Published in final edited form as:

Semin Cell Dev Biol. 2017 September ; 69: 70–82. doi:10.1016/j.semcdb.2017.05.027.

Functional roles of p120ctn family of proteins in central neurons

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Abstract

The cadherin-catenin complex in central neurons is associated with a variety of cytosolic partners, collectively called catenins. The p120ctn members are a family of catenins that are distinct from the more ubiquitously expressed α - and β -catenins. It is becoming increasingly clear that the functional roles of the p120ctn family of catenins in central neurons extend well beyond their functional roles in non-neuronal cells in partnering with cadherin to regulate adhesion. In this review, we will provide an overview of the p120ctn family in neurons and their varied functional roles in central neurons. Finally, we will examine the emerging roles of this family of proteins in neurodevelopmental disorders.

Keywords

p120ctn; δ -catenin; p0071; ARVCF; neuron

1. Introduction

1.1 The cadherin-catenin cell adhesion complex in central neurons

Cadherins are transmembrane proteins that mediate cell-cell adhesion in a variety of cell types. More recently, it has become clear that they have extensive functional roles in neurons and are associated with multiple neuronal functional roles including adhesion and synaptic plasticity. Their functional roles are of particular significance in multiple aspects of neuronal morphology, synaptic structure, synaptic efficacy and molecular processes related to learning and memory [1–3]. Cadherins mediate adhesion across synapses via homophilic *trans*-interactions across the synaptic cleft [2]. The cytosolic intracellular terminal of cadherins is associated with a variety of proteins, collectively called catenins. Of these, β -catenin is

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Conflict of interest

The authors declare no competing financial interests.

perhaps the most well studied and several studies indicate critical roles for this protein in a variety of neuronal phenotypes including pre- and postsynaptic development, memory and addiction [4–7]. A group of catenins associated with the classical cadherins also include members of the p120ctn family of proteins. The p120ctn family of proteins form a family distinct from the β -catenin and α -catenin families and bind to cadherin at a site distinct from the β -catenin binding site [8]. Over the last several years, it has become obvious that the functional roles of the p120ctn family of proteins are quite diverse and include both cadherin-dependent and -independent functional roles in various aspects of neuronal morphogenesis. Accordingly, members of this family have been linked to various neurodevelopmental disorders. In this review, we provide an overview of the p120ctn family in neurons and their varied functional roles in central neurons. Finally, we will examine the emerging roles of this family of proteins in neurodevelopmental disorders.

1.2 The p120ctn family of proteins

The p120ctn family includes 4 proteins encoded by four independent genes. These include p120ctn (encoded by *CTNND1*), δ -catenin (also called NPRAP or neurojungin [9], encoded by *CTNND2*), p0071 (plakophilin-4, encoded by *PKP4*) and ARVCF (encoded by *ARVCF*). Evolutionarily, they are generated from an ancient ‘ δ -catenin-like’ gene and divided into two major classes, one of which comprises p0071 and δ -catenin, while the other includes p120ctn and ARVCF [10]. p120ctn, ARVCF and p0071 are expressed in central neurons and widely distributed in non-neuronal tissues [11–14]. δ -catenin is unique in that it has a more restricted expression to central neurons [9,15].

The members of the p120ctn family share a common structural organization with some unique features. The protein structure includes an N-terminal domain, a series of 9 ARM repeats and C-terminal domain (Fig. 1). The C-terminal region of ARVCF, p0071 and δ -catenin include a PDZ-binding motif. Interestingly, this motif is lacking in p120ctn, suggesting that all members are unlikely to be completely functionally redundant. The N-terminal regions of ARVCF, p0071, δ -catenin and majority of p120ctn isoforms include a coiled-coiled domain in the brain [16,17].

Similar to the members of the larger catenin family, members of the p120ctn family of proteins can link to cadherin and indirectly to the actin cytoskeleton. However, unlike the α - and β -catenin family of proteins, they bind to cadherin at its juxtamembrane domain (JMD) at a site distinct from the binding sites for β -catenin [8]. The ARM domains include two groups of ARM repeats, each with 5 or 4 repeats, flanking an insert region. Our understanding of the structural association between p120ctn and cadherin is provided by the crystal structure of p120ctn in complex with the JMD of cadherin [18]. The crystal structure indicates that the core fragment of JMD interacts with the ARM 1–5 of p120ctn in an opposite orientation with respect to their N- and C-termini [18] and the C-terminal of JMD has stronger association with p120ctn. Since the ARM repeats are conserved between members of the family [18], this structure can likely be extrapolated to other members of the family. Mutation of a single amino acid in δ -catenin (K581) can significantly alleviate the interaction between δ -catenin and cadherin [19], emphasizing the critical nature of this residue for the interaction.

Multiple forms of each protein are generated by several mechanisms, including use of alternative translational start sites [11,13], splice variants, proteolysis [20,21] and posttranslational modifications [19,22]. Alternative translational start sites have been described for p120ctn and ARVCF [11,13], leading to differences in the composition of the N-terminal region. p120ctn also has 4 alternative exons, exons A to C and 4 [11,23], which can be differentially spliced leading to a total of up to 48 predicted isoforms, although there is incomplete experimental evidence for these isoforms. Exons A and B are located within the C-terminal region of p120ctn [11], while exon C (6 amino acids) is located within the ARM domains [11] and Exon 4 is localized to the N-terminal region [23]. Exons A and C are expressed in the brain [11].

