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Review article

# Involvement of myocyte enhancer factor 2c in the pathogenesis of autism spectrum disorder

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ABSTRACT

Myocyte enhancer factor 2 (*MEF2*), a family of transcription factor of *MADS* (minichromosome maintenance 1, agamous, deficiens and serum response factor)-box family needed in the growth and differentiation of a variety of human cells, such as neural, immune, endothelial, and muscles. As per existing literature, *MEF2* transcription factors have also been associated with synaptic plasticity, the developmental mechanisms governing memory and learning, and several neurologic conditions, like autism spectrum disorders (ASDs). Recent genomic findings have ascertained a link between *MEF2* defects, particularly in the *MEF2C* isoform and the ASD. In this review, we summarized a concise overview of the general regulation, structure and functional roles of the *MEF2C* transcription factor. We further outlined the potential role of *MEF2C* as a risk factor for various neurodevelopmental disorders, such as ASD, *MEF2C* Haploinsufficiency Syndrome and Fragile X syndrome.

## 1. Introduction

Neurodevelopmental disorders (NDDs) are extremely intricate brain deformities that are marked by an inability to meet normal social, cognitive, and motor developmental thresholds [1]. The term "NDD" has been extended to a diverse variety of mental illnesses involving some form of dysregulation in tightly orchestrated early embryonic events that led to brain development [2]. NDDs have a heterogeneous etiology that significantly contributes to impaired cognitive, poor communicative, and abnormal motor skills [3]. Autism spectrum disorders (ASDs), intellectual disability (ID), learning, vision, and hearing impairments, attention deficit hyperactivity disorder (ADHD), epilepsy, schizophrenia, and cerebral palsy are only a few examples of NDDs [2, 3, 4, 5, 6].

ASD is a complex neurodevelopmental condition linked with impaired cognitive abilities, poor communication skills, repetitive behaviors, and limited interests [7]. In 1943, Dr. Leo Kanner, an American psychiatrist, first published a paper on eleven of his patients at the Baltimore clinic entitled "*Autistic Disturbances of Affective Contact*" [8]. However, the term "autism" was first proposed in 1911 by a Swiss psychiatrist, Eugen Bleulerto, who described the peculiar characteristics displayed by a schizophrenic patient [9]. The prevalence rate of ASD is about 16.8 per 10,000 (one in 59) children aged 8 years [10]. According to the World Health Organization (WHO), about 1–1.5% of children worldwide suffer from ASD [11, 12]. Besides that, around 31% of individuals with ASD have intellectual impairments [10] and 20%–37% of them had epilepsy condition [13, 14]. In general, ASDs are divided into two categories: syndromic – such as Fragile X syndrome (FXS) [15], Rett syndrome (RS) [16] and tuberous sclerosis (TSC) [17] and non-syndromic. Furthermore, ASD has often been followed by psychological or medical conditions, including ADHD, depression, anxiety disorders, sleep disturbances, and gastrointestinal problems [18, 19, 20]. Numerous models of ASD pathogenesis and etiology have been postulated so far. It is, however, believed to be significantly linked to the interrelationships between environmental and genetic risk factors [21, 22].

The myocyte enhancer factor 2 (*MEF2*) transcription has been shown to influence ASD-associated gene expression and studies have also showed that autistic traits are triggered by impaired activity-dependent regulation of synaptic development [23, 24]. Such a transitory shift in the regulatory mechanism could have significantly altered the signaling of *MEF2* as a potential cause [25]. The *MEF2* family of transcription factors in vertebrates yields four members: *MEF2A*, *MEF2B*, *MEF2C*, and *MEF2D*. These *MEF2* members are strongly conserved and critical for a number of functions in a variety of different cell types, such as cellular differentiation and extracellular stimuli response. The significance of *MEF2* factors in the central nervous system (CNS) for neural cell survival, synaptic plasticity, and memory development is reinforced by the discovery that disruptions in *MEF2* factors trigger heritable neurological pathologies [26, 27]. Moreover, stimuli important for neuron formation

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and synapse maturation, such as growth factors and synaptic processes, may influence the regulatory mechanism of *MEF2* family members [28]. Considering the importance of *MEF2* in the neural system, it is of considerable interest to elucidate how *MEF2* factors regulate neuronal-specific gene expression. Nonetheless, gaining a thorough understanding of *MEF2* transcriptional mechanisms in the neural system is still hard to comprehend, primarily owing to the challenges of investigating gene expression mechanisms in the large and highly diverse neural cell populations, in addition to the overlaps in *MEF2* expression profiles across the neuronal network.

The *MEF2* proteins are essential for the optimal growth and efficient processing of the neural system. They have been found to regulate the process of neuronal differentiation [29, 30, 31, 32], neuronal migration [33], activity-dependent cell survival [34, 35, 36], dendrite formation and remodeling [37, 38, 39], and axonal guidance and pruning [40]. Gene expression studies also reveal a large number of *MEF2*-regulated genes involved in neural excitability, as well as synapse development and functioning [41, 42, 43]. *MEF2* synapse elimination tends to happen only in developing or mature neurons. The rate of synapse formation declines as neurons mature, but the rate of elimination remains high [44, 45]. Despite the fact that nothing much is interpreted regarding the cellular mechanisms and signaling pathways that govern synapse formation and curtailment rates during development. This is quite plausible to rely on an activity-dependent system that perceives when synaptic connections are mature and then prevents further synapse development and sustains curtailment rates [46]. *MEF2* factors are triggered by neuronal depolarization and successive calcium ion ($Ca^{2+}$) influx, which stimulates the *$Ca^{2+}$/Calmodulin* (CaM) effectors, *calcineurin*, *CaM* kinases and the protein phosphatase [28, 47]. The expression of a variety of proteins, including *FMRP* (fragile X mental retardation protein), *Arc* (activity-regulated cytoskeleton-associated protein), *calcineurin*, RNA-binding proteins, *PCDH10* (protocadherin 10), *mGluR1/5* (group I metabotropic glutamate receptors), *NR4A1* (nuclear receptor subfamily 4 group A member 1), *potentially Homer 1* and *MHC1* (major histocompatibility complex class I) has been linked to *MEF2*-induced excitatory synapse elimination [23, 24, 42, 48, 49, 50, 51, 52, 53]. Synaptic modulation mediated by *MEF2s* may be synapse-specific as they function upstream of proteins, such as *Arc* and *NPAS4* (neuronal PAS domain protein 4) that can selectively regulate specific synapses within a particular cell [42, 54, 55]. The *MEF2* proteins regulate the expression of multiple genes, many of which are essential for neuronal growth and differentiation, either directly or indirectly [41]. Taken together, this indicates that the reduced activity of *MEF2C* throughout early development has a strong impact on neural growth and development as well as neurotypical behaviors.

Human genomic experiments have highlighted the transcription factor *MEF2C* as a risk gene for a multitude of neurological conditions. Using human genome-wide association studies (GWAS) and genomic sequencing studies, it has been identified that *MEF2C* is a potential risk gene for a wide variety of mental illnesses, such as ASD [56], bipolar disorder [57, 58], major depressive disorder [59] and ADHD [60, 61]. A GWAS analysis of 74,046 people showed that the SNP (single-nucleotide polymorphism) rs190982 close to the *MEF2C* region is connected with an increased risk of late-onset Alzheimer's disease [62]. In several such studies, the effect of disease-linked SNPs on *MEF2C* expression or activity remains mostly unclear, but it highlights the significant characteristics of *MEF2C* in hale and healthy human brain. *MEF2C* Haploinsufficiency Syndrome (MCHS) is a neurodevelopmental disease that is caused by microdeletions at chromosome location 5q14.3 that contain the *MEF2C* gene or point mutations within the *MEF2C* protein-coding region [63, 64, 65]. The MCHS has been associated with ASD, ID, absence of speech, and numerous motor abnormalities, including hyperactivity, and schizophrenia that are believed to be precipitated by deficits in primary phases of neuronal development [63, 64].

## 2. The *MEF2* family of transcription factors

The *MEF2* family belongs to the *MADS* (minichromosome maintenance 1, agamous, deficiens and serum response factor)-box evolutionary conserved family of transcription factors which are essential for cellular growth and differentiation in a wide number of tissues, including the brain [66]. It was originally discovered in muscle tissues, but it was later reported to be differentially expressed in neurons throughout the multiple brain regions [67, 68].

*MEF2* is a single gene in fly *(Drosophila melanogaster)*, worm *(Caenorhabditis elegans)*, and yeast *(Saccharomyces cerevisiae)*, while in vertebrates four distinct isoforms of the *MEF2* family are identified, which are programmed by distinct genes and named as *MEF2A*, *MEF2B*, *MEF2C* and *MEF2D* (Figure 1) [69]. The *MEF2* gene in *Drosophila melanogaster* is found on chromosome 2 locus. According to prior studies, *MEF2A*, *MEF2C* and *MEF2D* in mice are situated at chromosome location 7, 13 and 3, respectively, while *MEF2B* situated at chromosome 8 and it is not linked to other *MEF2* genes, the intron-exon association of the *MEF2B* gene is identical to that of the other vertebrate *MEF2* genes and the single *Drosophila melanogaster MEF2* gene, indicative of the fact that these different *MEF2* genes have been transformed from a universal ancestral gene. In humans, *MEF2A*, *B*, *C* and *D* are reported to be positioned at chromosome locations 15q26, 19p12, 5q14 and 1q12-q23, respectively [70, 71] (Table 1).

*MEF2* proteins are associated with a number of other different factors, such as the N-terminal 56-amino acid sequence known as MADS-box, the minimal region which is responsible for sequential DNA-binding and protein dimerization. The MADS domain is a term for the earliest members of the protein family described: the yeast mating type regulator *MCM1* (minichromosome maintenance 1); the plant floral determinants Agamous and Deficiens/Apetala 3; and the animal protein serum response factor (SRF) [83, 84]. Throughout many species, it is a significantly conserved structural motif that governs growth and differentiation processes. A 29-amino-acid long *MEF2* domain resides next to the MADS-box, mediating DNA binding and homo-and heterodimerization with many other *MEF2* proteins [85]. The MADS-box proteins typically bind adenine(A)/thymine(T) rich DNA sequences, while *MEF2* binds preferably to the consensus sequence 5′-CC(A/T) (T/A)AAATAG-3′. Both the MADS-box and the *MEF2* domain are crucial for DNA binding, but neither has transcription activity of its own. *MEF2* proteins have a distinct transactivation domain at the C-terminal that promotes interactions with a variety of co-factors, including co-activators, such as p300 and acetyl-transferases CBP (CREB-binding protein), or co-repressor, such as class II histone deacetylases (HDACs) and NCoR (nuclear receptor co-repressor)/SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) co-repressor complex. The C-terminus region of *MEF2* is particularly subjected to alternate splicing dynamics and has a comparatively low level of amino acid similarity between the different *MEF2* isoforms [86, 87, 88]. During the maturation phase of neurons in the CNS region, the four distinct isoforms of *MEF2* proteins are expressed differentially in the frontal cortex, thalamus, hippocampal, cerebellum, midbrain, hindbrain, and olfactory bulb regions. *MEF2A*, *C*, and *D* mRNAs are abundantly expressed in the embryonic cortical neurons of rats, but *MEF2* proteins are only transcribed by the *MEF2C* gene in the developing brain first among many other *MEF2* isoforms [89, 90, 91, 92].

*MEF2D* isoform is expressed in proliferating glial and neuronal cells during development, i.e., expression of *MEF2D* isoform is enhanced in neurons following growth and differentiation and declines in matured glial cells [93]. In apoptotic cerebellar granule neurons (CGNs), all four *MEF2* protein isoforms are highly expressed, but only *MEF2A/D* proteins have been found to be phosphorylated [34]. The *MEF2C* isoform is expressed at the initial stages of embryonic brain development and continues to be expressed at excessive levels in adult brains, including the

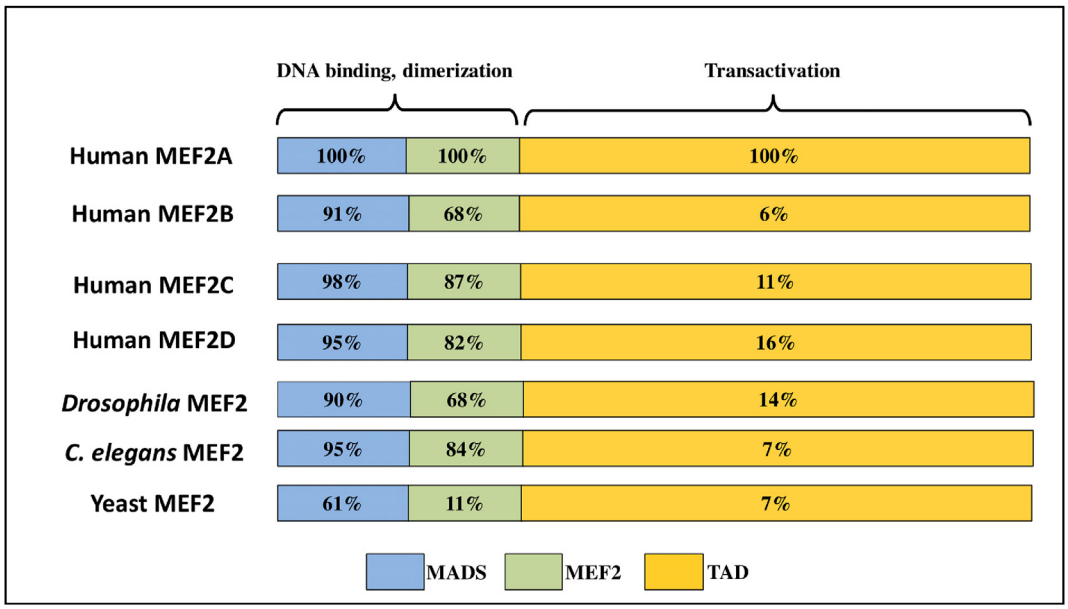



**Figure 1.** A schematic illustration of the sequence homology of the *MEF2* transcription factors family from fly *(Drosophila melanogaster)*, worm *(Caenorhabditis elegans)*, yeast *(Saccharomyces cerevisiae)* and human *(Homo sapiens)*. The percentage homology of amino acids within the three domains, namely MADS, MEF2 and TAD is standardized by human *MEF2A* isoform for different organisms. The N-terminal is to the left and the C-terminal to the right. Adapted from "MEF2: a central regulator of diverse developmental programs", Potthoff MJ, Olson EN, Vol. 134, Development. 2007. p. 4131–40 [95].

