported in 83.6% of patients.

3.3 | Physical features

Head circumference information was reported for 67 patients, of which 16 patients had a head circumference size consistent with microcephaly (23.9%). Only two patients were reported to have macrocephaly (3.0%) (Cardoso et al., 2009; Mikhail et al., 2011). Dysmorphic features when reported were typically mild and included a broad forehead, down-slanting palpebral fissures, large ears, prominent ear lobes, short philtrum, depressed nasal bridge, and tenting of the upper lip. One patient presented with a question mark ear but had normal ear canals (Gordon et al., 2018). Two patients presented with a jugular pit (Al-Shehhi et al., 2016; Berland & Houge, 2010). Two patients presented with capillary malformation-arteriovenous malformation (CM-AVM) syndrome in addition to features of the *MEF2C*-related disorders (Carr et al., 2011; Ilari et al., 2016). CM-AVM is characterized by small pink round or oval-shaped vascular lesions, many with telangiectatic vessels in the center. One of the patients had 17 typical CMs on her head, trunk, and extremities, as well as 2 irregular CMs on the popliteal fossa and upper left posterior thigh. The patient did not present with any AVMs or arteriovenous fistulas on cranial MRI (Carr et al., 2011). The second patient had CMs on the trunk and extremities as well, including the right arm and thorax. This patient had two reported AVMs, one on the right frontal area and the other on the basilar artery. This syndrome is typically caused by variations in *RASA1*, a gene in close proximity to *MEF2C*. For the two patients that presented with these features, each had one deletion that included both the *RASA1* and *MEF2C* genes. Two additional patients with deletions encompassing both *MEF2C* and *RASA1* presented with hemangiomas (Vrečar et al., 2017). Another patient with a

TABLE 2 Characteristics of included studies

	Included studies ($N = 43$)	
	N	(%)
Study type		
Case report	29	(67.4%)
Cohort study	6	(14.0%)
Review	4	(9.3%)
Review with a case report	3	(7.0%)
Multicenter study	1	(2.3%)
Location of study		
United States	7	(16.3%)
France	6	(14.0%)
China	5	(11.6%)
Italy	5	(11.6%)
Germany	3	(7.0%)
Japan	4	(9.3%)
United Kingdom	2	(4.7%)
Portugal	2	(4.7%)
Canada	1	(2.3%)
Cyprus	1	(2.3%)
Ireland	1	(2.3%)
Mexico	1	(2.3%)
Norway	1	(2.3%)
Poland	1	(2.3%)
South Korea	1	(2.3%)
Spain	1	(2.3%)
Multicenter study (Italy, Demark, UK)	1	(2.3%)

TABLE 3 Demographic information and variant types from patients with reported *MEF2C*-related disorders

Gender	No. (%)
Female	59 (50.4%)
Male	56 (47.9%)
Unknown	2 (1.7%)
Age group	No. (%)
Fetus (fetus)	2 (1.7%)
Newborn (birth to 1 month)	0 (0.0%)
Infant (>1 month to <24 months)	20 (17.1%)
Preschool (2 years to <6 years)	31 (26.5%)
Child (6 years to <13 years)	40 (34.2%)
Adolescent (13 years to <19 years)	14 (12.0%)
Adult (19 years to <45 years)	7 (6.0%)
Middle age (45 years to <65 years)	3 (2.6%)
Type	No. (%)
MEF2C affected/altered/disrupted	108 (92.3%)
Possible positional regulatory effect	9 (7.7%)
Type	No. (%)
Deletion	58 (59.8%)
Translocation	6 (5.1%)
Deletion with translocation	1 (0.9%)
Insertion	1 (0.9%)
Duplication	3 (2.6%)
Point variant (missense, nonsense, frameshift)	35 (29.9%)
Nonsense	8/35 (22.9%)
Missense	16/35 (45.7%)
Frameshift	8/35 (22.9%)
Stop loss	1/35 (2.9%)
Splicing	2/35 (5.7%)
Not provided	1 (0.9%)

MEF2C plus *RASA1* deletion presented with characteristic CM of the skin and atrophic skin adjacent to the suprasternal notch (Paciorkowski et al., 2013).