Multiple splice variants are known for each protein. Two splice variants are known for δ -catenin in the mouse [9]. One of these includes a 25 aa insertion at the beginning of the first helix of ARM 7. Both isoforms are expressed in various brain regions, and in both neuron and glia [24]. While no functional differences between the two isoforms are known, the 25 aa cassette is localized spatially proximal to the insert region on the arch of the ARM domain [18], suggesting it may regulate the structure and function of the insert region.

p0071 has two alternative splicing inserts that can be generated by alternative splicing of two exons. These are distinct from the exons described for p120ctn, ARVCF and δ -catenin. One is localized right before the first ARM repeat and the other is localized in the C-terminal domain [14]. The brain p0071 isoform predominantly does not include the exon localized before the first ARM repeat [14].

Splice variants in ARVCF include exons B and C. Exon C of ARVCF resembles exon C of p120ctn and has the same splice insertion site [13]. Exon B has identified in *Xenopus* but not in human, consists of 5 aa located right before exon C [13]. All three exons are expressed in the brain tissue of *Xenopus* [13], but their expression pattern in rodents or humans have not been explored.

A polyK sequence, resembling a putative nuclear localization signals (NLS), potentially promoting nuclear localization, is localized within the insert region between the ARM repeats. This sequence is common to all members of the family [9,12,14,18,25], although the exact sequence varies between members.

2. Expression and localization of p120ctn family of proteins

The expression patterns of members of the p120ctn family have been examined both at the level of transcript and protein. The expression patterns of p120ctn and δ -catenin are better characterized than those of p0071 and ARVCF. Both p120ctn and δ -catenin are widely expressed in different regions of the brain [9,24], both during early development and in the mature brain [17,26–28]. In the mouse hippocampus, δ -catenin has a higher and robust level of expression than p120ctn during the first four postnatal weeks that coincide with dendritic and synaptic development [27]. Unlike δ -catenin, the levels of p120ctn decrease after birth and the levels in the adult are lower than during development [17,27]. Both proteins are also expressed in neural progenitor cells, although their functional roles in these cells remains

incompletely characterized [29,30]. p0071 and ARVCF are detected in the brain at postnatal three weeks and adult rodent brains [28,31,32], however, it is unclear if p0071 and ARVCF are expressed during early postnatal stages.

Large scale transcriptomic studies have been valuable in identifying cell type specific expression patterns of the p120ctn family of proteins. Expression of p120ctn family members has been detected in both excitatory and inhibitory neurons and glia [27,33,34]. In addition, recent studies combining electrophysiological profiling with single-cell RNAseq analysis demonstrate the expression of δ -catenin is significantly lower in burst-spiking pyramidal cells compared to regular-spiking pyramidal cells in the subiculum [27], suggesting neuron type specific expression patterns and functional roles. Further, analysis of the primary visual cortical region in mice indicated that the expression of members of the p120ctn family is varied within neuronal subtypes [33,34]. δ -catenin is enriched in inhibitory somatosensory neurons, while p0071 is enriched in parvalbumin neurons and a subset of neurons in layer 6 [33,34]. ARVCF and p120ctn do not demonstrate obvious enrichment in any neuronal subtypes [33,34].

In primary neurons, p120ctn is localized to growth cones [17] and in pre- and postsynaptic terminals of pyramidal neurons [17]. Similarly, δ -catenin is localized to growth cones [35], dendritic segments and postsynaptic terminals in central neurons [36,37]. It is not entirely clear if δ -catenin is also localized at presynaptic terminals.

In addition, there is evidence to indicate that members of the p120ctn family of proteins can localize to nuclei. A polyK sequence that promotes nuclear localization is localized within the insert region of all members of the family [9,12,14,18,25]. In p120ctn, this polyK sequence *per se* is sufficient to induce nuclear translocation and mutation of the sequence perturbs nuclear localization [25,29]. However, this polyK sequence is likely not the sole factor driving the nuclear localization of p120ctn [25].

ARVCF is also localized to the nucleus [38,39]. Both p120ctn and ARVCF have splice variants that include an alternative exon, exon C, that allows for an insertion within the polyK sequence. This insertion can disrupt the intrinsic nuclear localization ability of the polyK sequence from p120ctn [40]. However, an ARVCF isoform that includes exon C is still able to localize to the nucleus [39], suggesting that there may be other determinants in these proteins that regulate nuclear localization [25,38,39].

Unlike p120ctn and ARVCF, the nuclear localization abilities of δ -catenin are less well defined. While the polyK sequence in δ -catenin is capable of promoting nuclear localization of the protein [20,41], it is unclear that the full length protein is localized to the nucleus [9,20,41], although it has been suggested to localize to the nucleus in SH-SY5Y cells [42]. Recent studies also indicate that proteolytic fragments generated by caspase 3-cleavage of δ -catenin can localize to nuclei [20], although the C-terminal fragment with the polyK sequence had enhanced nuclear localization compared to the non-polyK sequence containing N-terminal fragment [20]. Thus, while it is likely that δ -catenin can localize to nuclei, this localization may be context- and cell type-dependent. Little is known about the nuclear

localization of p0071, however, given the homology of p0071 to other members of the family, this remains a strong possibility.