**Table 1.** Salient characteristics of the different *MEF2* transcriptional factors.

| Gene Name | Gene Type | Cytogenetic Locus | Protein Name | Interacting Proteins | Major Molecular Functions | Associated Diseases | References |
|---|---|---|---|---|---|---|---|
| *MEF2A* | Protein coding | 15q26.3 | Myocyte Enhancer Factor 2A | HDAC1, HDAC3, HDAC4, HDAC5, HDAC7, HDAC9, 14-3-3, TBP, MAPK7, MAPK14, BPTF, CABIN1, EP300, CREBBP, SMAD2, SMAD4 | • Muscle development<br>• Neuronal differentiation<br>• Cell growth<br>• Apoptosis | Coronary artery disease 1 with Myocardial infarction (ADCAD1) | [72, 73, 74, 75, 76, 77] |
| *MEF2B* | Protein coding | 19p13.11 | Myocyte Enhancer Factor 2B | CABIN1, BPTF, HDAC4, HDAC6, HDAC9, 14-3-3, EP300, CREBBP | • Development and maintenance of various tissues, such as cardiomyocytes, skeletal muscle cells, and neuronal cells | Brachydactyly, Type E1 and Mantle Cell Lymphoma. | [71, 73, 74, 75, 78] |
| *MEF2C* | Protein coding | 5q14.3 | Myocyte Enhancer Factor 2C | HDAC4, HDAC5, HDAC7, 14-3-3, CABIN1, EP300, NOTCH1, GATA4, TWIST2, CREBBP, MAPK7, MAPK14, SMAD2, CDK1, SP1, HIPK2, IFRD1 | • Controls neurogenesis and myogenesis<br>• Vascular development<br>• Healthy neuronal growth, propagation, and electrical activity in the neocortex region<br>• Development of anterior heart field and neural crest<br>• Craniofacial development | ASD, ADHD, ID, Epilepsy | [27, 73, 74, 75, 79] |
| *MEF2D* | Protein coding | 1q22 | Myocyte Enhancer Factor 2D | HDAC1, HDAC3, HDAC4, HDAC5, 14-3-3, MAPK7, MAPK14, EP300, CREBBP, SP1, CARM1, SENP3, CASP7, BPTF, HIRA, CABIN1, 14-3-3 | • Regulation of neuronal survival and apoptosis<br>• Regulate muscle and neural cell growth and differentiation | Brachydactyly, Type E1 and Migraine with or without aura | [74, 75, 80, 81, 82] |

striatum, hippocampus and cortex, indicating potential roles in embryonic and adult brain activity [67, 89]. Out of the four *MEF2* proteins, *MEF2C* is the most pre-dominant form of *MEF2* in the developing cortex. The expression of *MEF2C* begins to appear on day 17 of the embryo and peaks at day 21. The level of expression of *MEF2C* in differentiating neurons can be detected by the presence of *MEF2C* in the cortical plate [94]. In previous studies, it was shown that *MEF2C* plays a fundamental role during the developmental phase of several lineages, including the CNS and craniofacial system [95, 96]. Several human genetic research have implicated *MEF2C* isoform as a crucial component in NDDs, including ASD [41, 42]. In mice, deletion of *MEF2C* in neural progenitor cells resulted in reduced brain masses, fewer mature neurons, and substantial behavioral deficits [33]. *MEF2C* is also expressed in microglia [97, 98]. Microglia is a population of tissue-resident macrophages, and are resident immune cells of the brain that control formation and pruning of synapses during early brain development [99, 100]. Furthermore, in comparison to other tissue-resident macrophages, *MEF2C* has been recognized as a critical transcription factor for microglia [101]. Microglia play a role in a variety of brain processes, including synapse development and elimination, longevity of oligodendrocyte precursor cells, networking of the corpus callosum, and phagocytosis of several other brain cells [102, 103, 104, 105]. Microglial cells were described as an essential players of brain growth and development [106]. Thus, disruption of these microglial cells might portray a major role in the pathology

of multiple NDDs, including ASD. In sum, this implies that *MEF2C* is a key element in the development and regulation of the CNS as well as plays a prominent role in several neurodevelopmental diseases.

## 3. Structure of *MEF2C*

The *MEF2C* gene is located at chromosome location 5q14.3 [107]. Three transcriptional initiation sites with variable 5′-UTRs are marked and the *MEF2C* gene comprises up to 13 exons and the primary transcript is alternatively spliced [108]. To date, a total of six human transcript variants have been annotated: NM002397, NM001131005, NM001193347, NM001193348, NM001193349, NM001193350 [65]. The *MEF2C* gene comprises three alternative exons: the mutually exclusive exons α1 and α2, the inclusion/skipping exon β and the 3′ splice site region γ. The mutually exclusive alternative splicing takes place in the exons α1 and α2 directly adjacent to the *MEF2* domain. The α2-*MEF2C* isoform is expressed predominantly in striated muscle tissues, while the α1-*MEF2C* variant is expressed in other different tissues [109]. Exon β, positioned at TAD II (transcriptional activation domain II), is a type of cassette exon. β exon in the second transactivation domain has increased transactivation activities and is expressed in several neural tissues [109, 110]. The 3′ splice site selection-type of alternate splicing, the γ region, is situated in the terminal coding exon of the *MEF2C* gene. It was revealed that the γ region encodes the transcriptional repression domain (Figure 2) [108,109].

*MEF2C* is a 186 kb (kilobase) long gene encoding a member of the MADS-box *MEF2* family of proteins [111]. The human *MEF2C* protein is made up of 6 domains and contains 473 amino acids, namely MADS, MEF2, HJURP-C (holliday junction recognition protein C-terminal), NLS (Nuclear localization sequence) and TAD (tRNA-specific adenosine deaminase) 1 and 2 (Figure 2). The MADS domain contains 56 amino acids at *MEF2C's* N-terminus. This area is strongly conserved and contains a number of A/T base pairs. This region's primary function is to aid dimerization, DNA binding, and co-factor interactions [84]. The MADS domain comprises 56 amino acids, the MEF2 domain begins at amino acid 57 to 86 and the HJURP-C domain contains a total of 30 amino acids, although the stereo-structure of the remainder of the domains remains unclear [112]. The MADS and the MEF2 domain are quite necessary to instigate DNA binding and dimerization, whereas other domains function as transcriptional activators [113]. Studies have confirmed that the hydrophobic furrow on the MADS-box domain of *MEF2* generated by leucine66, tyrosine69, and threonine70 and delimited by helix H2 and the flexible linker between H2 and β3 is crucial to facilitating transcriptional co-activators or co-repressors factors like class IIa HDACs [114], Cabin1 (calcineurin binding protein 1) [115], MyoD (myoblast determination protein) [116], p300 [117] and MASTR (MEF2-activating SAP transcriptional regulator) [116]. Hydrophobic residues in such members, for example leucine in HDAC (histone deacetylase) 4 and 9, Cabin1 and a phenylalanine in myocardin-related transcription factor, MASTR induce insertion into the groove and lead to interaction with MEF2 [116]. High affinity synthetic compounds were shown to inhibit the recruitment of transcriptional factors to *MEF2* [118,119]. Moreover, the HJURP-C domain, which has 30 amino acids, is located next to the MEF2 domain. TAD1 and TAD2 are transcriptional activation domains that complement the HJURP-C domain and are accountable for the activation of transcriptional processes [74, 120]. The NLS domain is positioned at the C-terminal of the *MEF2C* gene and regulates the translocation of proteins in the nucleus [73].

## 4. Functional roles of *MEF2C*

According to previous research, *MEF2C* was associated in a number of differentiation and developmental activities, such as myogenesis, neurogenesis, synaptic development, craniofacial and neural crest development, the growth of the anterior heart region, chondrocyte hypertrophy and vascularization, endothelial cell proliferation and survival [33, 95, 122], in addition, they have also been associated with the occurrence of different forms of cancer [123]. *MEF2* proteins are abundant in neurons and have disparate expression profiles in different parts of the brain, with the strongest concentrations in the cerebellum, cerebral cortex and hippocampus [85, 92]. *MEF2C* safeguards neural cells from apoptotic cell death, implying a significant function in memory and learning.

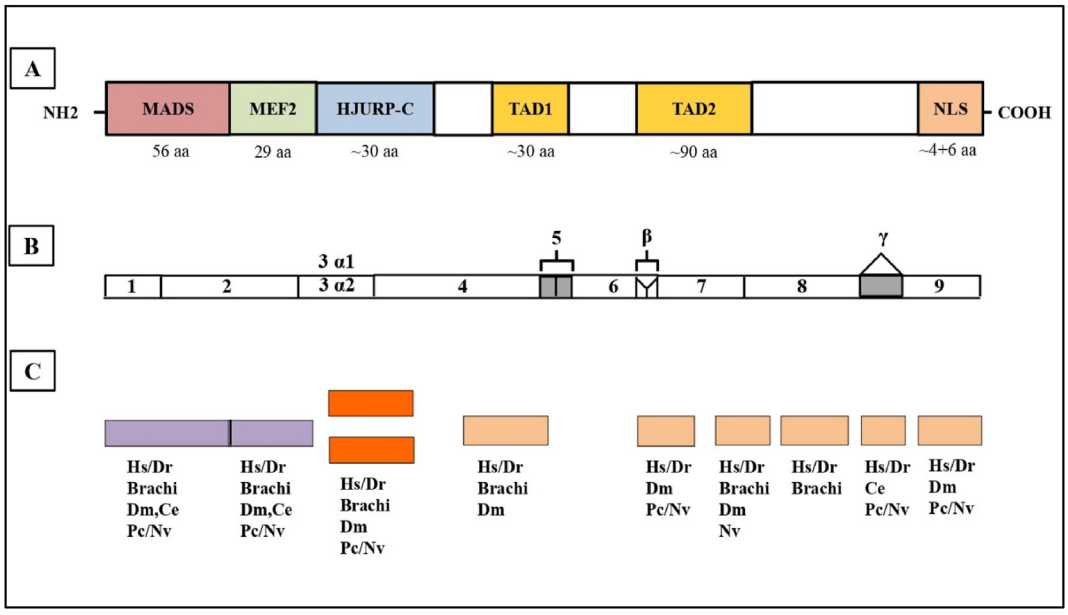
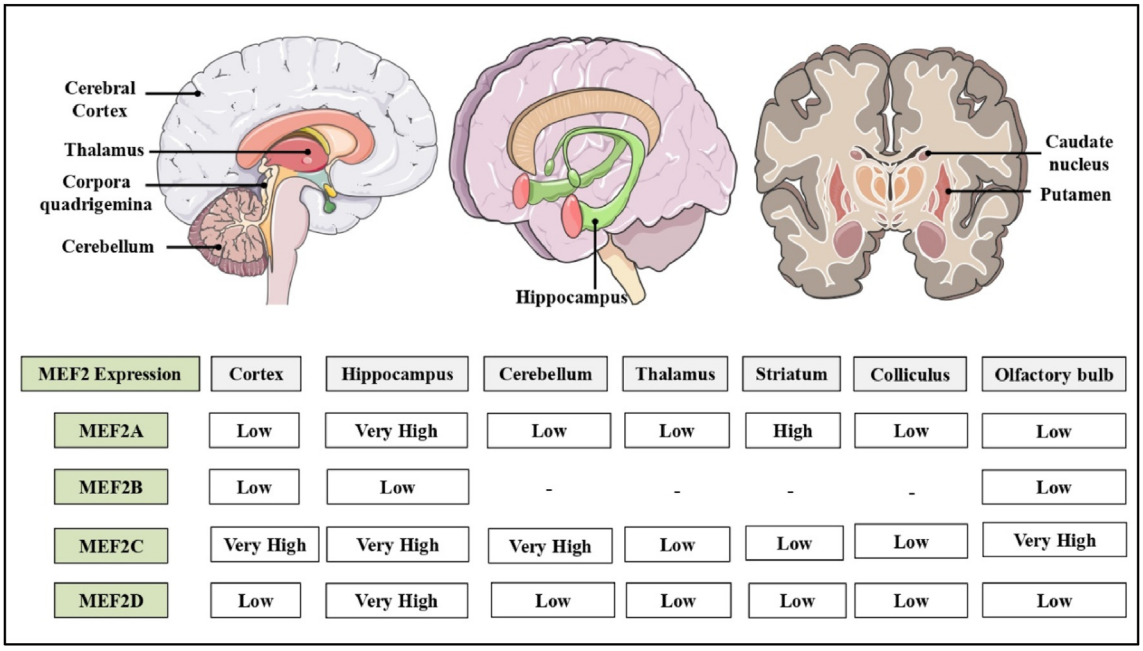



**Figure 2.** A graphical illustration of the *MEF2C* structure alignment [A] Protein domains and their sizes. There are total six domains in *MEF2C*: MADS, MEF2, HJURP-C, TAD1 and 2 and NLS from N-termini to C-termini. [B] Structure of conserved vertebrate exon exhibiting alternate splices with classification following Ganassi et al. (2014) [121]. Gray boxes represents alternate donor/acceptor splice site. Vertical black lines represent exon boundaries. [C] The conservation of domains is represented by color intensity. Species showing conserved regions are listed below: *Homo sapiens* (Hs), *Danio rerio* (Dr), *Terebratalia transversa* (Brachi), *Drosophila melanogaster* (Dm), *Caenorhabditis elegans* (Ce), *Podocoryne carnea* (Pc), *Nematostella vectensis* (Nv).




| MEF2 Expression | Cortex | Hippocampus | Cerebellum | Thalamus | Striatum | Colliculus | Olfactory bulb |
|---|---|---|---|---|---|---|---|
| MEF2A | Low | Very High | Low | Low | High | Low | Low |
| MEF2B | Low | Low | - | - | - | - | Low |
| MEF2C | Very High | Very High | Very High | Low | Low | Low | Very High |
| MEF2D | Low | Very High | Low | Low | Low | Low | Low |

**Figure 3.** This figure represents the relative expression of various *MEF2* proteins in diverse parts of the mouse brain. *MEF2A*, *MEF2B*, *MEF2C*, and *MEF2D* are four chief MEF2 proteins that expressed differentially in distinct but interrelated areas of the brain which specifies that these proteins have particular roles in different brain regions.

Craniofacial impairment and even child death can result from the dysfunction of the *MEF2C* gene in neural crest cells [124].

In both humans and mice, high levels of *MEF2C* gene expression have been identified in skeletal muscles, cardiac muscles, and the brain [79, 125]. During the development of the mouse CNS, high levels of expression have been found in the embryonal cerebral cortex, amygdala, hippocampus, olfactory bulb, midbrain, and cerebellum regions, plus in the adult cerebellum, hippocampus, thalamus, frontal cortex, and dentate gyrus (Figure 3) [89]. The expression profiles and transactivation activities of alternatively spliced *MEF2C* transcripts differ considerably, with some have been shown to be brain-specific [79, 107, 113]. The conditional homozygous deletion of mouse *MEF2C* in radial glial cells during late embryogenesis period and expression of the active form of *MEF2C* in neurons revealed that *MEF2C* contributes to hippocampal-dependent memory and learning by limiting the quantity of excitatory synapses and thereby governing evoked and basal synapse transmission [126]. In particular, another group revealed that mice with a conditional *MEF2C* knockout in neural progenitor cells had aberrant accumulation and compression of neurons traveling to the lower tiers of the neocortex throughout the developmental process [33]. It resulted in reduced brain masses with fewer, less developed neurons later in life, resulting in irregular electrical activities in cells and tissues and acute behavior disturbances close to those observed in murine models of Rett syndrome-like altered paw-clasping and anxiety [33]. Studies have also identified that *MEF2C*, when activated, directs the growth of neurons from murine stem cells [29]. This clearly demonstrates the prominent characteristics of *MEF2C* in early neural differentiation as well as provides a relationship to Rett syndrome.