3.4 | MRI and electroencephalogram

Abnormal electroencephalograms (EEGs) were reported in 68.5% of patients and findings included hypsarrhythmia, high voltage spike, poly-spike, and slow waves, focal or multifocal bilateral spikes, and a generalized epileptiform pattern. Abnormal MRI findings were reported in 67.4% of cases, typically including abnormalities of the corpus callosum (thinning, shortening, hypoplasia, aplasia, partial agenesis, thickening) (Al-Shehhi et al., 2016; Carr et al., 2011; Cesaretti et al., 2016; Engels et al., 2009; Ilari et al., 2016; Nowakowska et al., 2010; Paciorkowski et al., 2013; Raviglione et al., 2021; Saitsu et al., 2011; Shimojima et al., 2012; Toral-López et al., 2012; Vrečar et al., 2017; Yang et al., 2015). Abnormalities of the white matter (delayed myelination, reduced volume) were not uncommon (Borlot et al., 2019; Engels et al., 2009; Novara et al., 2010; Nowakowska et al., 2010; Paciorkowski et al., 2013; Raviglione et al., 2021; Saitsu et al., 2011; Shim et al., 2015; Shimojima et al., 2012; Sobreira et al., 2009; Vrečar et al., 2017; Zweier et al., 2010). Other findings included simplified gyri (Carr et al., 2011; Hotz et al., 2013), aplasia of the cerebellar vermis, moderate atrophy of supratentorial and infratentorial region, and prominence of arachnoid spaces (Engels et al., 2009), leukomalacia (Floris et al., 2008; Novara et al., 2010), ventriculomegaly (Cesaretti et al., 2016; Engels et al., 2009; Hotz et al., 2013; Novara et al., 2013; Nowakowska et al., 2010; Raviglione et al., 2021; Shimojima et al., 2012; Toral-López et al., 2012; Vrečar et al., 2017; Zweier et al., 2010), Dandy–Walker malformation (Toral-López et al., 2012), reduced brainstem volume (Hotz et al., 2013; Shimojima et al., 2012), cortical atrophy (Paciorkowski et al., 2013; Toral-López et al., 2012; Vrečar et al., 2017), cerebellar vermis hypoplasia (Paciorkowski et al., 2013; Raviglione et al., 2021), small forebrain