All of these data are derived from studies in non-neuronal cells and their significance for central neurons remains unclear. However, it is interesting to note that the p120ctn family of proteins is suited to perform functional roles associated with transfer of information between cellular compartments, for example synapse to nuclear signaling in which one can envision associations of the p120ctn family member with cadherin can be modulated by activity and used for signaling to other cellular compartments, including nuclei. There is currently no direct evidence for this kind of mechanism in neurons, however it remains an intriguing possibility.

3. Functional roles of the p120ctn family of proteins in central neurons

Our knowledge of the functional roles of ARVCF and p0071 in central neurons is quite limited, so the bulk of the discussion below will be mainly focused on p120ctn and δ -catenin (Table 1).

3.1 Regulation of the dendritic arbor

Both p120ctn and δ -catenin are key regulators of dendrite arborization in pyramidal neurons. Although both p120ctn and δ -catenin regulate dendrite morphogenesis, it is clear that they recruit both common and distinct effectors to participate in this functional role.

Loss of p120ctn *in vitro* in mouse primary neurons reduces dendritic arborization which can be restored by re-expression of p120ctn [43]. While there is overwhelming evidence for p120ctn regulating cytoskeletal remodeling via regulation of the small G proteins, Rac, Rho and cdc42 [44,45] in non-neuronal cell types, it is not entirely clear if the ability of p120ctn to regulate dendrite branching in neurons is through recruitment of these signaling pathways. The ability of p120ctn to regulate branching phenotype in non-neuronal cells is influenced by its ability to bind cadherin. Overexpression of the JMD domain of cadherin but not mutant JMD can successfully block the p120-induced branching phenotype in NIH3T3 cells [44]. Taken together, it is likely that p120ctn regulates dendritic branching in neurons via regulation of members of the Rho family of proteins and cadherins, however, experimental evidence for these in neurons is not yet available.

Similarly, loss of δ -catenin in hippocampal neurons by shRNA-mediated knockdown during the stages coinciding with dendrite development, reduces dendritic arbors [36]. While there are no published reports on a complete δ -catenin null mouse model, a mouse model that includes a truncated form of δ -catenin that includes the N-terminal region (δ -catenin N-term mice) has been described [46]. The mouse model expresses the first 461 amino acids of δ -catenin fused to GFP at its C-terminus [46]. Neurons from δ -catenin N-term mice shows similar compromise in dendritic arbors during development [36]. *In vivo* two photon imaging studies in cortical neurons of wild type and δ -catenin N-term mice indicate no alterations in the dendritic arbor at 5 weeks of age [47]. However, after 5 weeks of age, δ -catenin N-term mice have progressive retraction of the dendritic arbor, leading to functional deficits in cortical responsiveness [47]. Overexpression of δ -catenin enhances the branching

number of dendrites in primary hippocampal neurons [48,49]. Taken together, these data suggest that δ -catenin may regulate multiple aspects of dendrite morphogenesis, including developmental dendrite arborization and dendrite stability in the adult.

The ability of δ -catenin to influence dendritic branching is influenced by multiple effectors. Erbin is one such effector. Erbin, a PDZ domain-containing protein, binds to δ -catenin via PDZ-mediated interactions [50]. Erbin serves to localize δ -catenin appropriately, so it can regulate dendrite morphogenesis via downstream effectors, particularly those that interact with the C-terminal domain of δ -catenin. The cooperation of erbin and δ -catenin to modulate dendrite branching does not extend to erbin and p120ctn, likely because of an inability of erbin to bind to p120ctn which lacks the PDZ motif [50]. Interestingly, densin-180, a member of the erbin family that also interacts with δ -catenin likely regulates dendritic branching through δ -catenin [51]. However, in this case, the ability of δ -catenin to interact with densin-180 is perturbed by the association of densin-180 with shank [52].

The C-terminal region of δ -catenin is a critical determinant of its ability to regulate dendrite morphogenesis [53]. This region allows it interaction with cortactin, actin and 14-3-3 ϵ/ζ [30,35]. The interaction of δ -catenin with cortactin is regulated by phosphorylation, which promotes dissociation of δ -catenin from cortactin. Interestingly, BDNF promotes tyrosine phosphorylation of δ -catenin and subsequent dissociation from cortactin [35], although how this relates to the ability of δ -catenin to influence dendrite branching in neurons is not entirely clear.

The ability of δ -catenin to regulate dendrite morphogenesis is influenced by its ability to bind to cadherin. Knockdown of the nuclear protein KIDLIA, an X-linked autism protein, increases the total and surface levels of N-cadherin [54]. This leads to a sequestration of δ -catenin in the membrane pool resulting in decreased levels of free cytosolic δ -catenin [54]. This increases activation of Rho which results in decreased actin mobility in the neurite growth cone that in turn inhibits neurite outgrowth and branching [54].

Similar to p120ctn, δ -catenin influences the activities of the small G proteins, Rac, Rho and cdc42. However, some of these mechanisms are likely cell type specific. δ -catenin overexpression promotes Rho activation [35,48,55,56], however, this may not be universal [57], since no alterations were observed in the levels of active Rac and Rho in primary neurons from heterozygous and homozygous δ -catenin N-term mice. Similarly, overexpression of δ -catenin alters activity of Rac and cdc42 in some cell types (Chinese hamster ovary cells [55] and lymphatic endothelial cells [58] but not others [48]).