*MEF2C* has been described to comply with many different co-factors and to stimulate the expression of several genes, and some of those are themselves accountable for ID. Evidence has reported that fragile X mental retardation protein (*FMRP*) is needed to facilitate MEF2 proteins to eradicate excitatory synapses in the hippocampus neurons [127]. Expression profiles in hippocampal neurons of rats have exhibited that MEF2 also regulates multiple transcripts, such as *DIA1* (diaphanous-related formin 1), *PCDH10*, and *UBE3A* (ubiquitin-protein ligase E3A) in which shortcomings are known to induce NDDs like autism, ID, and epilepsy [25, 42]. However, in spite of the potential of *MEF2C* as a critical activity-dependent regulator of neuronal activities, its expression profiles and functional status were only ascertained in selected regions of the brain. Genetic research findings have established critical features of *MEF2* in cerebral cortex and hippocampal neurons, and the implications of *MEF2* gene deletion for cerebellum development have been studied or documented by various different experiments [34, 36, 92, 128].

In the CNS, sensory stimulus triggers the stimulation of *MEF2* factors and many other activity-regulated transcription factors which, consecutively, stimulate the expression of various genes necessary for development and remodeling of synapses [129]. By carrying out a number of genome-wide experiments in hippocampal regions during the development of synapses, Flavell et al., classified around 180 activity-regulated *MEF2* target genes which responsible for a multitude of different characteristics of synapse activities, including inhibitory synapse development, excitatory synapse maturation and excitatory synapse strengthening and weakening [42]. A number of *MEF2* target genes were shown (for e.g. *lgi1*; leucine-rich, glioma inactivated 1, *arhgef9*; Cdc42 guanine nucleotide exchange factor *(GEF)* 9, *kcna1*; potassium voltage-gated channel, shaker-related subfamily, member 1, *ube3a*; ubiquitin protein ligase E3A, *slc9a6*; solute carrier family 9 (sodium/-hydrogen exchanger), member 6, *pcdh10*; protocadherin 10, *c3orf58*; chromosome 3, open reading frame 58) to increase propensity to neurological diseases in human populations, such as ASD and epilepsy, implying that such disorders could be triggered at least partly by interference of activity-dependent gene mechanisms that regulate synaptic or neural circuit development [42]. Moreover, their methodology for identifying *MEF2* target genes exhibited that neural activity facilitates the usage of alternative sites of polyadenylation at several *MEF2* target genes, resulting in activity-dependent generation of truncated mRNAs and proteins which may represent distinct roles than their pre-existing, full-length variants [42]. In sum, their study disclosed that the activity-regulated *MEF2* factors regulate maturation of synapses during brain growth and development.

### 4.1. Functional role of MEF2C in neuronal differentiation

The expression of *MEF2* members typically starts when a neuron commences to differentiate, signifying that *MEF2* portrays a potential

part in this process [81, 85, 89, 93]. *MEF2C* is the most predominant isoform of the four *MEF2* proteins expressed in the developing cerebral cortex region. The expression of *MEF2C* is evident on embryonic day (E) 17 and peaks around E21 [36]. *MEF2C* was found to be predominantly expressed in the cortical plate regions though not discernible in the ventricular zones, indicating that it is specifically expressed in differentiating neurons [36]. Members of the *MEF2* family perform an essential part in nerve cell differentiation, as it was exhibited to facilitate the neuronal gene expression in P19 embryonal carcinoma cells, along with the neurogenic *bHLH* (basic helix-loop-helix) transcription factor *MASH1* (mammalian achaete scute homolog-1) [130]. *MEF2C* might have a neurogenic role in murine embryonal stem cells [29], and stimulate the production of neurons in *hESC* (human embryonic stem cell)-derived neural stem progenitor cells [30]. In a study, Mao et al. found that cells expressing the neuronal marker *TUJ1* (β-tubulin type III) express *MEF2C*, while cells expressing the glial marker *GFAP* (glial fibrillary acidic protein) do not express *MEF2C* [36]. This indicates that *MEF2C* expression is strictly limited to neurons and that *MEF2C* is essential for neural differentiation. Nevertheless, possibly the most compelling evidence suggesting that *MEF2* is essential in differentiation of neuronal cells emerges from research of *MEF2C*-conditional knockout murine models in radial glial progenitors. Cortical layer deformities and deficiencies in neural cell maturation were observed in these conditional knockout models [33]. However, mice with an identical absence of *MEF2C* gene in premature neural progenitors have not been recognized as possessing neural maturation deficits, rather late developmental synapse deformities [126]. Although such synapse deformities may be inferior to more prominent primary deficits in neural maturation, such findings continue to be ambiguous.

Another major factor culpably involved in neuropsychiatric and neurodevelopmental conditions is disparity in the equilibrium between inhibitory and excitatory activity of neurons [131, 132]. The *MEF2* members are transcribed in both inhibitory and excitatory neurons during development and adulthood [28, 33]. According to several experiments, loss of *MEF2C* causes an upsurge in inhibitory cortical synapse connectivity while a decline in excitatory cortical synaptic connectivity means that *MEF2C* acts as a master regulator of both inhibitory and excitatory synapse activities in cortical neurons [41, 133, 134]. *MEF2C*, a transcription factor linked to ASD, has been reported to identify early parvalbumin (PVALB) precursors from other medial ganglionic eminences (MGE)-derived interneuron types [134]. PVALB neurons are fast-spiking interneurons that express the calcium-binding protein PVALB. They are further classified into two subtypes: (1) basket and (2) chandelier cells in the cortex region [135]. PVALB neurons have become quite popular over the past few years due to their increasing role in neurodevelopmental disorders, including ASD [136]. PVALB neurons drive their activity via extensive axonal arborization, primarily inhibiting proximal dendrites and cell soma of their post-synaptic targets [137]. PVALB cells are biologically engineered to provide rapid, robust and effective inhibition of their post-synaptic cells [138]. These cells have also been found to be correlated with plasticity and learning [139, 140]. Oftentimes, PVALB transcript and PV protein concentrations were found to be reduced in ASD patients' brain. Mayer et al. reported that *MEF2C*-conditional deletion in inhibitory neurons leads to a particular deficiency of PVALB interneurons by P20 in cortical layers 2–6, indicating that *MEF2C* is an imperative element for growth and development of healthy populations [134]. In sum, these findings suggest that *MEF2C* is an important *MEF2* factor and plays a potential role in early cortical synaptic growth, and its embryonic depletion triggers behavioral phenotypes reflective of multiple neurodevelopmental disorders, including ASD.

### 4.2. Functional role of MEF2C in neural circuit development

The research of *MEF2* transcription factors in the nervous system has now been exaggerated to evaluate their function in the generation and development of neural circuits *in vivo*. In general, this entailed the alterations of *MEF2*-associated activities in selected regions of the brain and the recognition of changes in behavior linked to disparities in density of dendritic spines, which are neural entities that correspond with the involvement of excitatory synapses. According to a study in mice, prolonged use of cocaine suppresses *MEF2A/D* expression in the nucleus accumbens (NAc) region. This repression results in an upsurge of dendritic spine concentration that may possibly silence the sensitized drug responses. Moreover, upregulation of the constitutively active protein *MEF2-VP16* (a fusion between MEF2 and viral transcription factor VP16) suppresses the upsurge in dendritic spine concentration and enhances the behavioral sensitivity to the drug by disrupting this reaction [141]. In sum, their findings reported that *MEF2* acts as a fundamental regulator of structural synaptic plasticity.

Members of the *MEF2* family were also associated with memory formation by modulating spine growth and development [75]. The analysis of negative or constitutively active *MEF2* transcription factors in addition to loss-of-function studies has revealed an underlying concept of how *MEF2* plays a part in memory formation. The formation of memory corresponds to inhibitory phosphorylation of *MEF2A/D* at S408/S444 residues that causes an increase in spine development which is typically associated with memory formation [142]. Increasing the activity of *MEF2* factors by expressing *MEF2-VP16* inhibits the upsurge in spines, and, subsequently, the generation of new memories. In the hippocampus, amygdala, and anterior cingulate cortex, this mechanistic pathway has been linked to spine development and memory formation [142, 143]. In addition, experiments have shown that *MEF2*-dependent spine regulation is largely reliant on the *MEF2* modulation of its formerly discovered gene *Arc* [42, 142]. By increasing the endocytosis function of AMPA-type glutamate receptors (AMPARs), *Arc* limits their surface expression [144], resulting in reduced synapse potency and synaptic depletion, analogous to homeostatic synaptic scaling or long-term depression [145, 146]. Cole et al. observed that in mice with markedly elevated levels of *MEF2* in the amygdala regions, the consequent disturbance of AMPAR-mediated endocytosis (using an inhibitory peptide) redeemed the *MEF2* associated alterations in fear based memory [142]. Huber and colleagues, on the other hand, suggested a rather completely different mechanism for *MEF2*-mediated synaptic density modulation, though it is still associated with regulation of AMPAR expression [48]. They demonstrated that the stimulation of *MEF2* in hippocampus neurons has contributed to an upsurge in the production of *PCDH10*, a protein that is actively involved in the ubiquitination and lysosomal targeting of the synaptic scaffold protein PSD-95 (postsynaptic density protein 95). Amplification of *PCDH10*-mediated PSD-95 degradation in hippocampal neurons inhibited both *MEF2*-mediated PSD-95 degradation and *MEF2*-mediated synapse removal. PSD-95 links AMPARs and other different proteins at the synapse, and lowering functional synaptic PSD-95 causes synaptic AMPARs to diffuse out of the synaptic cleft and endocytosis of AMPARs [147, 148]. Thus, this is quite plausible that *MEF2* controls AMPAR expression and synaptic integrity by diverse cellular processes. Based on these findings, it was theorized that *MEF2* usually impairs memory formation by accelerating the expression of *Arc* that afterwards curtails the expression of AMPARs, resulting in disruption and removal of synapses.

Considering the impacts on memory observed across specific brain regions, it is anticipated that memory dysfunction will also be seen in brain-specific conditional *MEF2* knockout models. The hippocampus is concerned with memory and learning, where neuronal activity contributes to synapse number regulation [28]. Brain-specific *MEF2A/D* deletions showed no deformity in memory formation [149]. However, multiple studies have revealed that the brain-specific *MEF2C* knockout disrupts hippocampus-dependent memory and learning via boosting the number and transmission of synapses [30, 126]. In a study, Barbosa et al. concluded that *MEF2C* promotes context-dependent fear conditioning, which is a prominent feature of hippocampus-dependent memory and learning formation during development, by repressing the amount of

excitatory synapses and thereby influencing basal and evoked synapse transmission [126]. Gain of *MEF2C* function restricts the number and function of synapses, thereby preserving physiologic responses, while loss of *MEF2C* results in disrupted physiologic regulation of synapse numbers and hampers fear conditioning [126]. Nevertheless, postnatal *MEF2C* deletion in the brain does not alter memory and learning, the assessment of synapse plasticity [150], asserting a distinct role of *MEF2C* gene in the postnatal vs. prenatal brain.

### 4.3. Functional role of MEF2C in neuronal survival

The majority of the preliminary studies that have investigated the functional dynamics of *MEF2* in neural system explored the characteristics of *MEF2's* in the advancement of neural survival and inhibition of apoptotic death. *MEF2* has been found to be vital for the survival of cerebellar granule neurons (CGNs) [36]. Apoptosis-inducing death of differentiating cells is frequently reported in the developing fetal brain [151]. Likewise, the cellular mechanism of apoptosis can also be seen in neuronal differentiating P19 cells. Thereby, P19 cells are believed to constitute an exemplary *in vitro* experimental model for neural differentiation of the CNS *in vivo* [32]. It has been postulated that *MEF2* is a fundamental factor for survival of neurons throughout the development process, and that dysregulations in *MEF2* function by dominant negative regulation could upsurge the apoptosis of differentiating P19 cells. Nonetheless, the cellular mechanism of apoptosis in P19 cells can be reinstated by the expression of the constitutively active *MEF2C* factor, confirming that transcriptional activity of *MEF2* is deemed necessary to prevent cell death during neuronal development [32]. According to studies, when neural activities are suppressed in cultured CGNs, they typically die [36]. It has been documented that the constitutively active form of *MEF2* is expressed to prevent CGNs from apoptotic death; nevertheless, the activation of the dominant negative form has escalated this process [36]. This was thought to be a mechanism that depends upon the stimulation of the *P38 MAPK* (mitogen-activated protein kinase) signaling. The P38 MAPK signaling was identified as a critical switch of cell death and survival in a number of different cells [152]. The *P38/MEF2* signaling has been shown to be a prerequisite for $Ca2^{+}$ mediated CGNs survival in a developing culture, implying that *P38/MEF2* is certainly necessary in primary neurons [36]. Two critical *P38 MAPK* family members [1]: P38α and [2] P38β2, are recognized to trigger *MEF2* via phosphorylation of Ser/Thr residues [153, 154]. It was demonstrated that P38α is phosphorylated throughout the growth and development of nervous tissues [32]. Additionally, it was ascertained that the transfection of dominant negative P38α significantly accelerated the apoptosis in differentiating cells. However, the co-expression of the *MEF2C* gene dramatically salvaged these differentiating cells from apoptotic death [32]. Such findings, thus, reinforce the concept that the *P38α/MEF2* signaling cascade performs a substantial part in mitigating apoptosis during differentiation of neurons.