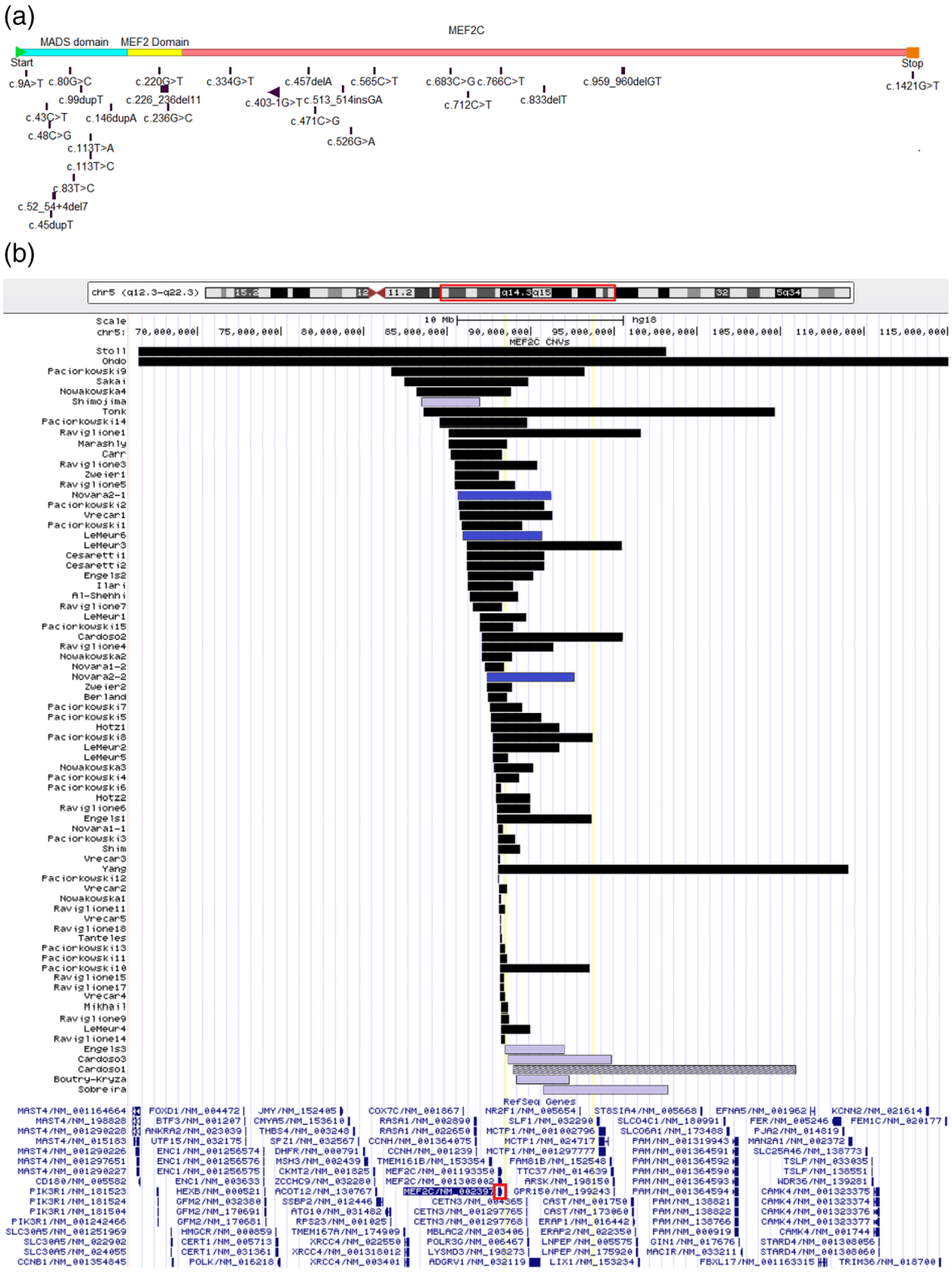

FIGURE 2 Variant locations from patients with reported *MEF2C*-related disorders. (a) Locations of point variants (nonsense, missense, frameshift, splicing, stop loss) across the *MEF2C* coding region. (b) Map of microdeletions and duplications involving or associated with *MEF2C*, using UCSC hg18 genome build. Black = deletion; blue = duplication; pink = *MEF2C* not involved, possible regulatory positional effect; pink and gray stripes = deleted region (*MEF2C* not involved) compounded with a translocation in the patient

and frontal lobes (Hotz et al., 2013), periventricular heterotopia (Cardoso et al., 2009), abnormalities in the posterior fossa including Chiari Type 1 malformation, enlarged cisterna magna, and hippocampal abnormalities (Raviglione et al., 2021), and cysts (septum pellucidum, pineal) (Nowakowska et al., 2010; Wang et al., 2018; Yang et al., 2015).

TABLE 4 Phenotypes found in patients with reported *MEF2C*-related disorder

Type	No. (%)
Developmental delay	96/97 (99.0%)
Seizures	89/102 (87.3%)
Intellectual disability	83/85 (97.6%)
Hypotonia	58/59 (98.3%)
Absent speech (age >3 years)	65/70 (92.9%)
Social and behavioral issues	62/71 (87.3%)
Dysmorphic features	68/69 (98.6%)
Stereotypic movements	46/55 (83.6%)
Abnormal MRI	58/86 (67.4%)
Feeding and digestion issues	35/36 (97.2%)
Abnormal EEG	50/73 (68.5%)
Inability to walk (age >18 months)	31/55 (56.4%)
Vision issues	24/24 (100.0%)
Sleeping issues	20/28 (71.4%)
Cardiac issues	17/17 (100.0%)

Note: Not all phenotypes were reported for all patients and thus sample size varies.
Abbreviation: EEG, electroencephalogram.