The ability of δ -catenin to recruit the small GTP binding proteins Rac and Rho to participate in dendrite morphogenesis remains incompletely defined. Some studies provide evidence for inhibition of enhanced dendritic arborization with overexpression of δ -catenin in neurons by dominant-active Rho and exaggeration by Rho GTPase inhibitor C3, suggesting that δ -catenin regulates neural process morphogenesis via a Rho-dependent pathway [35]. However, these results are in contrast to another study. δ -catenin heterozygous mice do not exhibit any alterations in dendrite architecture [36]. No alterations in the levels of active Rac and Rho are observed in primary neurons from δ -catenin N-term mice in comparison to

heterozygous mice [36]. However, δ -catenin N-term and heterozygous mice have more activated Rho, but less activated Rac and cdc42 in microvascular endothelial cells in comparison to their wild type littermates [59]. There is no evidence for a direct interaction between δ -catenin and member of the Rho family of proteins. However, as described below, δ -catenin can regulate the Rho family of proteins via its ability to interact with other regulators of Rho family of proteins.

Phosphorylation of δ -catenin at T454 by Akt leads to a decrease in p190RhoGEF mediated activation of Rho, by sequestering p190RhoGEF [48]. Abolishing the ability of this site to be phosphorylated by Akt by introducing the T454A mutation inhibits the ability of δ -catenin to positively influence dendrite like branching in NIH3T3 cells [48]. These results likely suggest that while δ -catenin can influence the activity of Rac, Rho and cdc42 and these are likely to be highly relevant to dendrite arborization in neurons, there may be cell type specific or cell compartment specific mechanisms that contribute to this influence.

JNK and activity-mediated phosphorylation of δ -catenin at S447 is also critical in the ability of δ -catenin to regulate dendritic outgrowth [49]. Mutation of S447 to A enhances the ability of δ -catenin to promote dendrite outgrowth. The upstream effectors that allow this phosphorylation *in vivo* are unknown, however, these data are consistent with the ability of δ -catenin to modulate dendrite outgrowth by linking to multiple signaling pathways.

Similar to p120ctn and δ -catenin, *Xenopus* ARVCF can influence dendrite-like process in NIH3T3 cells [60]. This may due to the conservation of the RhoA-binding domain in the insert region between p120ctn and ARVCF. However, overexpression of human ARVCF did not induce a similar branching phenotype [38]. One possibility for this discrepancy is that these differences may arise from the exclusion of exon C.

In *Xenopus*, another common effector that binds to ARVCF, δ -catenin and p0071, but not p120ctn is KazrinA [61]. KazrinA is a binding partner of p190B RhoGAP and negatively regulates RhoA [61], thus providing another potential link between p120ctn family and Rho activation. Further, in human cell lines, p120ctn can inhibit Rho activation via interaction between its C-terminal domain and p190A RhoGAP [62]. These results indicate that RhoGAP may be a common downstream effector for all p120ctn family members, however, how these interactions contribute to the dendritic branching abilities of 120ctn family members remains incompletely understood.

p0071 overexpression in neurons promotes dendritic arborization in hippocampal neurons [63]. FMRP binds to the RNA encoding p0071 and loss of FMRP enhances the levels of p0071 through RNA-dependent mechanisms [63]. Loss of FMRP increases dendrite arborization in young hippocampal neurons [63]. Interestingly, concurrent knockdown of p0071 with FMRP knockdown restores the enhanced dendritic arbor observed with FMRP knockdown. The effects of FMRP on the dendritic arbor are known to be quite varied and some of these effects may be dependent on neuron type and developmental stage [64,65]. It is unclear if this cooperation extends to other stages of dendrite development.

p0071 is a binding partner for Kazrin A, which is a binding partner of p190B RhoGAP [61]. Interestingly, p190B RhoGAP and Kazrin are enriched in parvalbumin neurons [33,34],

similar to p0071, in mouse primary visual cortex, providing an interesting speculation that the different signal pathways for RhoA inhibition by p120ctn family may have cell type-specificity.

Similar to δ -catenin and ARVCF, p0071 binds erbin [66] and densin-180 [51], however it is unclear if these effectors influence the ability of p0071 to regulate dendrite outgrowth in neurons. p0071 may also link to the Rho pathway via its ability to interact with RhoGEF Ect2 [67], however the functional effects of these interactions on dendrite outgrowth in neurons remains incompletely explored.

Thus, the ability of members of the p120ctn family to influence dendrite outgrowth and branching is likely a consequence of its ability to integrate information from upstream effectors and transduce this to downstream effectors that ultimately alter the cytoskeleton to regulate the dendritic arbor. Some of these effectors may be commonly used by all members of the family, while some may be unique to each member. The ability of these proteins to be regulated by multiple regulators perhaps confers on them the ability to tie dendritic extension to both intracellular and extracellular cues during development.

3.2 Regulation of synaptic density, architecture, plasticity and function

Given the key links between the cadherin-catenin cell adhesion complex and the actin cytoskeleton, it is perhaps not surprising that members of the p120ctn family of proteins regulate synaptic densities and architecture in neurons.