A mechanistic pathway for neural cell death encompassing caspase-catalyzed dissociation of *MEF2* proteins adversely affects the typical pro-survival activity of the *P38/MEF2* signaling and leads to neural apotosis [155]. Caspases are proteases which are necessary for the process of apoptosis [156]. They are formulated as inactive pro-enzymes and triggered in a proteolytic cascade after being exposed to an apoptotic signal [155]. In a study, Li et al. described the dissociation of *MEF2A/D* in CGNs following $K^{+}$ depletion. However, their result did not validate a definite association of caspases with *MEF2* factors and they were unable to locate a specific *MEF2* cleavage site [34]. In another study, Okamoto et al. demonstrated that when cerebrocortical neurons are exposed to excitotoxic concentrations of NMDA (N-methyl-D-aspartate), a stimulant reported to trigger P38 signaling and caspase-related enzymes, causes caspases to cleave *MEF2A*, *MEF2C*, and *MEF2D* [155]. Target sites of caspase on *MEF2* proteins are present in the transactivation domain with cleavage facilitating the generation of endogenous dominant-interfering forms of *MEF2*. Such dominant-negative *MEF2* is capable of blocking intact *MEF2* from activation, thus leading to neuronal apoptosis [155]. Another potential pathway for neuronal damage concerning *MEF2* is the disruption of the peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) signaling and protein S-nitrosylation of *MEF2C* in Parkinson's disease (PD) [157]. PGC1α was considered as a substantial *MEF2* effector due to its function in mitochondria and neuroprotection in PD models [158, 159]. To clarify the importance of *MEF2C* in PGC1α signal transduction, Ryan et al. has shown that basal and toxin-induced nitrosative stress (a nitric oxide-mediated nitrosylation of redox-sensitive thiols) can cause S-nitrosylation of *MEF2C* in A53T α-synuclein mutant A9 dopaminergic neurons. This reaction interrupts the *MEF2C-PGC1α* transcriptional pathway, leading to mitochondrial dysfunction and ultimately results in apoptosis [157]. Nitric oxide (NO) works as a signal molecule that influences a number of different targets. NO regulates diverse physiological functions inside the brain, like development of neurons, synapse plasticity, and release of neurotransmitters. However, excessive NO output in the brain is related to many acute and chronic neurodegenerative disorders, shifting the nitrosylation/denitrosylation homeostasis equilibrium towards intensified nitrosylation [160, 161]. Previous research has shown that NO can facilitate redox reactions through S-nitrosylation, demonstrating the transition of NO to a vital molecule called cysteine thiol, culminating in neurogenesis regulation and survival of neurons in multiple brain regions [162]. Recently, Ryan et al. reported that, following exposure of the recombinant *MEF2C* to endogenous nitric oxide S-nitrocysteine (SNOC), *MEF2C* can be S-nitrosylated, and this modulation tends to occur on cysteine (Cys39) as sulfonation, leading to the suppression of *MEF2C* transcriptional activities and cell death by PGC1α-mediated pathway [157]. In sum, all these studies concluded that reduced *MEF2* leads to the suppression of PGC1α activation, and S-nitrosylation is a potential factor in suppression of *MEF2* expression. The effect of S-nitrosylation of MEF2C, on the other hand, affects not only neuronal viability in the brain during injury, such as ischemia, but also adult neurogenesis [163]. A study by Okamoto et al. revealed that redox-modification by NO interacting with several cysteine residues of *MEF2* factors serves as a cellular trigger to regulate neurogenesis and apoptosis in the brain [163]. As per their findings, *MEF2A* stimulates the adult hippocampus neurogenesis *in vivo* and *in vitro*, but the S-nitrosylation of *MEF2A* suppresses this activity by inhibiting TLX (T cell leukemia homeobox) cascade [163]. In contrast, S-nitrosylation of *MEF2C* leads to NO-mediated apoptosis in cerebrocortical neurons during ischemic injury and in Alzheimer's disease (AD) mice models by obstructing the Bcl-xL (B-cell lymphoma-extra large) anti-apoptotic pathway [163]. Although this pathway is quite different from the *MEF2C-PGC1α* anti-apoptotic pathway mentioned by Ryan et al. [157]. As per these findings, S-nitrosylation of *MEF2* factors serves as a redox transition switch, suppressing both neurogenesis and survival of neurons.

In addition, a number of stimuli and distortions impair the function of *MEF2* in neuronal survival. Numerous kinases were defined that cause phosphorylation of *MEF2* factors and restrict their activities, causing neural apoptosis. In a study, Wang et al. have demonstrated that GSK3β (glycogen synthase kinase 3 beta) causes the phosphorylation of total 3 residues in *MEF2D*, which suppresses the *MEF2D*-related activities that eventually contribute to apoptosis of CGNs [164]. Another group has demonstrated that stimulation of PKA (protein kinase A) via cAMP (cyclic adenosine monophosphate) leads to PKA-regulated inhibition of phosphorylation of *MEF2D* at S121/S190 residue resulting in apoptosis of hippocampus neurons [165]. Furthermore, neurotoxic stimuli may stimulate CDK5 facilitated inhibitory phosphorylation of *MEF2A/D* at S408 and S444 residue, respectively, ultimately resulting in apoptotic death of cortical neurons [35]. *In vivo* research has shown the significance of *MEF2*'s in the survival of neurons [149]. To more thoroughly investigate the specific and redundant characteristics of *MEF2* factors in regulating survival of neurons *in vivo*, Akhtar et al. produced a brain-specific triple knockout ($MEF2A/C/D^{TKO}$) mouse model [149]. Mice with a homozygous *MEF2A* null mutation die prematurely during

the 1st week of life owing to lack of cardiovascular activities [166]. Therefore, Akhtar and his colleagues created a conditional *MEF2A* null allele with loxP (locus of X-over P1) sites ($MEF2A^{loxP}$) in the intron flanking the second coding exon [149]. Deletion of the genetic region amid the loxP sites disrupts the activity of the *MEF2A* gene [166]. *MEF2A* was then deleted explicitly throughout the CNS region via mating $MEF2A^{loxP/loxP}$ mice with transgenic lab mice, which express cyclic (Cre)-recombinase under the regulation of the human GFAP promoter (hGFAP-Cre), which is transcribed in neural progenitor cells throughout late embryogenesis [149, 167]. Similarly, hGFAP-Cre line was also used to delete *MEF2C* in the nervous system via mating $MEF2C^{loxP/loxP}$ female mice to $MEF2C^{KO/+}$ heterozygous male fostering a transgene, which expresses Cre-recombinase under the influence of hGFAP-Cre [126]. *MEF2A* knockout and *MEF2A/D* double knockout mice have normal and healthy brain size and shape and display no signs of neuronal cell death, while mice with a triple deletion ($MEF2A/C/D^{TKO}$) throughout the brain exhibit reduced brain sizes and early postnatal lethality followed by enhanced neural cell death comparative to controls [149]. Notably, the brain-specific *MEF2C* deletion solely may not induce any deformities in brain size, shape or apoptosis, indicating that mice with mutations in either one or two of the *MEF2* factors seemed to have no such complications, possibly because of the propensity of co-expressed *MEF2* members to supplement one another. Furthermore, their *MEF2A/C/D* triple knockout mice demonstrate impairments in the measurement of hippocampus short-term plasticity. This indicates that *MEF2A*, *C* and *D* act superfluously in the survival of neurons, but that *MEF2C* is the isoform comprised in hippocampal synaptic activity [149]. Taken together, these observations contribute to an extensive elucidation of the *MEF2* factors in memory and learning, and synaptic activities.

## 5. *MEF2C* as a risk factor for ASD

All *MEF2* factors, particularly *MEF2C*, are transcribed abundantly in the neuronal cells [107]. Research has shown that the production of *MEF2C* is important for neural differentiation and survival, as well as in the development of synapses in the brain. However, prior reports have displayed that mice with a complete *MEF2C* knockout are embryonically lethal by E9.5-10 due to incomplete cardiac morphogenesis [168]. And, since the heart forms before the brain, there is evidently no brain development, resulting in embryonic lethality [168]. Thus, to study the functions of the *MEF2C* gene in brain development, scientists have generated brain-specific conditional knockout models to evaluate the detailed characteristics of the *MEF2C* gene in growth and development of the brain. For example [1]: nestin-driven *Cre* is used to knockout *MEF2C* at the neural stem/progenitor cell (NSC) stage. In this they cross those mice which are expressing the nestin-Cre transgene ($n\text{-}Cre^{+}$) with mice which carry the conventional exon 2-deleted allele of *MEF2* ($MEF2C^{\Delta 2}$) to generate $n\text{-}Cre^{+}/MEF2^{+/\Delta 2}$ mice. These mice will then cross with the $MEF2C^{loxp/loxp}$ mice to acquire the $n\text{-}Cre^{+}/MEF2C^{loxp/\Delta 2}$ conditional null mice [33, 168, 169], whereas [2] *GFAP* and *Emx1* (empty spiracles homeobox 1) are used to knockout *MEF2C* at a somewhat later stage [41, 126, 170]. Geneticists delineated the overlapping regions of 5q14.3q15 loci microdeletions that induce neural defects in individuals, and determined *MEF2C* haploinsufficiency as the significant trigger. ASD, ID, absence of speech, stereotyped behavior, epilepsy, and other motor abnormalities, including hyperactivity, are among the signs and symptoms shown by these patients [63, 79, 171, 172]. The MEF2C haploinsufficiency syndrome refers to a group of conditions accompained by MEF2C haploinsufficiency (MCHS). MCHS accounts for a small percentage of all ASD-related cases, though certain MEF2C-mediated genes were linked with distinct ASD types. Conditional gene disruption of the *MEF2C* exon 2 in mice, which transcribes a significant proportion of the DNA binding domain, generates mice with multiple structural, behavioral, and synapse-related abnormalities in several neural subpopulations in the developing regions of the brain [33, 126, 173]. Tu et al. have developed $MEF2C^{+/-}$ (*MEF2C-het*) mice to investigate the human MCHS-related ASD. In their study, it was shown that *MEF2C-het* mice had synaptic and neuronal abnormalities, indicating that *MEF2C* haploinsufficiency plays a significant part in MCHS/ASD-like behavioral characteristics [173].

According to Z. Li et al., disruptions in *MEF2* function and expression may occur very early in development, particularly in embryonal neural stem cells (NSCs). Conditional *MEF2C* knockout in NSCs develops certain ASD-like neurodevelopmental abnormalities [29]. In contrast, adult *MEF2C* conditional knockout null mice that live to adulthood exhibit features indicative of Rett syndrome [29].

Interaction of *MEF2C* with the other genes, such as *MeCP2* (methyl CpG binding protein 2), *CDKL5* (cyclin-dependent kinase-like 5) [79, 174] and *UBE3A* [175] is linked to Rett and Angelman syndromes, respectively. *MeCP2* is a significant contributing factor to Rett syndrome when mutated and can bind to the promoter of *MEF2C* gene [174]. It was discovered that abnormalities in *MeCP2* result in neurological symptoms that mirror Rett syndrome [174]. According to a previous study, *MeCP2*-null mice remain normal and healthy till 6 weeks of age. Thereafter, they acquire serious neurophysiological dysfunctions leading to death by 12 weeks of age [176]. Expression profiles of *CDKL5* and *MeCP2* were assessed in blood serum samples of individuals with *MEF2C* mutations or 5q14.3q15 microdeletions; in all individuals, the profile of *MeCP2* expression was reported to be substantially decreased, implying an analogous mechanism of *MEF2C* and *MeCP2*. Likely, the levels of *CDKL5* expression have also decreased [79]. Earlier molecular experimental studies have established the involvement of *CDKL5* and *MeCP2* in the mutual pathway [177]. As per the co-transfection studies, *CDKL5* and *MeCP2* regulation are within the transcriptional control of the *MEF2C* gene [79]. In a study, Zweier et al. described four distinct *de novo* heterozygous mutations in the *MEF2C* gene in 4 out of 362 probands with psychological disabilities who had been monitored for dysregulations in the *MEF2C* gene [79]. Two of the mutations were missense mutations, and the other two were truncating mutations. Heterozygous deletions of the *MEF2C* gene were seen in two other patients with similar condition. In all individuals with deletions in the *MEF2C* gene or involving the *MEF2C* gene region, as well as the individuals described by Le Meur et al. (2010) [63], Guerrini et al. (2009) [178], and Engels et al. (2009) [179], blood-derived RNA results showed a substantial decrease in the amount of *MEF2C* isoform 2 mRNA levels, indicating haploinsufficiency. The levels of *MEF2C* mRNA were not reported to be lower in two individuals who had a missense mutation. Both deletion and mutation caused a significant reduction in the transcriptional function of the *MEF2C* gene, which might be rescued by the wild-type *MEF2C* gene. Eventually, all of the individuals, along with the two who had missense mutations, reported relatively low *MECP2* mRNA expression levels, and all but two individuals had reduced *CDKL5* mRNA expression levels [79]. Moreover, a key finding from the Chahrour et al. study demonstrated that *MeCP2* governs the expression of several genes in the hypothalamic region, functioning not only as a transcriptional activator but also as a repressor [174]. They also stated that alterations in transcriptional activities imply that duplication of phenotype is caused because of *MeCP2* gain of function instead of loss of *MeCP2* function, and that RTT is mainly caused by loss of transcriptional activation instead of derepression [174]. This indicates that the gain of *MeCP2* function induces considerably further activation than suppression, while the loss of *MeCP2* function has the complete opposite effect.

Angelman syndrome, also known as happy puppet syndrome, is a rare developmental and neurological disorder that mainly affects the nervous system. It is defined by microcephaly (shorter-than-normal head), ataxia, seizures, muscle hypotonia (decreased muscle tone) with hyper-reflexia, and motor disabilities. It is triggered by the loss of the maternal allele of the *UBE3A* gene in chromosome 15 locus [180], which is essential for ubiquitin-proteasome signaling and the development of synapses [181]. Adequate number of copies of a *UBE3A* gene is essential for healthy brain growth, as asserted by NDDs linked with *UBE3A* mutations, deletions,

and copy number variations (CNVs) [182]. Some of the traits of Angelman syndrome can indeed be found on the autism spectrum, for example poor communication skills, absence of speech, attention deficits, hyperactivity, insomnia, and a deficiency in motor growth and development [183, 184]. Recently, employing a fly (*Drosophila melanogaster*) as a screening model for gene interactions and by consequent co-immunoprecipitation in human cell lines, Straub et al. reported a specific functional correlation between *MEF2C* and *UBE3A* that could eventually lead to the phenotypic overlap between *MEF2C*-related ID and Angelman syndrome [185]. Nevertheless, there is still a need for more comprehensive scientific support of *UBE3A* influencing *MEF2C* gene in an ubiquitous manner.