3.5 | Social, behavioral, and sleep issues

Autistic traits or behaviors were reported in 24 patients (Berland & Houge, 2010; Boutry-Kryza et al., 2015; Floris et al., 2008; Hotz et al., 2013; Nowakowska et al., 2010; Raviglione et al., 2021; Schluth-Bolard et al., 2019; Vidal et al., 2019; Vrečar et al., 2017; Wang et al., 2018; Zweier et al., 2010). Additionally, other social and behavioral issues were reported. Most patients displayed a lack of social smile and interest in surroundings, or limited social interactions (Engels et al., 2009; Ilari et al., 2016; Novara et al., 2010; Rocha et al., 2016; Shim et al., 2015; Wang et al., 2018) and poor eye contact (Berland & Houge, 2010; Bienvenu et al., 2013; Gordon et al., 2018; Le Meur et al., 2010; Novara et al., 2010; Paciorkowski et al., 2013; Rocha et al., 2016; Wang et al., 2018; Yang et al., 2015). Some patients had a lack of social interaction (Ilari et al., 2016; Nowakowska et al., 2010; Vrečar et al., 2017), whereas a few were reported to enjoy human contact, especially with other children (Vrečar et al., 2017). Many patients were described as having a generally happy disposition (Berland & Houge, 2010; Bienvenu et al., 2013; Paciorkowski et al., 2013; Raviglione et al., 2021). Only a few patients were reported to have negative behaviors, including obsessive behaviors, severe attention deficit hyperactivity disorder and aggressive behaviors (Sobreira et al., 2009), agitation, and self-mutilation (Paciorkowski et al., 2013), and self-biting (Rocha et al., 2016). A few patients were noted to easily startle with loud noises (Berland & Houge, 2010; Borlot et al., 2019; Nowakowska et al., 2010; Tanteles et al., 2015). Finally, some patients had fascinations with random items and events, including running water or water in general, bright objects, and opening and closing doors (Berland & Houge, 2010; Gordon et al., 2018; Tanteles et al., 2015; Vrečar et al., 2017).

Sleep issues were reported in 41.4% of patients and included sleeping a lot with short awakening stages, sleep disturbance, and irregular sleep initiation and maintenance (Engels et al., 2009; Hotz et al., 2013; Le Meur et al., 2010; Paciorkowski et al., 2013; Vrečar et al., 2017; Wang et al., 2018; Yang et al., 2015; Zweier et al., 2010).

3.6 | Feeding and gastrointestinal issues

Feeding and digestion issues were common and included constipation, feeding difficulties, poor sucking as an infant, frequent vomiting, inability to feed self, needing puree foods only, gastrostomy tube fed, slow gastric emptying, dysphagia, episodes of appetite loss, and gastroesophageal reflux disease (Al-Shehhi et al., 2016; Bienvenu et al., 2013; Engels et al., 2009; Gordon et al., 2018; Le Meur et al., 2010; Novara et al., 2013; Nowakowska et al., 2010; Paciorkowski et al., 2013; Saitsu et al., 2011; Sakai et al., 2013; Schluth-Bolard et al., 2019; Shimojima et al., 2012; Vrečar et al., 2017; Wang et al., 2018; Zweier et al., 2010).

3.7 | Ophthalmological issues

Eye concerns included bilateral optic atrophy and hyperopia (Engels et al., 2009; Novara et al., 2013; Zweier et al., 2010), strabismus (Berland & Houge, 2010; Bienvenu et al., 2013; Engels et al., 2009; Novara et al., 2010; Zweier et al., 2010), myopia (Schluth-Bolard et al., 2019; Vrečar et al., 2017), bilateral esotropia (Marashly et al., 2010; Nowakowska et al., 2010; Shim et al., 2015), nystagmus (Berland & Houge, 2010; Zweier et al., 2010), bilateral ptosis (Nowakowska et al., 2010), coloboma of the iris in two patients (Cardoso et al., 2009; Sobreira et al., 2009), and cortical blindness in one patient (Le Meur et al., 2010).

3.8 | Cardiac phenotype

Cardiac issues have not typically been associated with *MEF2C*-haploinsufficiency. However, cardiac issues could be expected due to the role of *MEF2C* in myogenesis and heart development. Cardiac issues were reported in 17 patients in total. Cardiac phenotypes included concentric myocardial hypertrophy, patent foramen ovale, patent ductus arteriosus (PDA), abnormal fetal cardiac rhythm, biventricular hypertrophy, moderate tricuspid valve insufficiency, moderate bilateral ventricular valve insufficiency, and murmur. Nine patients were reported with cardiac phenotypes in addition to other features commonly found in *MEF2C*-related disorders (Cesaretti et al., 2016; Engels et al., 2009; Le Meur et al., 2010; Novara et al., 2013; Nowakowska et al., 2010; Stoll et al., 1980; Vrečar et al., 2017). Three articles focused solely on cardiac studies and did not report any noncardiac phenotypes in

those 10 patients (Lu et al., 2018; Qiao et al., 2017; Yuan et al., 2018).