Loss of p120ctn in a mouse model severely diminishes the density of excitatory spines in hippocampal neurons [43]. This is accompanied by a reduction in the expression of excitatory synaptic markers [43]. Interestingly, these alterations are also accompanied by an increase in the density of perforated synapses as examined by electron microscopy [43]. These alterations are accompanied by reduction in active Rac and increase in active Rho levels [43]. The ability of p120ctn to regulate spine density is independent of its ability to bind cadherin, but is dependent on the ability of p120ctn to regulate the activity of Rho [43].

p120ctn also regulates presynaptic development. Loss of p120ctn disrupts the localization of presynaptic vesicles [68]. These disruptions can be recapitulated by depletion of the cytoplasmic tyrosine kinase, Fer, or the protein phosphatase SHP-2 [68]. A downstream effector for this mechanism is β -catenin. The phosphorylation status of β -catenin is regulated by cooperation of Fer and SHP-2. Overexpression of β -catenin can rescue the effects of loss of Fer on presynaptic vesicles and this is dependent on the ability of an interaction between Fer and p120ctn to regulate the phosphorylation of β -catenin that in turn regulates vesicle localization [68].

The effects of loss of δ -catenin on excitatory spine density remain somewhat confusing. Studies indicate that overexpression of δ -catenin in mature primary hippocampal neurons increases the density of synapses [55]. These abilities of δ -catenin to enhance spine densities could be inhibited by the use of a dominant negative Rac construct [55], indicating the ability of δ -catenin to influence spine and synapse density is regulated by its ability to regulate these small G proteins which in turn regulate the actin cytoskeleton. Conversely, the

authors demonstrated that loss of δ -catenin using siRNA-mediated knockdown leads to a decrease in the density of spines and synapses [55]. Importantly, these reduced densities could be rescued by the introduction of an siRNA-resistant construct of δ -catenin, confirming specificity [55]. These studies are also supported by other published studies which indicate that overexpression of δ -catenin promotes an increase in the density of spines and synapses in primary hippocampal neurons [69]. However, these studies are in contrast to another study in primary hippocampal neurons in which loss of δ -catenin leads to an increase in the density and function of excitatory synapses both with specific shRNA knockdown and in primary neurons from the δ -catenin N-term mice [19,70]. Further, these abilities of δ -catenin were dependent on its ability to cooperate with PDZ domain-containing regulators via its PDZ-binding motif, but like p120ctn, it is also independent of cadherin binding [19,70]. It is unclear how these contrasting results can be reconciled. One possibility is that since δ -catenin is a component of the cadherin-catenin cell adhesion complex, the ability of δ -catenin to influence spine and synapse densities is related to the density of neurons in the culture. Other possibilities include splice variant type specific effects or the levels of δ -catenin or neuron subtype specific effects. While it is clear that δ -catenin is a key regulator of excitatory synapse density and function, further studies are necessary to resolve the exact nature of its abilities.

Spines are highly plastic, a key feature that enables structural and functional modulation that forms the basis for long-term memory [71,72]. Loss of p120ctn in a mouse model reduces both the length and headwidth of spines [43]. The ability of p120ctn to regulate spine headwidth is dependent on its ability to both bind to cadherin and modulate active Rac levels, while the ability of p120ctn to influence spine length is dependent only on its ability to modulate the activity of Rac and Rho [18,43]. It is unclear, but quite likely, if these deficits in spine headwidth and length in absence of p120ctn reflect a compromise in the activity-dependent structural spine plasticity.

Similar to p120ctn, loss of δ -catenin impairs both spine headwidth and length in hippocampal neurons [37]. Unlike p120ctn, the ability of δ -catenin to modulate spine architecture is mediated by its ability to link to cadherins and PDZ domain effectors, suggesting that the signaling pathways recruited by p120ctn and δ -catenin to modulate spine architecture are not similar. Knockdown of δ -catenin also impairs structural plasticity in hippocampal neurons. More specifically, knockdown of δ -catenin impairs the ability of primary hippocampal neurons to alter spine headwidth in response to treatment with tetrodotoxin [70].

The PDZ-binding motif of δ -catenin confers on the protein the ability to link to and functionally influence a variety of synaptic scaffolding proteins. AMPA receptors (AMPA) interact with δ -catenin via scaffolding protein ABP/GRIP to localize to plasma membrane [73]. Overexpression of δ -catenin increases the level of GRIP, surface GluR2 and ratio of AMPA/NMDA [74]. In contrast, knock down of δ -catenin leads to decrease of GRIP and surface GluR2, with no change of the AMPA/NMDA ratio, which may due to the difference of experimental systems [74]. Unlike the effects on the AMPAR, there is no alteration in NMDA receptor response with loss or overexpression of δ -catenin [74]. The ability of δ -catenin to regulate synaptic density is influenced by its ability to be phosphorylated by

cyclin dependent kinase 5 (CDK5). δ -catenin can be directly phosphorylated by CDK5 at residues S300 and S357 [75]. This phosphorylation promotes its membrane association [75]. A mutant form of δ -catenin expressing S to A mutations at residues 300 and 357, representing constitutively activated forms, enhances the density of dendritic protrusions [75]. Loss of CDK5-mediated phosphorylation of δ -catenin enhances the association between δ -catenin and N-cadherin, GRIP and PSD95, resulting in an increase in the surface AMPAR and ratio of AMPA/NMDA compared to the wild type δ -catenin [75].

δ -catenin also binds to the postsynaptic scaffolding proteins PSD95 and SSCAM [73,76]. Interestingly, PSD95 and SSCAM also regulate localization of AMPAR to the plasma membrane [77,78]. Since δ -catenin has a single PDZ-binding motif, it is unclear what the stoichiometry of PDZ proteins associated with the cadherin- δ -catenin complex is and how these proteins cooperate to regulate the trafficking and stabilization of AMPA receptors.