To specifically assess the functions of the *MEF2C* gene in the postnatal brain directly, Adachi et al. produced conditional *MEF2C* knockout mice model by means of calcium/calmodulin-dependent protein kinase II (CaMKII)-Cre93 line [150]. These conditional knockout mice have been produced by pairing floxed *MEF2C* (*fMEF2C*) mice with mice transgenic for Cre-recombinase under the regulation of the CaMKII-Cre93 (CaMKII promoter), which directs the deletion of genes in anterior regions of the brain, such as the cerebral hemispheres, the thalamus, and the hypothalamus, including the hippocampus, at postnatal days 10–14 [150]. They discovered that postnatal brain deletion of the *MEF2C* gene ultimately led to a substantial rise in the numbers of spines in the hippocampal regions. Conditional brain-specific deletion of *MEF2C* in mice also exhibits variations in motor activities and abnormalities in motor coordination. Nevertheless, in mice, deletion of the *MEF2C* gene in the postnatal brain did not influence memory and learning function, synapse plasticity measurements, and a number of other behavioral assessments put forward to summarize the ASD-related characteristics [150]. Due to the massive frequent involvement of *MEF2C* gene in the negative regulation of synaptogenesis, the above observations reveal that the impact of *MEF2C* gene as a regulator of spine numbers is independent of embryonic and postnatal stages of growth and development. Although the functional role of the *MEF2C* gene as a chief regulator of memory and learning, plasticity of synapses, and behavioral assessments of ASDs relies on the expression of *MEF2C* throughout embryonic growth and development and is not specifically related to alterations in the numbers of spines [150]. In sum, this research gives a profound understanding into the relevance of the developmentally specific gene modulation of endogenous expression of *MEF2C* as a critical factor in articulating the mechanisms and functions of *MEF2* in the CNS. To model human MCHS, a group of scientists developed mice with only one operational copy of the *MEF2C* gene, and they discovered that these mice presented increased premature death rates, had autism-like characteristics, and had decreased viability relative to wild-type mice [173]. Using this type of MCHS murine model, scientists have classified irregularities in inhibitory (I) and excitatory (E) neuronal transmission, in the expression of synapse protein, and in neural numbers. In short, the fall of *MEF2C* resulted in an excitatory(E)/inhibitory(I) imbalance [173]. In their work, they examined the activity of NitroSynapsin, a memantine-like molecule, in MCHS mice. Their findings revealed that the NitroSynapsin therapy rescued autism-like characteristics and restored the equilibrium of E/I in MCHS mice. Notably, treatment with NitroSynapsin did not considerably influence the social behavioral activity of wild-type mice. In sum, their results indicate that NitroSynapsin compound may reduce MCHS-like behavioral and neurological deformities resulting from the depletion of the *MEF2C* gene. As a result, the NitroSynapsin compound may therefore provide a new potential alternative for MCHS. In addition, NitroSynapsin therapy can also have positive clinical efficacy in various other neurodevelopmental conditions. Since the *MEF2C* gene regulates a wide number of ASD-related genes, as per the researchers, a therapeutic compound for MCHS might work effectively towards different other types of ASD forms [173]. Another study stated that the MCHS-linked missense mutation complexes in the conserved DNA binding domain and adversely affect the DNA binding of *MEF2C* [170]. To model the genetic accuracy of MCHS in mice, the authors developed a heterozygous *MEF2C* (*Mef2c-Het*) mice via breeding *Mef2c-flox* mice to protamine-1 promoter (Prm)-Cre mice. Subsequently, the *Prm-Cre* allele was deleted from C57BL/6J wild-type mice through repeated backcrossing. Conditional *Mef2c-cHet* mice were produced via breeding *Mef2c-flox* mice with *Emx1-Cre*, a cell type-selective Cre-expressing transgenic mice to generate $Mef2c^{fl/+}$ [170]. In this study, authors ascertained that DNA binding–deficient *Mef2c-Het* mice exhibited a number of MCHS-related traits like deficits in social communication and interaction, hyperactivity, monotonous behaviors, anxiety, lessened sensitivity towards painful stimuli (e.g. foot-shock), alterations in cortical gene expression, and disruptions in excitatory synapse transmission [170]. Multiple deregulated genes have been recognized in the *Mef2c-Het* cortex, as well as extensive accumulation of autism susceptibility and excitatory neuronal genes [170]. Their results inferred that hypofunction of *MEF2C* during the period of growth and development induces myriad dynamic alterations in gene expression, cortical synapse transmission, and behaviors suggestive of ASD and MCHS. This research has revealed that *MEF2C* governs normal brain functions and development via different cell types, including excitatory neural and neuro-immune populations. However, the conditions with respect to ASD and MCHS are much more complicated. The decrease in MEF2C due to haploinsufficiency could result in a decrease in synapse number during development. And the occurrence of a one good copy of MEF2C gene on the normal allele could still lead to reduced spine numbers in mature neurons that develop under MCHS conditions. Therefore, this situation is not yet clear and further work is required.

Microglia, both developing and adult, play an essential part in the growth and development of the brain like neurogenesis, myelinogenesis, synaptic phagocytosis, and synapse patterning [99, 100, 102, 186]. *MEF2C* has been reported to be expressed in both mouse and human microglial cells, and *MEF2* members are involved in the development and regulation of microglia [98]. Microglia-enriched RNAs have been shown to be deregulated in the human cortex in idiopathic ASD individuals brain [187] and in the *Mef2c-Het* mouse cortex [170]. Recently, a study demonstrated that hypofunction of *MEF2C* gene in microglial cells is enough to induce autism-like symptoms in mice and to influence cortical glutamatergic pathways [170]. In order to discover the prominent characteristics of microglia in the occurrence of MCHS-like phenotypes, the authors generated two experimental models: (1) mice heterozygous for *MEF2C* in Emx1-lineage cells *(*$Mef2c\text{-}cHet^{Emx1\text{-}cre}$*)* which account for around 85% of forebrain excitatory neurons in the cortical and hippocampal regions. $Mef2c\text{-}cHet^{Emx1\text{-}cre}$ mice showed deregulated anxiety-like activities and male-selective upsurge in locomotor and monotonous hopping activities; however, they displayed none variations in social activities or shock sensitivity. In $Mef2c\ cKO^{Emx1\text{-}cre}$ mice, the amplitude of mEPSC (miniature excitatory postsynaptic current) in layer 2/3 pyramidal neurons was reduced, while in $Mef2c\text{-}cHet^{Emx1\text{-}cre}$ mice, the amplitude of mEPSC was increased. This indicates that the Emx1-lineage excitatory forebrain neurons significantly support the growth of some, though not all, of the behavioral characteristics. (2) Microglia-selective *Mef2c-Het* mice *(*$Mef2c\text{-}cHet^{Cx3cr1\text{-}cre}$*)* displayed social impairments in the three-chamber social interaction test. Moreover, $Mef2c\text{-}cHet^{Cx3cr1\text{-}cre}$ mice displayed a substantial rise in male-specific monotonous jumping, anxiety, and shock sensitivity activities. They also found a decrease in the eEPSC (evoked excitatory postsynaptic current) amplitude in the $Mef2c\text{-}cHet^{Cx3cr1\text{-}cre}$ mice. Moreover, their findings also indicate that the lack of one *MEF2C* allele may not always typically generate traditional microglia instigation, but also impairment in the growth, maturation and function of microglia [170]. Future studies would therefore be necessary to ascertain the strategic roles of *MEF2C* in the growth and development of microglia, and whether or not *MEF2C* heterozygosity influences several of the described functions of microglial cells in brain growth and development.

Fragile X syndrome (FXS), also termed as Martian-Bell syndrome, is a non-Mendelian trinucleotide repeat disorder [188]. FXS has been the most frequent cause of IDs and the most predominant monogenic cause of

ASD [189]. Lubs and his associates discovered FXS in 1969, but the first fragile X-linked sequence of inheritance was described in 1949 by Martian and Bell [190, 191]. The Fragile X syndrome is typically triggered via alterations in the *FMR1* (Fragile X Mental Retardation 1) gene which typically entails an increase of >200 CGG repeat sequences in the 5′ UTR region of the *FMR1* gene, leading to transcriptional silencing of the *FMR1* gene and the lack or significant reduction of the transcribed protein (Fragile X Mental Retardation 1 protein; FMRP) [191, 192]. Studies have shown that FMRP is a significant regulator for the translation process of several mRNAs which are involved in synapse plasticity, neuronal morphology, and cognitive development, and its absence contributes to differing degrees of ID [193, 194]. Evidence shows that FMRP is needed to allow *MEF2* members to remove excitatory synapses in mice's hippocampus neurons [127]. The density of dendritic spines in the dentate gyrus region is significantly greater in *FMR1* knockout mice during development than in wild-type mice, indicating a lag in the down-regulation of synapse [195]. In the hippocampal neurons of *FMR1* knockout mice, though, *MEF2*-mediated elimination of synapses and the upsurge in synapse number because of *MEF2* blockade were suppressed. These forms of deficiencies may be rescued by the acute post-synaptic FMRP expression, which demonstrates that post-synaptic communication activity among FRMP and *MEF2* is disrupted in FXS [127]. A study by Zang et al. reported that in the hippocampal regions, FMRP can bi-directionally regulate the excitatory synapse activities in dendrons via linking to dendritic RNA, i.e. by fostering maturation of synapses throughout the first postnatal week 6–7, whereas disrupting synapse development during the second postnatal week 13–16 [50]. In addition, the expression of FMRP has also been regulated via *MEF2* factors, which, consecutively, are attuned by neural depolarization and are stimulated following the developmental time frame [50]. In sum, this study demonstrated the potential roles of *MEF2* in FXS via FMRP.

Furthermore, prior studies have demonstrated that delta (δ)-catenin, a key constituent of the cadherin–catenin cell adhesion complex, is localized to synapses and partly co-localized with synaptic proteins, implying a functional involvement at synaptic regions [196, 197]. The absence of the *CTNND2* (catenin delta 2) gene, which encodes δ-catenin, was linked with the ID phenotype, indicating that therapeutic interventions that reinstate the critical functions of δ-catenin might aid the intellectual phenotypes [198]. A study by Yuan and colleagues stated that the deficiency of δ-catenin was related to intellectual disability [199]. In their study, they reported that the concentration of endogenous *MEF2C* is not disrupted due to the loss of δ-catenin. However, the *MEF2C* gene expression may facilitate the removal of excess dendritic spines observed with the loss of δ-catenin. Even in the absence of δ-catenin, the protein levels of *MEF2C* remain unchanged, indicating that the altered numbers of synapses found in the absence of δ-catenin may not correspond to a reduction in *MEF2C* levels [199]. Even though mice associated with the loss of δ-catenin display serious learning disabilities, transitory induction of *MEF2C* during the developmental phase would be expected to minimize some of the learning-related deficiencies [199]. In summary, their analysis has ascertained that *MEF2C* can facilitate the removal of an excessive number of spines produced in the absence of δ-catenin. Taken together, all the above studies on *MEF2* or *MEF2*-regulated transcripts in synapse removal, regulation and plasticity specify that *MEF2* transcription factors play a potential role in neurodevelopmental disorders.

## 6. Concluding remarks

Deficits in the molecular and cellular mechanisms, as well as signaling pathways that regulate neuronal and synapse development, transmission, and neural activities in the brain may eventually lead to neurodevelopmental ailments, like intellectual disability and ASDs. Therefore, to characterize the significant factors that exacerbate these brain developmental disorders, we need to search for new therapeutic targets. One such possible therapeutic target is the *MEF2C* gene, which has been implicated in muscle growth and development, and is ubiquitously transcribed in the developing brain regions. Several people with autism, schizophrenia and ID have genetic mutations within or close to the *MEF2C* gene. *MEF2*, a transcription factor, functions in brain development and regulates excitatory synapses formation and removal in response to neuronal activities. *MEF2C*, a family member of the *MEF2* family, is a transcriptional activator that binds directly to the *MEF2* component. It plays an important role in various critical developmental activities, such as neurogenesis, myogenesis, synaptogenesis and hematopoiesis. The *MEF2C* gene is essential for normal synapse and neuron development. Studies have postulated that irregularities in *MEF2C* may increase susceptibility to several neurological disorders by hampering the equilibrium of inhibitory and excitatory synapses in the developing brain regions. According to recent genomic investigations, it has been ascribed that the mutation or deletion of the *MEF2C* gene is linked to a number of neurological conditions with ASD and ID-like characteristics. In addition, research shows that *MEF2C* is also correlated with other different brain-associated diseases. Previous data strongly suggests that the *MEF2C* gene in several brain regions responds to differing arrays of activities. The neuronal cells in the brain become more responsive as the brain matures and establishes various new connections. And here *MEF2C* is vital since it regulates and modulates a number of endogenous downstream factors that aid in the growth of neurons and in the formation of neuronal connections. If the neurons lose such consistency or balance, they will have an entirely abnormal set of connections. Earlier research has revealed that *MEF2* factors perform a critical function in shaping and guiding the organization of brain connections at an early stage of development. Synapses between neurons are believed to form quite strenuously during brain development; however, they are chopped down during the late adolescent stage. *MEF2* members, including *MEF2C*, tend to perform a substantial part in this critical process. Therefore, we should further investigate the molecular and cellular mechanism of the activity of *MEF2* proteins in autism-like behaviors, and the impaired dysregulated genes, plus the function of the *MEF2C* gene in brain circuitry, which could further facilitate one of the most preponderant conjectures regarding the underlying cause of autism, which refers to a disparity in neural connectivity and/or synapse formation between brain cells. Equipped with these profound insights, it might then be possible to treat the complex symptoms of such neurodevelopmental disorders.