Lu et al. (2018) performed Sanger sequencing of the *MEF2C* gene on a cohort of 186 unrelated patients with congenital heart defects and 300 healthy matched controls. One patient who had a family history of ventricular septal defect (VSD) and double outlet right ventricle (DORV) was identified with a heterozygous missense variant (c.43C > T; p.Arg15Cys) in *MEF2C*. This variant was not present in any of the 300 controls. Family studies revealed that the variant was paternally inherited and that the proband's uncle also carried the variant. All three individuals carried the missense change and had the phenotype of VSD and DORV. The proband's grandfather was deceased but shared the phenotype so may also have carried the variant as well. No other phenotypic information was reported apart from the cardiac phenotype.

Yuan et al. (2018) also performed Sanger sequencing on a cohort to identify *MEF2C* variants associated with dilated cardiomyopathy (DCM). There were 172 unrelated individuals with DCM and 300 healthy controls sequenced. A heterozygous nonsense variant (c.471C > G; p.Tyr157Ter) was detected in a patient with a positive family history and phenotype of adult-onset DCM. The patient's daughter and brother both carried the variant. The daughter shared the phenotype of DCM, and the patient's brother had a phenotype of DCM and VSD. These patients were also reported to have intellectual disability, childhood epilepsy, stereotypic movements, and absent speech. These features overlap with the traditionally reported phenotype of *MEF2C*-related disorders and haploinsufficiency.

Finally, Qiao et al. (2017) performed Sanger sequencing on a cohort of 200 unrelated patients with a congenital heart defect and 300 healthy controls. A heterozygous missense variant (c.113 T > C; p.Leu38Pro) was identified in a 1-year-old male with PDA and VSD. The patient's father, uncle, and female first cousin all carried the variant and shared a similar cardiac phenotype. All family members had PDA. The proband's father shared the same phenotype of PDA and VSD. The proband's uncle had pulmonary stenosis (PS) in addition to PDA. The proband's cousin was only reported to have PDA. The proband's grandfather was reported to have all three cardiac features (PDA, VSD, and PS); however, the grandfather was deceased therefore carrier status could not be assessed. The father and uncle were also reported to have intellectual disability, stereotypic movements, and paroxysmal epilepsy.

3.9 | Nonclassical findings

There were a number of patients in the literature with either nonclassical symptoms or unique pathogenesis. As previously mentioned, one patient presented with a question mark ear (Gordon et al., 2018) and two patients presented with a jugular pit (Al-Shehhi et al., 2016; Berland & Houge, 2010). One other patient was reported to have mild to moderate hypoglycemia, with a blood glucose level not exceeding 90 mg/dl even after a meal (Sakai et al., 2013). This is perhaps the only reported neuroendocrine phenotype related to deletions in the 5q14.3 region that included *MEF2C*. However, this phenotype could be present but unrecognized in additional patients due to the severity of the other features (i.e., intellectual disability and seizures). This patient had a normal hypothalamus by MRI; therefore, the deficits likely occur within the hypothalamic signaling pathway. Other genes within this patient's deletion were not expected to be expressed in the endocrine system, therefore were deemed not the likely cause of the neuroendocrine phenotype leaving the authors to suspect *MEF2C*. The authors performed expression studies in the mouse brain and found *MEF2C* was highly expressed in neuropeptide Y (NPY)-positive hypothalamic interneurons. Conversely, NPY-positive neurons had lower expression of *MECP2*, the gene associated with Rett syndrome. Further analysis showed *MECP2* is involved in the repression of *MEF2C* and *NPY*. The common pathway of *MEF2C* and *MECP2* could explain the phenotypic similarities between *MEF2C*-related disorders and Rett syndrome.

Nine patients who did not have a deleted or disrupted *MEF2C* gene yet presented with a similar phenotype as the other diagnosed *MEF2C* patients (Boutry-Kryza et al., 2015; Cardoso et al., 2009; Engels et al., 2009; Floris et al., 2008; Marashly et al., 2010; Saitsu et al., 2011; Shimojima et al., 2012; Sobreira et al., 2009; Yauy et al., 2019). It was hypothesized that there may be a regulatory positional effect for copy number variations with a breakpoint on either side of the *MEF2C* gene. Of these nine, six had deletions that did not encompass *MEF2C* and three were translocations that did not disrupt *MEF2C*. In the patient reported by Engels et al. (2009), *MEF2C* expression levels were confirmed to be decreased in an RNA study in collaboration with Zweier et al. (2010). One patient with a balanced translocation actually had *MEF2C* overexpression (Yauy et al., 2019). Two patients had normal *MEF2C* expression levels by lymphoblast RNA testing, one of which had a deletion and the other a translocation (Saitsu et al., 2011; Shimojima et al., 2012). This could be explained by tissue-specific expression where the sample type tested had normal *MEF2C* expression, but tissue from another location (i.e., the brain), if tested, may actually have decreased expression. The remaining five patients had no mention of expression levels but could still fall within the category of patients affected due to the positional effect of their deletion to *MEF2C*.