Knockdown of δ -catenin in primary neurons impairs the ability of neurons to promote an increase in the density and length of protrusions in response to stimulation by DHPG, which promotes activation of the Group 1 mGluR receptors [55]. DHPG stimulation promotes phosphorylation of δ -catenin at multiple residues, dissociation from PSD95 and cadherin and increased association with cortactin, suggesting that the abilities of δ -catenin to regulate spine density in a DHPG-dependent manner may be at least in part due to its ability to alter links with regulators of the actin cytoskeleton, including cortactin, and cadherin in a phosphorylation-dependent manner [55].

Members of the p120ctn family of proteins are also being recognized as key players in the molecular machinery underlying learning. Chemical long-term potentiation (LTP) promotes the palmitoylation of δ -catenin by DHHC5 at residue C960-961 located within the 3rd helix of ARM 8 and this promotes interaction of δ -catenin with cadherin at synapses, activity-induced stabilization of cadherin at synapses and spine enlargement and insertion of GluA1 and GluA2 receptors [19]. Further context-dependent fear conditioning in mice promotes δ -catenin palmitoylation and increased δ -catenin-cadherin associations at hippocampal synapses [19]. Thus, δ -catenin is a critical component of the machinery that allows coordination of synaptic alterations to processes involved in memory formation. Interestingly, this palmitoylation site is conserved in p0071, however its functional consequences remains unclear.

δ -catenin N-term mice have behavioral deficits, including deficient spatial learning in water maze and associate learning in fear conditioning [46]. Consistently, these δ -catenin mutant mice have abnormal LTP [46].

Similar to δ -catenin, both ARVCF and p0071 have PDZ-binding motifs. However, it is unclear if they bind to the same repertoire of PDZ proteins. Similar to δ -catenin, p0071 binds to ABP [73], however, the functional consequences of this association remain unexplored. It would be interesting to examine if functional overlap exists between the complexes associated with the PDZ-binding motifs of ARVCF and p0071 and δ -catenin in synaptic development.

It is clear that both p120ctn and δ -catenin have critical roles in synapse morphogenesis and plasticity. p120ctn and δ -catenin likely influence these mechanisms using common and unique effectors. The functional roles of ARVCF and p0071 in synapse morphogenesis and plasticity are currently unknown. However, given their homology to p120ctn and δ -catenin and expression patterns, it is likely that such functional roles will be identified in the future.

4. Posttranslational modifications

Three types of posttranslational modifications have been described in members of the p120ctn family of proteins. These include phosphorylation, ubiquitination and palmitoylation. The majority of these modifications have been described for p120ctn and δ -catenin, with little data for ARVCF and p0071, particularly in neurons. All members of the p120ctn family are palmitoylated [79,80] in central nervous system. However, functional consequences for palmitoylation has only been described for δ -catenin as discussed above [19].

Posttranslational modifications, including phosphorylation and ubiquitination, can alter protein localization, structure, interactions and function. While several modifications have been described for members of the p120ctn family [30,55,81,82], the functional consequences of these modifications are incompletely understood.

Advances in mass spectrometry and large-scale proteomic studies have been quite informative in identifying the sites of these modifications on members of the p120ctn family. Multiple residues spanning the entire protein are phosphorylated in the central nervous system as indicated in Fig. 2 which includes data pooled from multiple sources [28,30–32,48,55,75,81,83–86]. p0071 has the highest number of phosphorylation sites, followed by δ -catenin, p120ctn, finally ARVCF. The majority of phosphorylation sites are localized to the N- and C- termini with fewer residues within the ARM domain. Two regions flanking either end of the ARM domain appear to be particularly enriched in phosphorylated residues (regions A and B in Fig 2). The functional consequences of the phosphorylation are not well defined. However, based on the structure of the interaction sites of cadherin and p120ctn [18], it is likely that these phosphorylation may alter the association of cadherin and members of the p120ctn family. Consistent with this, mGluR activity-dependent phosphorylation sites in δ -catenin (S1063, T1064 and S1098) are in region B, and their phosphorylation correlates to mGluR-mediated dissociation of δ -catenin and N-cadherin [55].

A head-to-tail intermolecular oligomerization of p120ctn ARM domain-JMD complex has been observed previously [18]. If p120ctn family members do form such oligomer *in vivo*, the phosphorylation sites in region A may be located proximal to insert region of the ARM domain. As the insert region bears functional motifs for signal transductions, for example NLS and RhoA-binding motif, the phosphorylation site in region A may affect the accessibility of the region to its binding partners. The experimental evidence for such a mechanism is lacking, however it remains a possibility and a mechanism to alter protein-protein interactions mediated by members of the p120ctn family of proteins.

Consistent with the possibility that phosphorylation alters protein localization, stability or interactions, δ -catenin phosphorylation is associated with alterations in membrane localization, protein-protein interaction and protein degradation in the central nervous system (Table 2). However, for a variety of these modifications, the functional consequences remain unclear.

Although multiple phosphorylation sites have been identified in other p120ctn family members [38,82], however, it is still unclear if these modifications occur in central neurons and if they have functional consequences.