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## References


[1] I. Parenti, L.G. Rabaneda, H. Schoen, G. Novarino, Neurodevelopmental disorders: from genetics to functional pathways, Trends Neurosci. 43 (2020) 608–621.
[2] A. Thapar, M. Cooper, M. Rutter, Neurodevelopmental disorders, The Lancet Psychiatry 4 (2017) 339–346.
[3] D.C. Tărlungeanu, G. Novarino, Genomics in neurodevelopmental disorders: an avenue to personalized medicine, Exp. Mol. Med. 50 (2018).
[4] A. Thapar, D.S. Pine, J.F. Leckman, S. Scott, M.J. Snowling, E. Taylor, Rutter's Child and Adolescent Psychiatry, sixth ed., 2015, pp. 1–1077.
[5] M.K. Stachowiak, A. Kucinski, R. Curl, C. Syposs, Y. Yang, S. Narla, et al., Schizophrenia: a neurodevelopmental disorder - integrative genomic hypothesis and therapeutic implications from a transgenic mouse model, Schizophr. Res. 143 (2013) 367–376.
[6] F. Craig, R. Savino, A. Trabacca, A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder, Eur. J. Paediatr. Neurol. 23 (2019) 31–42.
[7] C. Lord, M. Elsabbagh, G. Baird, J. Veenstra-Vanderweele, Autism spectrum disorder, Lancet 392 (2018) 508–520.
[8] L. Kanner, Autistic disturbances of affective contact, Acta Paedopsychiatr. 35 (4) (1968) 100–136.
[9] H. Asperger, Autistic psychopathy in childhood (translated by Frith, Uta), in: Autism and Asperger Syndrome, 1991, pp. 37–92.
[10] J. Baio, L. Wiggins, D.L. Christensen, M.J. Maenner, J. Daniels, Z. Warren, et al., Prevalence of autism spectrum disorder among children aged 8 Years - autism and developmental disabilities monitoring network, 11 Sites, United States, 2014, MMWR Surveill Summ 67 (6) (2018).
[11] M. Elsabbagh, G. Divan, Y.J. Koh, Y.S. Kim, S. Kauchali, C. Marcín, et al., Global prevalence of autism and other pervasive developmental disorders, Autism Res. 5 (3) (2012) 160–179.
[12] K. Lyall, L. Croen, J. Daniels, M.D. Fallin, C. Ladd-Acosta, B.K. Lee, et al., The changing epidemiology of autism spectrum disorders, Annu. Rev. Publ. Health 38 (2017) 81–102.
[13] R. Canitano, Epilepsy in autism spectrum disorders, Eur. Child Adolesc. Psychiatr. 16 (1) (2007) 61–66.
[14] A. Yasuhara, Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD), Brain Dev. 32 (10) (2010) 791–798.
[15] N. Devitt, L. Gallagher, R. Reilly, Autism spectrum disorder (ASD) and fragile X syndrome (FXS): two overlapping disorders reviewed through electroencephalography—what can be interpreted from the available information? Brain Sci. 5 (2) (2015) 92–117.
[16] J.L. Neul, The relationship of Rett syndrome and MECP2 disorders to autism, Dialogues Clin. Neurosci. 14 (3) (2012) 253–262.
[17] A. Vignoli, F. La Briola, A. Peron, K. Turner, C. Vannicola, M. Saccani, et al., Autism spectrum disorder in tuberous sclerosis complex: searching for risk markers, Orphanet J. Rare Dis. 10 (1) (2015).
[18] M. Valicenti-McDermott, K. McVicar, I. Rapin, B.K. Wershil, H. Cohen, S. Shinnar, Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease, J. Dev. Behav. Pediatr. 27 (2 SUPPL. 2) (2006).
[19] A.L. Richdale, K.A. Schreck, Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies, Sleep Med. Rev. 13 (2009) 403–411.
[20] S.W. White, D. Oswald, T. Ollendick, L. Scahill, Anxiety in children and adolescents with autism spectrum disorders, Clin. Psychol. Rev. 29 (2009) 216–229.
[21] S. De Rubeis, X. He, A.P. Goldberg, C.S. Poultney, K. Samocha, A.E. Cicek, et al., Synaptic, transcriptional and chromatin genes disrupted in autism, Nature 515 (7526) (2014) 209–215.
[22] M. Ng, J.G. de Montigny, M. Ofner, M.T. Do, Environmental factors associated with autism spectrum disorder: a scoping review for the years 2003–2013, Health Promotion and Chronic Disease Prevention in Canada 37 (2017) 1–23.
[23] B.M. Elmer, M.L. Estes, S.L. Barrow, A.K. McAllister, MHCI requires MEF2 transcription factors to negatively regulate synapse density during development and in disease, J. Neurosci. 33 (34) (2013) 13791–13804.
[24] Z. Zhang, M. Cao, C.-W. Chang, C. Wang, X. Shi, X. Zhan, et al., Autism-associated chromatin regulator brg1/SmarcA4 is required for synapse development and MEF2-mediated synapse remodeling, Mol. Cell Biol. (2015). MCB.00534-15.
[25] E.M. Morrow, S.Y. Yoo, S.W. Flavell, T.K. Kim, Y. Lin, R.S. Hill, et al., Identifying autism loci and genes by tracing recent shared ancestry, Science (80-) 321 (5886) (2008) 218–223.
[26] F. Novara, S. Beri, R. Giorda, E. Ortibus, S. Nageshappa, F. Darra, et al., Refining the phenotype associated with MEF2C haploinsufficiency, Clin. Genet. 78 (5) (2010) 471–477.
[27] T. Bienvenu, B. Diebold, J. Chelly, B. Isidor, Refining the phenotype associated with MEF2C point mutations, Neurogenetics 14 (1) (2013) 71–75.
[28] S.W. Flavell, C.W. Cowan, T.K. Kim, P.L. Greer, Y. Lin, S. Paradis, et al., Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number, Science (80-) 311 (5763) (2006) 1008–1012.
[29] Z. Li, S.R. McKercher, J. Cui, Z. Nie, W. Soussou, A.J. Roberts, et al., Myocyte enhancer factor 2C as a neurogenic and antiapoptotic transcription factor in murine embryonic stem cells, J. Neurosci. 28 (26) (2008) 6557–6568.
[30] E.G. Cho, J.D. Zaremba, S.R. McKercher, M. Talantova, S. Tu, E. Masliah, et al., MEF2C enhances dopaminergic neuron differentiation of human embryonic stem cells in a parkinsonian rat model, PloS One 6 (8) (2011).
[31] B. Zhu, R.E. Carmichael, L. Solabre Valois, K.A. Wilkinson, J.M. Henley, The transcription factor MEF2A plays a key role in the differentiation/maturation of rat neural stem cells into neurons, Biochem. Biophys. Res. Commun. 500 (3) (2018) 645–649.
[32] S.I. Okamoto, D. Krainc, K. Sherman, S.A. Lipton, Antiapoptotic role of the p38 mitogen-activated protein kinase-myocyte enhancer factor 2 transcription factor pathway during neuronal differentiation, Proc. Natl. Acad. Sci. U. S. A. 97 (13) (2000) 7561–7566.
[33] H. Li, J.C. Radford, M.J. Ragusa, K.L. Shea, S.R. McKercher, J.D. Zaremba, et al., Transcription factor MEF2C influences neural stem/progenitor cell differentiation and maturation in vivo, Proc. Natl. Acad. Sci. U. S. A. 105 (27) (2008) 9397–9402.
[34] M. Li, D.A. Linseman, M.P. Allen, M.K. Meintzer, X. Wang, T. Laessig, et al., Myocyte enhancer factor 2A and 2D undergo phosphorylation and caspase-mediated degradation during apoptosis of rat cerebellar granule neurons, J. Neurosci. 21 (17) (2001) 6544–6552.
[35] X. Gong, X. Tang, M. Wiedmann, X. Wang, J. Peng, D. Zheng, et al., Cdk5-mediated inhibition of the protective effects of transcription factor MEF2 in neurotoxicity-induced apoptosis, Neuron 38 (1) (2003) 33–46.
[36] Z. Mao, A. Bonni, F. Xia, M. Nadal-Vicens, M.E. Greenberg, Neuronal activity-dependent cell survival mediated by transcription factor MEF2, Science (80-) 286 (5440) (1999) 785–790.
[37] S.X. Chen, A. Cherry, P.K. Tari, K. Podgorski, Y.K.K. Kwong, K. Haas, The transcription factor MEF2 directs developmental visually driven functional and structural metaplasticity, Cell 151 (1) (2012) 41–55.
[38] B. Ataman, G.L. Boulting, D.A. Harmin, M.G. Yang, M. Baker-Salisbury, E.L. Yap, et al., Evolution of Osteocrin as an activity-regulated factor in the primate brain, Nature 539 (7628) (2016) 242–247.
[39] S.E. Latchney, Y. Jiang, D.P. Petrik, A.J. Eisch, J. Hsieh, Inducible knockout of Mef2a, -c, and -d from nestin-expressing stem/progenitor cells and their progeny unexpectedly uncouples neurogenesis and dendritogenesis in vivo, Faseb. J. 29 (12) (2015) 5059–5071.
[40] Q. Ma, F. Telese, Genome-wide epigenetic analysis of MEF2A and MEF2C transcription factors in mouse cortical neurons, Commun. Integr. Biol. 8 (6) (2015) 1–5.
[41] A.J. Harrington, A. Raissi, K. Rajkovich, S. Berto, J. Kumar, G. Molinaro, et al., MEF2C regulates cortical inhibitory and excitatory synapses and behaviors relevant to neurodevelopmental disorders, Elife 5 (OCTOBER2016) (2016).
[42] S.W. Flavell, T.K. Kim, J.M. Gray, D.A. Harmin, M. Hemberg, E.J. Hong, et al., Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection, Neuron 60 (6) (2008) 1022–1038.
[43] S.F. Chan, X. Huang, S.R. McKercher, R. Zaidi, S.I. Okamoto, N. Nakanishi, et al., Transcriptional profiling of MEF2-regulated genes in human neural progenitor cells derived from embryonic stem cells, Genomics Data 3 (2015) 24–27.
[44] W.S. Chung, B.A. Barres, The role of glial cells in synapse elimination, Curr. Opin. Neurobiol. 22 (2012) 438–445.
[45] A. Holtmaat, K. Svoboda, Experience-dependent structural synaptic plasticity in the mammalian brain, Nat. Rev. Neurosci. 10 (2009) 647–658.
[46] Y. Goda, G.W. Davis, Mechanisms of synapse assembly and disassembly, Neuron 40 (2003) 243–264.
[47] A. Shalizi, B. Gaudillière, Z. Yuan, J. Stegmüller, T. Shirogane, Q. Ge, et al., A calcium-regulated MEF2 sumoylation switch controls postsynaptic differentiation, Science (80-) 311 (5763) (2006) 1012–1017.
[48] N.P. Tsai, J.R. Wilkerson, W. Guo, M.A. Maksimova, G.N. Demartino, C.W. Cowan, et al., Multiple autism-linked genes mediate synapse elimination via proteasomal degradation of a synaptic scaffold PSD-95, Cell 151 (7) (2012) 1581–1594.
[49] X. Tian, L. Kai, P.E. Hockberger, D.L. Wokosin, D.J. Surmeier, MEF-2 regulates activity-dependent spine loss in striatopallidal medium spiny neurons, Mol. Cell. Neurosci. 44 (1) (2010) 94–108.
[50] T. Zang, M.A. Maksimova, C.W. Cowan, R. Bassel-Duby, E.N. Olson, K.M. Huber, Postsynaptic FMRP bidirectionally regulates excitatory synapses as a function of developmental age and MEF2 activity, Mol. Cell. Neurosci. 56 (2013) 39–49.
[51] M.W. Waung, B.E. Pfeiffer, E.D. Nosyreva, J.A. Ronesi, K.M. Huber, Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate, Neuron 59 (1) (2008) 84–97.
[52] J.C. Darnell, S.J. Van Driesche, C. Zhang, K.Y.S. Hung, A. Mele, C.E. Fraser, et al., FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism, Cell 146 (2) (2011) 247–261.
[53] C. Sala, K. Futai, K. Yamamoto, P.F. Worley, Y. Hayashi, M. Sheng, Inhibition of dendritic spine morphogenesis and synaptic transmission by activity-inducible protein Homer1a, J. Neurosci. 23 (15) (2003) 6327–6337.
[54] B.L. Bloodgood, N. Sharma, H.A. Browne, A.Z. Trepman, M.E. Greenberg, The activity-dependent transcription factor NPAS4 regulates domain-specific inhibition, Nature 503 (7474) (2013) 121–125.
[55] H. Okuno, K. Akashi, Y. Ishii, N. Yagishita-Kyo, K. Suzuki, M. Nonaka, et al., Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKIIβ, Cell 149 (4) (2012) 886–898.
[56] W.Z. Zhou, J. Zhang, Z. Li, X. Lin, J. Li, S. Wang, et al., Targeted resequencing of 358 candidate genes for autism spectrum disorder in a Chinese cohort reveals diagnostic potential and genotype–phenotype correlations, Hum. Mutat. 40 (6) (2019) 801–815.

[57] Z. Xie, X. Yang, X. Deng, M. Ma, K. Shu, A genome-wide association study and complex network identify four core hub genes in bipolar disorder, Int. J. Mol. Sci. 18 (12) (2017).

[58] J.I. Nurnberger, D.L. Koller, J. Jung, H.J. Edenberg, T. Foroud, I. Guella, et al., Identification of pathways for bipolar disorder: a meta-analysis, JAMA Psychiatry 71 (6) (2014) 657–664.

[59] C.L. Hyde, M.W. Nagle, C. Tian, X. Chen, S.A. Paciga, J.R. Wendland, et al., Identification of 15 genetic loci associated with risk of major depression in individuals of European descent, Nat. Genet. 48 (9) (2016) 1031–1036.

[60] A.A. Shadrin, O.B. Smeland, T. Zayats, A.J. Schork, O. Frei, F. Bettella, et al., Novel loci associated with attention-deficit/hyperactivity disorder are revealed by leveraging polygenic overlap with educational attainment, J. Am. Acad. Child Adolesc. Psychiatry 57 (2) (2018) 86–95.

[61] N. Sobreira, M.F. Walsh, D. Batista, T. Wang, Interstitial deletion 5q14.3-q21 associated with iris coloboma, hearing loss, dental anomaly, moderate intellectual disability, and attention deficit and hyperactivity disorder, Am. J. Med. Genet. 149 (2009) 2581–2583.

[62] J.C. Lambert, C.A. Ibrahim-Verbaas, D. Harold, A.C. Naj, R. Sims, C. Bellenguez, et al., Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease, Nat. Genet. 45 (12) (2013) 1452–1458.

[63] N. Le Meur, M. Holder-Espinasse, S. Jaillard, A. Goldenberg, S. Joriot, P. Amati-Bonneau, et al., MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations, J. Med. Genet. 47 (1) (2010) 22–29.

[64] I. Vrečar, J. Innes, E. Jones, H. Kingston, W. Reardon, B. Kerr, et al., Further clinical delineation of the MEF2C haploinsufficiency syndrome: report on new cases and literature review of severe neurodevelopmental disorders presenting with seizures, absent speech, and involuntary movements, J. Pediatr. Genet. 6 (3) (2017) 129–141.

[65] M. Zweier, A. Rauch, The MEF2C-related and 5q14.3q15 microdeletion syndrome, Mol Syndromol 2 (3–5) (2012) 164–170.

[66] L.A. Gossett, D.J. Kelvin, E.A. Sternberg, E.N. Olson, A new myocyte-specific enhancer-binding factor that recognizes a conserved element associated with multiple muscle-specific genes, Mol. Cell Biol. 9 (11) (1989) 5022–5033.

[67] D. Leifer, J. Golden, N.W. Kowall, Myocyte-specific enhancer binding factor 2C expression in human brain development, Neuroscience 63 (4) (1994) 1067–1079.

[68] J.D. Molkentin, B.L. Black, J.F. Martin, E.N. Olson, Cooperative activation of muscle gene expression by MEF2 and myogenic bHLH proteins, Cell 83 (7) (1995) 1125–1136.

[69] A. Keren, Y. Tamir, E. Bengal, The p38 MAPK signaling pathway: a major regulator of skeletal muscle development, Mol. Cell. Endocrinol. 252 (1–2) (2006) 224–230.

[70] G.M. Hobson, R. Krahe, E. Garcia, M.J. Siciliano, V.L. Funanage, Regional chromosomal assignments for four members of the mads domain transcription enhancer factor 2 (MEF2) gene family to human chromosomes 15q26, 19p12, 5q14, and 1q12-q23, Genomics 29 (3) (1995) 704–711.

[71] J.D. Molkentin, A.B. Firulli, B.L. Black, J.F. Martin, C.M. Hustad, N. Copeland, et al., MEF2B is a potent transactivator expressed in early myogenic lineages, Mol. Cell Biol. 16 (7) (1996) 3814–3824.

[72] T.A. McKinsey, C.L. Zhang, E.N. Olson, Activation of the myocyte enhancer factor-2 transcription factor by calcium/calmodulin-dependent protein kinase-stimulated binding of 14-3-3 to histone deacetylase 5, Proc. Natl. Acad. Sci. U. S. A. 97 (26) (2000) 14400–14405.