4 | DISCUSSION

We performed a systematic review to assemble the most comprehensive list of patients with a *MEF2C*-related disorder along with their phenotypes. One hundred and seventeen patients were identified with a *MEF2C*-related disorder and the phenotypes reported included intellectual disability, developmental delay, seizures, hypotonia, absent speech, inability to walk, stereotypic movements, and MRI abnormalities. Additional features detected were jugular pit, cardiac issues, and a neuroendocrine phenotype of hypoglycemia. Although the patients shared many of the same features, differences between patient phenotypes could be explained by the difference in the type of variants (point mutations rather than chromosomal rearrangements), variant

locations within the *MEF2C* gene, or deletion sizes and whether additional genes were involved in the deletion along with *MEF2C*. Genotype–phenotype correlation analysis may provide some insights into the clinical variability across individuals with MEF2C-related disorders. Other divergencies between the phenotypes reported in the articles could be due to the purpose of the study. Authors may have focused on only one feature for their study (e.g., epilepsy), thereby limiting the phenotypic information presented for other features. For example, of the six cohort studies, three focused on the cardiac phenotype, one on infantile spasms, one on developmental disorders, and one on intellectual disability. In contrast, 29 articles (67.4%) were case reports in which more general phenotypic information was presented.

Nine patients were reported to have chromosomal rearrangements not encompassing or disrupting the *MEF2C* gene; however, these patients still exhibited a similar phenotype to the other reported patients. This could be explained by a possible positional regulatory effect. Six patients had no expression studies performed, two patients had normal *MEF2C* expression, and one patient had decreased *MEF2C* expression. Further studies will be needed to understand this positional effect and determine if expression could be tissue-specific.

Several clinical implications can be deduced given the results of this literature review. Early referral for therapies (such as physical, occupational, and speech) is recommended. Patients should undergo a full neurological evaluation including an EEG and brain MRI if concerning neurological symptoms arise. If seizures, constipation, or gastroesophageal reflux are occurring, treatment should be as per standard care. Also recommended is an evaluation with a developmental specialist to screen for ASD and behavioral issues, such as ADHD and anxiety. Given the cardiac findings from this review, a cardiac evaluation with an echocardiogram and EKG is recommended. Finally, the *MEF2C* gene should be included in all Next Generation Sequencing epilepsy/seizure panels.

There are some limitations to this study. Despite the rigorous method and two independent article reviewers, relevant articles matching the inclusion criteria might have been missed. During the review, two articles were excluded as they were not in English and one other article could not be obtained. Additionally, we only searched three major databases indexing biomedical literature; therefore, any articles matching the inclusion criteria in other databases were not included. A final limitation arises from using the systematic review method where the data of this study relies on the information each article contained. The articles may have focused only on specific clinical features without reporting other potentially relevant information. As our study was a review of the literature, we were not able to pursue additional patient information to fill the gaps. Thus, the sample size for each feature assessed varied. Future studies could involve contacting the authors of the 43 manuscripts included in this study to gather the same clinical information across all reported patients.

This review characterizes the phenotype of *MEF2C*-related disorders and documents the severity of this condition, which can aid healthcare providers in diagnosing patients and delivering the best care possible to current patients and their families. Detailed information on the 117 patients is provided in the supplemental table which may be a valuable resource for investigators interested in pursuing specific genotype–phenotype correlations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Jessica A. Cooley Coleman created the search strategy and keywords and performed the literature search. Article titles and abstracts returned by the search were independently screened by both **Jessica A. Cooley Coleman** and **Jane M. DeLuca**. **Sara M. Sarasua** was available as a third reviewer in case of any disagreements for the inclusion or exclusion of articles. **Jessica A. Cooley Coleman** took the lead in data extraction, analysis, and drafting the manuscript. All authors contributed by critically revising the manuscript and have given approval of the final version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

ORCID

Jessica A. Cooley Coleman https://orcid.org/0000-0002-7050-8796
Sara M. Sarasua https://orcid.org/0000-0002-1625-7404
Luigi Boccuto https://orcid.org/0000-0003-2017-4270

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SUPPORTING INFORMATION

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