Similar to the data obtained for sites of phosphorylation, large scale proteomic and mass spectrometric studies have been very informative in identifying sites of ubiquitination on members of the p120ctn family of proteins [87]. Unlike the phosphorylation sites, there are much fewer sites of ubiquitination on members of the p120ctn family (Fig. 2). One of these includes a site located between the 2nd and 3rd helix of ARM 4 [18] that is conserved in p120ctn (K517), δ -catenin (K700) and p0071 (K680 and K682). This position is on the arch of the ARM domain, opposite to the JMD-binding surface. Also, this linker region is longer compared to the linker regions between 2nd and 3rd helix in other ARM repeats, suggesting it may be functional meaningful and serve as common motif for regulating protein stability in p120ctn family. Additionally, another site identified in this study also is conserved between p0071 (K517) and δ -catenin (K537), which is located before the start of ARM1 repeat [18]. This site is proximal to the region A, thus the phosphorylation of region A may affect the ubiquitination at this position.

It is worth mentioning that K756 in N-cadherin has also been identified as a site for ubiquitination [87,88] in the brain. This ubiquitination site is also conserved in E- and P-cadherin [89]. This lysine is located within the JMD and close to the endocytosis LL-motif [90]. Ubiquitination of this site could potentially destabilize the association between cadherin and p120ctn family, suggesting that ubiquitination may also be regulatory mechanism for their association.

Members of the p120ctn family are likely regulated by multiple signaling pathways with varying functional consequences. Thus, they are in a unique position to serve as signal transducers between multiple signaling pathways.

5. Nuclear functional roles for p120ctn family

Members of the p120ctn family of proteins have more recently been identified to localize to nuclei and have critical nuclear functional [91,92], particularly in regulating transcription via nuclear effectors. P120ctn has been the most well characterized protein in the family with respect to its nuclear roles. However, most of these studies have been described in non-neuronal cell types [25,29,93] and its functional roles in post mitotic neurons remains incompletely characterized. These functional roles are predominantly in regulating transcription. P120ctn and other members of the family do not have any predicted DNA binding domains. Consistently, p120ctn regulates transcription via cooperation with other effectors, including components of the Wnt signaling pathway [94]. One of these effectors is

Kaiso [93], a BTB/POZ zinc-finger transcription factor. P120ctn can relieve kaiso-mediated transcriptional repression in non-neuronal cells [25]. Interestingly, Kaiso is expressed in neurons and Kaiso null mice have behavioral deficits, particularly increased locomotion, exploration in the open field, novel object and elevated plus-maze test and elevated amplitudes and pre-pulse inhibitions of the acoustic startle reflex [95]. It would be interesting to examine if these behavioral deficits have origins in p120ctn-kaiso mediated transcriptional regulation in neurons. P210ctn also interacts and cooperates with the REST/Co-REST transcriptional complex to regulate gene expression [29]. The REST/CoREST complex represses the expression of neural differentiation genes. P120ctn relieves REST/CoREST mediated transcriptional repression and thus promotes neural differentiation of mouse embryonic stem cells. Available data suggests that the levels of E-cadherin drop as the stem cells differentiate, leading to increased availability of free p120ctn that can then translocate to the nucleus to cooperate with REST/CoREST to regulate gene expression.

Another nuclear functional partner of p120ctn is Glis2, a zinc-finger Kruppel-like transcriptional repressor [96] that cooperates with Src to promote the recruitment of p120ctn to the nucleus. P120ctn promotes the cleavage of Glis2 within its zinc finger domain. This cleavage reduces the ability of Glis2 to promote neural differentiation.

δ -catenin cooperates with the transcriptional repressor Kaiso [97], WNT pathway transcriptional factor LEF1 [98] and Krab-domain zinc-finger transcriptional repressor ZIFCAT [20]. The interaction of δ -catenin with Kaiso regulates its ability to drive expression of the rapsyn promoter at the neuromuscular junction [97]. The functional consequences of the interactions of δ -catenin and LEF1/ZIFCAT in post mitotic neurons remains incompletely understood. ARVCF [38] is localized to the nuclei in non-neuronal cells, however, whether its nuclear localization and potential functional roles in transcription extend to neurons remains unknown.

6. Emerging roles for p120ctn family in neurodevelopmental and neurological disorders

It is now clear that catenins regulate a multitude of critical neuronal processes, thus they are critical for the cellular processes that underlie neural circuit formation and function in the developing brain. It is therefore conceivable that genetic mutations or loss of these genes may disrupt normal neuronal wiring, especially during the early stages of development. Consistently, genetic aberrations in genes encoding these proteins have been associated with neurodevelopmental and neurological disorders.

There is no published data on mutations in *CTNND1* associated with human neurological disorders. This is perhaps not as surprising, given the wide tissue distribution of the protein and early lethality associated with loss of protein in mice.

Unlike *CTNND1*, mutations and variations in *CTNND2* have been associated with several neurological and neurodevelopmental disorders. The cri du chat syndrome is associated with a cat-like cry, dysmorphic facial features, microcephaly, and intellectual disability [99]. The syndrome is associated with variable deletions of chromosome 5p resulting in loss of one or

more genes from the locus. *CTNND2* is localized at 5p15.2 and the loss of *CTNND2* in these individuals correlates with the intellectual disability phenotype [100]. Additional studies indicate a strong correlation with hemizyosity of *CTNND2* and intellectual disability. An out of frame deletion spanning exons 4–7 of *CTNND2* in a human has been associated with altered facial features and borderline intellectual disability [101]. In addition, two patients with intronic or exonic deletions of *CTNND2* have been described to have intellectual disability [102]. Consistent with the critical role of the gene in intellectual disability, an individual with the cri du chat syndrome with an additional complex genetic rearrangement resulting in a partial deletion and partial duplication of *CTNND2* has a mild cognitive phenotype [103,104].