[73] S. Borghi, S. Molinari, G. Razzini, R. Parise, R. Battini, S. Ferrari, The nuclear localization domain of the MEF2 family of transcription factors shows member-specific features and mediates the nuclear import of histone deacetylase 4, J. Cell Sci. 114 (24) (2001) 4477–4483.

[74] W. Wu, S. de Folter, X. Shen, W. Zhang, S. Tao, Vertebrate paralogous MEF2 genes: origin, conservation, and evolution, PloS One 6 (3) (2011).

[75] A.J. Rashid, C.J. Cole, S.A. Josselyn, Emerging roles for MEF2 transcription factors in memory, Gene Brain Behav. 13 (1) (2014) 118–125.

[76] Y. Liu, W. Niu, Z. Wu, X. Su, Q. Chen, L. Lu, et al., Variants in exon 11 of MEF2A gene and coronary artery disease: evidence from a case-control study, systematic review, and meta-analysis, PloS One 7 (2012).

[77] Y. Xiong, L. Wang, W. Jiang, L. Pang, W. Liu, A. Li, et al., MEF2A alters the proliferation, inflammation-related gene expression profiles and its silencing induces cellular senescence in human coronary endothelial cells, BMC Mol. Biol. 20 (1) (2019).

[78] A.I. Rodríguez, G. Csányi, D.J. Ranayhossaini, D.M. Feck, K.J. Blose, L. Assatourian, et al., MEF2B-Nox1 signaling is critical for stretch-induced phenotypic modulation of vascular smooth muscle cells, Arterioscler. Thromb. Vasc. Biol. (2015).

[79] M. Zweier, A. Gregor, C. Zweier, H. Engels, H. Sticht, E. Wohlleber, et al., Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression, Hum. Mutat. 31 (6) (2010) 722–733.

[80] S.J. Choi, S.Y. Park, T.H. Han, 14-3-3τ associates with and activates the MEF2D transcription factor during muscle cell differentiation, Nucleic Acids Res. 29 (13) (2001) 2836–2842.

[81] H. Ikeshimaa, Imai S. ichiro, K. Shimoda, J ichi Hata, T. Takano, Expression of a MADS box gene, MEF2D, in neurons of the mouse central nervous system: implication of its binary function in myogenic and neurogenic cell lineages, Neurosci. Lett. 200 (2) (1995) 117–120.

[82] Q. Yang, H. She, M. Gearing, E. Colla, M. Lee, J.J. Shacka, et al., Regulation of neuronal survival factor MEF2D by chaperone-mediated autophagy, Science (80-) 323 (5910) (2009) 124–127.

[83] P. Shore, A.D. Sharrocks, The MADS-box family of transcription factors, Eur. J. Biochem. 229 (1) (1995) 1–13.

[84] B.L. Black, E.N. Olson, Transcriptional control of muscle development by myocyte enhancer factor-2 (MEF2) proteins, in: Annual Review of Cell and Developmental Biology, 14, 1998, pp. 167–196.

[85] K.A. Heidenreich, D.A. Linseman, Myocyte enhancer factor-2 transcription factors in neuronal differentiation and survival, Mol. Neurobiol. 29 (2004) 155–165.

[86] V. Andres, M. Cervera, V. Mahdavi, Determination of the consensus binding site for MEF2 expressed in muscle and brain reveals tissue-specific sequence constraints, J. Biol. Chem. 270 (40) (1995) 23246–23249.

[87] F. Telese, Q. Ma, P.M. Perez, D. Notani, S. Oh, W. Li, et al., LRP8-Reelin-Regulated neuronal enhancer signature underlying learning and memory formation, Neuron 86 (3) (2015) 696–710.

[88] T.A. McKinsey, C.L. Zhang, J. Lu, E.N. Olson, Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation, Nature 408 (6808) (2000) 106–111.

[89] G.E. Lyons, B.K. Micales, J. Schwarz, J.F. Martin, E.N. Olson, Expression of mef2 genes in the mouse central nervous system suggests a role in neuronal maturation, J. Neurosci. 15 (8) (1995) 5727–5738.

[90] X. Lin, S. Shah, R.F. Bulleit, The expression of MEF2 genes is implicated in CNS neuronal differentiation, Mol. Brain Res. 42 (2) (1996) 307–316.

[91] M.R. Lyons, C.M. Schwarz, A.E. West, Members of the myocyte enhancer factor 2 transcription factor family differentially regulate Bdnf transcription in response to neuronal depolarization, J. Neurosci. 32 (37) (2012) 12780–12785.

[92] S.P. Kamath, A.I. Chen, Myocyte enhancer factor 2c regulates dendritic complexity and connectivity of cerebellar purkinje cells, Mol. Neurobiol. 56 (6) (2019) 4102–4119.

[93] B.Y.H. Lam, S. Chawla, MEF2D expression increases during neuronal differentiation of neural progenitor cells and correlates with neurite length, Neurosci. Lett. 427 (3) (2007) 153–158.

[94] J.B. Dietrich, The MEF2 family and the brain: from molecules to memory, Cell Tissue Res. 352 (2013) 179–190.

[95] M.J. Potthoff, E.N. Olson, MEF2: a central regulator of diverse developmental programs, Development 134 (2007) 4131–4140.

[96] B.L. Black, R.M. Cripps, Myocyte enhancer factor 2 transcription factors in heart development and disease, in: Heart Development and Regeneration, 2010, pp. 673–699.

[97] A. Deczkowska, O. Matcovitch-Natan, A. Tsitsou-Kampeli, S. Ben-Hamo, R. Dvir-Szternfeld, A. Spinrad, et al., Mef2C restrains microglial inflammatory response and is lost in brain ageing in an IFN-I-dependent manner, Nat. Commun. 8 (1) (2017).

[98] D. Gosselin, D. Skola, N.G. Coufal, I.R. Holtman, J.C.M. Schlachetzki, E. Sajti, et al., An environment-dependent transcriptional network specifies human microglia identity, Science (80-) 356 (6344) (2017) 1248–1259.

[99] R.C. Paolicelli, G. Bolasco, F. Pagani, L. Maggi, M. Scianni, P. Panzanelli, et al., Synaptic pruning by microglia is necessary for normal brain development, Science (80-) 333 (6048) (2011) 1456–1458.

[100] D.P. Schafer, E.K. Lehrman, A.G. Kautzman, R. Koyama, A.R. Mardinly, R. Yamasaki, et al., Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner, Neuron 74 (4) (2012) 691–705.

[101] Y. Lavin, D. Winter, R. Blecher-Gonen, E. David, H. Keren-Shaul, M. Merad, et al., Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment, Cell 159 (6) (2014) 1312–1326.

[102] C.N. Parkhurst, G. Yang, I. Ninan, J.N. Savas, J.R. Yates, J.J. Lafaille, et al., Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor, Cell 155 (7) (2013) 1596–1609.

[103] L. Pont-Lezica, W. Beumer, S. Colasse, H. Drexhage, M. Versnel, A. Bessis, Microglia shape corpus callosum axon tract fasciculation: functional impact of prenatal inflammation, Eur. J. Neurosci. 39 (10) (2014) 1551–1557.

[104] N. Hagemeyer, K.M. Hanft, M.A. Akriditou, N. Unger, E.S. Park, E.R. Stanley, et al., Microglia contribute to normal myelinogenesis and to oligodendrocyte progenitor maintenance during adulthood, Acta Neuropathol. 134 (3) (2017) 441–458.

[105] Y. Shigemoto-Mogami, K. Hoshikawa, J.E. Goldman, Y. Sekino, K. Sato, Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone, J. Neurosci. 34 (6) (2014) 2231–2243.

[106] Q. Li, B.A. Barres, Microglia and macrophages in brain homeostasis and disease, Nat. Rev. Immunol. 18 (2018) 225–242.

[107] D. Leifer, D. Krainc, Y.T. Yu, J. McDermott, R.E. Breitbart, J. Heng, et al., MEF2C, a MADS/MEF2-family transcription factor expressed in a laminar distribution in cerebral cortex, Proc. Natl. Acad. Sci. U. S. A. 90 (4) (1993) 1546–1550.

[108] B. Zhu, T. Gulick, Phosphorylation and alternative pre-mRNA splicing converge to regulate myocyte enhancer factor 2C activity, Mol. Cell Biol. 24 (18) (2004) 8264–8275.

[109] N.H.A. Hakim, T. Kounishi, A.H.M.K. Alam, T. Tsukahara, H. Suzuki, Alternative splicing of Mef2c promoted by Fox-1 during neural differentiation in P19 cells, Gene Cell. 15 (3) (2010) 255–267.

[110] Y. Sekiyama, H. Suzuki, T. Tsukahara, Functional gene expression analysis of tissue-specific isoforms of Mef2c, Cell. Mol. Neurobiol. 32 (1) (2012) 129–139.

[111] F. Rivadeneira, A.G. Uitterlinden, Osteoporosis genes identified by genome-wide association studies, in: Genetics of Bone Biology and Skeletal Disease, second ed., 2018, pp. 377–395.

[112] J. Wang, Q. Zhang, Y. Chen, S. Yu, X. Wu, X. Bao, et al., Novel MEF2C point mutations in Chinese patients with Rett (-like) syndrome or non-syndromic intellectual disability: insights into genotype-phenotype correlation, BMC Med. Genet. 19 (1) (2018).

[113] C.G. Janson, Y. Chen, Y. Li, D. Leifer, Functional regulatory regions of human transcription factor MEF2C, Mol. Brain Res. 97 (1) (2001) 70–82.
[114] A. Han, J. He, Y. Wu, J.O. Liu, L. Chen, Mechanism of recruitment of class II histone deacetylases by myocyte enhancer factor-2, J. Mol. Biol. 345 (1) (2005) 91–102.
[115] A. Han, F. Pan, J.C. Stroud, H.D. Youn, J.O. Liu, L. Chen, Sequence-specific recruitment of transcriptional co-repressor Cabin1 by myocyte enhancer factor-2, Nature 422 (6933) (2003) 730–734.
[116] Y. Wu, R. Dey, A. Han, N. Jayathilaka, M. Philips, J. Ye, et al., Structure of the MADS-box/MEF2 domain of MEF2A bound to DNA and its implication for myocardin recruitment, J. Mol. Biol. 397 (2) (2010) 520–533.
[117] M.M. Andzelm, T.J. Cherry, D.A. Harmin, A.C. Boeke, C. Lee, M. Hemberg, et al., MEF2D drives photoreceptor development through a genome-wide competition for tissue-specific enhancers, Neuron 86 (1) (2015) 247–263.
[118] N. Jayathilaka, A. Han, K.J. Gaffney, R. Dey, J.A. Jarusiewicz, K. Noridomi, et al., Inhibition of the function of class IIa HDACs by blocking their interaction with MEF2, Nucleic Acids Res. 40 (12) (2012) 5378–5388.
[119] J. He, J. Ye, Y. Cai, C. Riquelme, J.O. Liu, X. Liu, et al., Structure of p300 bound to MEF2 on DNA reveals a mechanism of enhanceosome assembly, Nucleic Acids Res. 39 (10) (2011) 4464–4474.
[120] V. Infantino, P. Convertini, A. Menga, V. Iacobazzi, MEF2C exon α: role in gene activation and differentiation, Gene 531 (2) (2013) 355–362.
[121] M. Ganassi, S. Badodi, A. Polacchini, F. Baruffaldi, R. Battini, S.M. Hughes, et al., Distinct functions of alternatively spliced isoforms encoded by zebrafish mef2ca and mef2cb, Biochim Biophys Acta - Gene Regul Mech. 1839 (7) (2014) 559–570.
[122] S. Stehling-Sun, J. Dade, S.L. Nutt, R.P. DeKoter, F.D. Camargo, Regulation of lymphoid versus myeloid fate "choice" by the transcription factor Mef2c, Nat. Immunol. 10 (3) (2009) 289–296.
[123] J.R. Pon, M.A. Marra, MEF2 transcription factors: developmental regulators and emerging cancer genes, Oncotarget 7 (3) (2016) 2297–2312.
[124] M. Parra, T. Mahmoudi, E. Verdin, Myosin phosphatase dephosphorylates HDAC7, controls its nucleocytoplasmic shuttling, and inhibits apoptosis in thymocytes, Genes Dev. 21 (6) (2007) 638–643.
[125] D.G. Edmondson, G.E. Lyons, J.F. Martin, E.N. Olson, Mef2 gene expression marks the cardiac and skeletal muscle lineages during mouse embryogenesis, Development 120 (5) (1994) 1251–1263.
[126] A.C. Barbosa, M.S. Kim, M. Ertunc, M. Adachi, E.D. Nelson, J. McAnally, et al., MEF2C, a transcription factor that facilitates learning and memory by negative regulation of synapse numbers and function, Proc. Natl. Acad. Sci. U. S. A. 105 (27) (2008) 9391–9396.
[127] B.E. Pfeiffer, T. Zang, J.R. Wilkerson, M. Taniguchi, M.A. Maksimova, L.N. Smith, et al., Fragile X mental retardation protein is required for synapse elimination by the activity-dependent transcription factor MEF2, Neuron 66 (2) (2010) 191–197.
[128] S.P. Majidi, N.C. Reddy, M.J. Moore, H. Chen, T. Yamada, M.M. Andzelm, et al., Chromatin environment and cellular context specify compensatory activity of paralogous MEF2 transcription factors, Cell Rep. 29 (7) (2019) 2001–2015, e5.
[129] S.W. Flavell, M.E. Greenberg, Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system, Annu. Rev. Neurosci. 31 (2008) 563–590.
[130] I.S. Skerjanc, S. Wilton, Myocyte enhancer factor 2C upregulates MASH-1 expression and induces neurogenesis in P19 cells, FEBS Lett. 472 (1) (2000) 53–56.
[131] H.Y. Zoghbi, Postnatal neurodevelopmental disorders: meeting at the synapse? Science 302 (2003) 826–830.
[132] K. Garber, Autism's cause may reside in abnormalities at the synapse, Science 317 (2007) 190–191.
[133] D. Cosgrove, L. Whitton, L. Fahey, P. Ó Broin, G. Donohoe, D.W. Morris, Genes influenced by MEF2C contribute to neurodevelopmental disease via gene expression changes that affect multiple types of cortical excitatory neurons, bioRxiv (2019).
[134] C. Mayer, C. Hafemeister, R.C. Bandler, R. Machold, R. Batista Brito, X. Jaglin, et al., Developmental diversification of cortical inhibitory interneurons, Nature 555 (7697) (2018) 457–462.
[135] J.S. Hu, D. Vogt, M. Sandberg, J.L. Rubenstein, Cortical interneuron development: a tale of time and space, Development 144 (2017) 3867–3878 (Cambridge).
[136] B.R. Ferguson, W.J. Gao, Pv interneurons: critical regulators of E/I balance for prefrontal cortex-dependent behavior and psychiatric disorders, Front. Neural Circ. 12 (2018).
[137] T.F. Freund, I. Katona, Perisomatic inhibition, Neuron 56 (2007) 33–42.
[138] H. Hu, J. Gan, P. Jonas, Fast-spiking, parvalbumin+ GABAergic interneurons: from cellular design to microcircuit function, Science 345 (2014).
[139] F. Donato, S.B. Rompani, P. Caroni, Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning, Nature 504 (7479) (2013) 272–276.
[140] D.R. Sparta, N. Hovelsø, A.O. Mason, P.A. Kantak, R.L. Ung, H.K. Decot, et al., Activation of prefrontal cortical parvalbumin interneurons facilitates extinction of reward-seeking behavior, J. Neurosci. 34 (10) (2014) 3699–3705.
[141] S. Pulipparacharuvil, W. Renthal, C.F. Hale, M. Taniguchi, G. Xiao, A. Kumar, et al., Cocaine regulates MEF2 to control synaptic and behavioral plasticity, Neuron 59 (4) (2008) 621–633.
[142] C.J. Cole, V. Mercaldo, L. Restivo, A.P. Yiu, M.J. Sekeres, J.H. Han, et al., MEF2 negatively regulates learning-induced structural plasticity and memory formation, Nat. Neurosci. 15 (9) (2012) 1255–1264.
[143] G. Vetere, L. Restivo, C.J. Cole, P.J. Ross, M. Ammassari-Teule, S.A. Josselyn, et al., Spine growth in the anterior cingulate cortex is necessary for the consolidation of contextual fear memory, Proc. Natl. Acad. Sci. U. S. A. 108 (20) (2011) 8456–8460.
[144] S. Chowdhury, J.D. Shepherd, H. Okuno, G. Lyford, R.S. Petralia, N. Plath, et al., Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking, Neuron 52 (3) (2006) 445–459.
[145] M.A. Gainey, J.R. Hurvitz-Wolff, M.E. Lambo, G.G. Turrigiano, Synaptic scaling requires the GluR2 subunit of the AMPA receptor, J. Neurosci. 29 (20) (2009) 6479–6489.
[146] R. Malinow, R.C. Malenka, AMPA receptor trafficking and synaptic plasticity, Annu. Rev. Neurosci. 25 (2002) 103–126.
[147] M. Colledge, E.M. Snyder, R.A. Crozier, J.A. Soderling, Y. Jin, L.K. Langeberg, et al., Ubiquitination regulates PSD-95 degradation and AMPA receptor surface expression, Neuron 40 (3) (2003) 595–607.
[148] C. Bats, L. Groc, D. Choquet, The interaction between stargazin and PSD-95 regulates AMPA receptor surface trafficking, Neuron 53 (5) (2007) 719–734.
[149] M.W. Akhtar, M.S. Kim, M. Adachi, M.J. Morris, X. Qi, J.A. Richardson, et al., In vivo analysis of mef2 transcription factors in synapse regulation and neuronal survival, PloS One 7 (4) (2012).
[150] M. Adachi, P.Y. Lin, H. Pranav, L.M. Monteggia, Postnatal loss of Mef2c results in dissociation of effects on synapse number and learning and memory, Biol. Psychiatr. 80 (2) (2016) 140–148.
[151] A.J. Blaschke, K. Staley, J. Chun, Widespread programmed cell death in proliferative and postmitotic regions of the fetal cerebral cortex, Development 122 (4) (1996) 1165–1174.
[152] L. New, J. Han, The p38 MAP kinase pathway and its biological function, Trends Cardiovasc. Med. 8 (5) (1998) 220–228.
[153] M. Zhao, L. New, V.V. Kravchenko, Y. Kato, H. Gram, F. di Padova, et al., Regulation of the MEF2 family of transcription factors by p38, Mol. Cell Biol. 19 (1) (1999) 21–30.
[154] S.-H. Yang, A. Galanis, A.D. Sharrocks, Targeting of p38 mitogen-activated protein kinases to MEF2 transcription factors, Mol. Cell Biol. 19 (6) (1999) 4028–4038.
[155] S.I. Okamoto, Z. Li, C. Ju, M.N. Schölzke, E. Mathews, J. Cui, et al., Dominant-interfering forms of MEF2 generated by caspase cleavage contribute to NMDA-induced neuronal apoptosis, Proc. Natl. Acad. Sci. U. S. A. 99 (6) (2002) 3974–3979.
[156] G.S. Salvesen, V.M. Dixit, Caspases: intracellular signaling by proteolysis, Cell 91 (1997) 443–446.
[157] R. Ambasudhan, S.D. Ryan, N. Dolatabadi, S.F. Chan, X. Zhang, M.W. Akhtar, et al., Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1α transcription, Cell 155 (6) (2013) 1351.
[158] J. Clark, D.K. Simon, Transcribe to survive: transcriptional control of antioxidant defense programs for neuroprotection in Parkinson's disease, Antioxidants Redox Signal. 11 (2009) 509–528.
[159] A.W.E. Jones, Z. Yao, J.M. Vicencio, A. Karkucinska-Wieckowska, G. Szabadkai, PGC-1 family coactivators and cell fate: roles in cancer, neurodegeneration, cardiovascular disease and retrograde mitochondria-nucleus signalling, Mitochondrion 12 (2012) 86–99.
[160] T. Nakamura, S. Tu, M.W. Akhtar, C.R. Sunico, S ichi Okamoto, S.A. Lipton, Aberrant Protein S-nitrosylation in neurodegenerative diseases, Neuron 78 (2013) 596–614.
[161] M.R. Hara, S.H. Snyder, Cell signaling and neuronal death, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 117–141.
[162] D.T. Hess, A. Matsumoto, S.O. Kim, H.E. Marshall, J.S. Stamler, Protein S-nitrosylation: purview and parameters, Nat. Rev. Mol. Cell Biol. 6 (2005) 150–166.
[163] S ichi Okamoto, T. Nakamura, P. Cieplak, S.F. Chan, E. Kalashnikova, L. Liao, et al., S-nitrosylation-mediated redox transcriptional switch modulates neurogenesis and neuronal cell death, Cell Rep. 8 (1) (2014) 217–228.
[164] X. Wang, H. She, Z. Mao, Phosphorylation of neuronal survival factor MEF2D by glycogen synthase kinase 3β in neuronal apoptosis, J. Biol. Chem. 284 (47) (2009) 32619–32626.
[165] J. Salma, J.C. McDermott, Suppression of a MEF2-KLF6 survival pathway by PKA signaling promotes apoptosis in embryonic hippocampal neurons, J. Neurosci. 32 (8) (2012) 2790–2803.
[166] F.J. Naya, B.L. Black, H. Wu, R. Bassel-Duby, J.A. Richardson, J.A. Hill, et al., Mitochondrial deficiency and cardiac sudden death in mice lacking the MEF2A transcription factor, Nat. Med. 8 (11) (2002) 1303–1309.
[167] L. Zhuo, M. Theis, I. Alvarez-Maya, M. Brenner, K. Willecke, A. Messing, hGFAP-cre transgenic mice for manipulation of glial and neuronal function in vivo, Genesis 31 (2) (2001) 85–94.
[168] Q. Lin, J. Schwarz, C. Bucana, E.N. Olson, Control of mouse cardiac morphogenesis and myogenesis by transcription factor MEF2C, Science (80-) 276 (5317) (1997) 1404–1407.
[169] L.H. Vong, M.J. Ragusa, J.J. Schwarz, Generation of conditional Mef2cloxp/loxp mice for temporal- and tissue-specific analyses, Genesis 43 (1) (2005) 43–48.
[170] A.J. Harrington, C.M. Bridges, S. Berto, K. Blankenship, J.Y. Cho, A. Assali, et al., MEF2C hypofunction in neuronal and neuroimmune populations produces MEF2C haploinsufficiency syndrome–like behaviors in mice, Biol. Psychiatr. 88 (6) (2020) 488–499.
[171] A.R. Paciorkowski, R.N. Traylor, J.A. Rosenfeld, J.M. Hoover, C.J. Harris, S. Winter, et al., MEF2C Haploinsufficiency features consistent hyperkinesis, variable epilepsy, and has a role in dorsal and ventral neuronal developmental pathways, Neurogenetics 14 (2) (2013) 99–111.
[172] B.A. Nowakowska, E. Obersztyn, K. Szymańska, M. Bekiesińska-Figatowska, Z. Xia, C.B. Ricks, et al., Severe mental retardation, seizures, and hypotonia due to deletions of MEF2C, Am. J. Med. Genet. Part B Neuropsychiatr Genet 153 (5) (2010) 1042–1051.

[173] S. Tu, M.W. Akhtar, R.M. Escorihuela, A. Amador-Arjona, V. Swarup, J. Parker, et al., NitroSynapsin therapy for a mouse MEF2C haploinsufficiency model of human autism, Nat. Commun. 8 (1) (2017).
[174] M. Chahrour, Y.J. Sung, C. Shaw, X. Zhou, S.T.C. Wong, J. Qin, et al., MeCP2, a key contributor to neurological disease, activates and represses transcription, Science (80-) 320 (5880) (2008) 1224–1229.
[175] P.L. Greer, R. Hanayama, B.L. Bloodgood, A.R. Mardinly, D.M. Lipton, S.W. Flavell, et al., The angelman syndrome protein Ube3A regulates synapse development by ubiquitinating arc, Cell 140 (5) (2010) 704–716.
[176] J. Guy, B. Hendrich, M. Holmes, J.E. Martin, A. Bird, A mouse Mecp2-null mutation causes neurological symptoms that mimic rett syndrome, Nat. Genet. 27 (3) (2001) 322–326.
[177] F. Mari, S. Azimonti, I. Bertani, F. Bolognese, E. Colombo, R. Caselli, et al., CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome, Hum. Mol. Genet. 14 (14) (2005) 1935–1946.
[178] R. Guerrini, C. Cardoso, A. Boys, E. Parrini, C. Mignon-Ravix, J.M. McMahon, et al., Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion, Neurology 72 (9) (2009) 784–792.
[179] H. Engels, E. Wohlleber, A. Zink, J. Hoyer, K.U. Ludwig, F.F. Brockschmidt, et al., A novel microdeletion syndrome involving 5q14.3-q15: clinical and molecular cytogenetic characterization of three patients, Eur. J. Hum. Genet. 17 (12) (2009) 1592–1599.
[180] J.L. Bai, Y.J. Qu, L.P. Zou, X.Y. Yang, L.J. Liu, F. Song, A novel missense mutation of the ubiquitin protein ligase E3A gene in a patient with angelman syndrome, Chin. Med. J. 124 (1) (2011) 84–88.
[181] T. Kishino, M. Lalande, J. Wagstaff, UBE3A/E6-AP mutations cause Angelman syndrome, Nat. Genet. 15 (1) (1997) 70–73.
[182] N. Khatri, H.Y. Man, The autism and Angelman syndrome protein Ube3A/E6AP: the gene, E3 ligase ubiquitination targets and neurobiological functions, Front. Mol. Neurosci. 12 (2019).
[183] C.A. Williams, A.L. Beaudet, J. Clayton-Smith, J.H. Knoll, M. Kyllerman, L.A. Laan, et al., Angelman syndrome 2005: updated consensus for diagnostic criteria, Am. J. Med. Genet. 140 A (5) (2006) 413–418.
[184] C.A. Williams, A. Lossie, D. Driscoll, Angelman syndrome: mimicking conditions and phenotypes, Am. J. Med. Genet. 101 (1) (2001) 59–64.
[185] J. Straub, A. Gregor, T. Sauerer, A. Fliedner, L. Distel, C. Suchy, et al., Genetic interaction screen for severe neurodevelopmental disorders reveals a functional link between Ube3a and Mef2 in Drosophila melanogaster, Sci. Rep. 10 (1) (2020).
[186] Y. Zhan, R.C. Paolicelli, F. Sforazzini, L. Weinhard, G. Bolasco, F. Pagani, et al., Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior, Nat. Neurosci. 17 (3) (2014) 400–406.
[187] D. Velmeshev, L. Schirmer, D. Jung, M. Haeussler, Y. Perez, S. Mayer, et al., Single-cell genomics identifies cell type–specific molecular changes in autism, Science (80-) 364 (6441) (2019) 685–689.
[188] M.Y. Ono, F. Farzin, R.J. Hagerman, Fragile X syndrome, in: Encyclopedia of Infant and Early Childhood Development. Treasure Island (FL), 2008, pp. 544–552.
[189] R. Lozano, A. Azarang, T. Wilaisakditipakorn, R.J. Hagerman, Fragile X syndrome: a review of clinical management, Intractable and Rare Diseases Research 5 (2016) 145–157.
[190] H.A. Lubs, A marker X chromosome, Am. J. Hum. Genet. 21 (3) (1969) 231–244.
[191] A.J.M.H. Verkerk, M. Pieretti, J.S. Sutcliffe, Y.H. Fu, D.P.A. Kuhl, A. Pizzuti, et al., Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome, Cell 65 (5) (1991) 905–914.
[192] S.A. Kidd, A. Lachiewicz, D. Barbouth, R.K. Blitz, C. Delahunty, D. McBrien, et al., Fragile X syndrome: a review of associated medical problems, Pediatrics 134 (2014) 995–1005.
[193] J.C. Darnell, J.D. Richter, Cytoplasmic RNA-binding proteins and the control of complex brain function, Cold Spring Harbor Perspectives in Biology 4 (2012).
[194] M.R. Santoro, S.M. Bray, S.T. Warren, Molecular mechanisms of fragile X syndrome: a twenty-year perspective, Annu. Rev. Pathol. 7 (2012) 219–245.
[195] A.W. Grossman, G.M. Aldridge, K.J. Lee, M.K. Zeman, C.S. Jun, H.S. Azam, et al., Developmental characteristics of dendritic spines in the dentate gyrus of Fmr1 knockout mice, Brain Res. 1355 (2010) 221–227.
[196] C.P. Poore, J.R. Sundaram, T.K. Pareek, A. Fu, N. Amin, N.E. Mohamed, et al., Cdk5-mediated phosphorylation of δ-catenin regulates its localization and GluR2-mediated synaptic activity, J. Neurosci. 30 (25) (2010) 8457–8467.
[197] J. Arikkath, I.F. Peng, G.N. Yu, I. Israely, X. Liu, E.M. Ullian, et al., Δ-catenin regulates spine and synapse morphogenesis and function in hippocampal neurons during development, J. Neurosci. 29 (17) (2009) 5435–5442.
[198] M. Medina, R.C. Marinescu, J. Overhauser, K.S. Kosik, Hemizygosity of δ-catenin (CTNND2) is associated with severe mental retardation in cri-du-chat syndrome, Genomics 63 (2) (2000) 157–164.
[199] Y. Yuan, D. Singh, J. Arikkath, Mef2 promotes spine elimination in absence of δ-catenin, Neurosci. Lett. 536 (1) (2013) 10–13.