More recent studies suggest a critical role for *CTNND2* in the pathology of autism. Significant excess of missense and copy number variations have been identified in individuals with autism [69]. Interestingly, these variations span the entire protein and are not restricted to a single domain, suggesting that likely several key functional features of δ -catenin are required for its ability to participate in neural circuit wiring crucial to higher order functions.

Copy number variations in *CTNND2* have more recently been identified in cerebral palsy [105], although the correlation between these variants and the pathology of the disorder remains incompletely characterized. Copy number variations associated with gene duplication and disruption of the terminal portion of *CTNND2* have been identified in schizophrenia [106]. Recent studies have also implicated *CTNND2* in anxiety disorders [107], although these links need further exploration and validation.

Genetic variations in *CTNND2* have also been implicated in the development of cortical lens opacities associated with cataract and cognitive change that precede the development of Alzheimer's disease [108]. This variant leading to a single amino acid substitution, G810R, in δ -catenin, promotes an increase in the secretion of $A\beta_{1-42}$, suggesting a pathological mechanism for a link between this variation in *CTNND2* and the pathology of cataracts and Alzheimer's disease. It would be interesting to examine variations in *CTNND2* in larger cohorts of Alzheimer's disease patients to define the extent of contribution of variations in *CTNND2* to the pathology of Alzheimer's disease.

While little is known about the links between ARVCF and neurological disorders, available studies suggest that variations in ARVCF may have links to neurodevelopmental and neuropsychiatric disorders, similar to other members of the p120ctn family. ARVCF was originally identified in the deletion associated with the velo-cardio-facial syndrome. And its strongest links have been identified for schizophrenia [109]. A recent study implicated the association of haplotypes in ARVCF to schizophrenia in a cohort of Chinese individuals. Consistent with this association, there are notable similarities between patients with velo-cardio-facial syndrome and schizophrenia, particularly with regards to neurocognitive deficits and structural abnormalities in the brain [110]. Another study proposed that a functional variant in ARVCF is associated with increased risk for schizophrenia [111–113].

While there are no published strong associations between variations in p0071 and neurodevelopmental and neurological disorders, some functional studies on p0071 suggest the possibility that such links may exist. Loss of FMRP is associated with the fragile X syndrome. ARVCF is a target of FMRP and both proteins cooperate to regulate neurite outgrowth and branching [63].

Thus, while significant links have been identified for the members of the p120ctn family in neurological disorders, it is likely that much remain to be identified. With the technological advances in human genetics, it is likely that the next several years may bring forth a wealth of data implicating these genes in a variety of neuronal disorders associated with disrupted neuronal homeostasis.

7. Future studies

The major focus of functional studies in neurons for members of the p120ctn family of proteins have been restricted to p120ctn and δ -catenin. While it is clear that both p0071 and ARVCF are expressed in the brain [33,34], their functional roles remain unclear. Available data suggesting overlapping expression patterns in neurons for members of the p120ctn family, however, their ability to functionally compensate for loss of one member of the family remains unclear. While loss of δ -catenin does not lead to an obvious alteration in the levels of p120ctn [70], it is unclear if this is true for other members of the family.

It is clear that the p120ctn family of proteins have functional roles that are both dependent and independent of their ability to bind to cadherin. While there is no clear evidence to indicate that p120ctn family members associate with other cadherin superfamily members, it is tempting to speculate if other such interactions exist and if the so-called cadherin-independent functions are mediated by virtue of their ability to link to other members of the cadherin superfamily including protocadherins or non-cadherin family associated interactions.

6.1 Compositions of cadherin-p120ctn family complexes in central neurons

Unlike β -catenin which has its own binding domain on cadherin, the four members of the p120ctn family share the same binding domain, JMD, on cadherin. Although some previous studies have assessed whether there is a competition between certain p120ctn family members for binding to cadherin [38], it is still unclear that whether these competitions occur in the same cell, or same intracellular compartment like synapses. It is clear members of the p120ctn family have functions in common to other members and unique functions. For example, unlike δ -catenin, ARVCF and p0071, p120ctn bound to cadherin is unable to recruit PDZ domain-containing proteins due to the absence of the PDZ-binding motif in p120ctn. This clearly limits its ability to recruit the same signaling pathways that are recruited by other members of the family. It is entirely conceivable that competition for the cadherin binding site by different members of the family may also be regulated by cellular context and activity dependent signaling resulting in neuron type and synapse type specific alterations in intracellular signaling.

6.2 Roles in synaptic specificity and plasticity

While it is clear that all members of the p120ctn family are expressed in the brain, their expression patterns related to developmental stage, brain region, neuron type and subcellular localization remain incompletely characterized. Cadherins are key regulators of synaptic specificity in developing neural circuits [114] and it would be interesting to determine if p120ctn family members contribute to this ability. Since p120ctn family members also appear to have functional roles that are both cadherin-dependent and -independent, allowing them to link to multiple intracellular signaling pathways in a context-dependent manner, it would also be interesting to dissect if these abilities allow them to contribute to the molecular changes involved in synapse reorganization underlying learning and memory.

6.3 Roles in neurodevelopmental and neurodegenerative disorders

The known and predicted functional roles of the members of the p120ctn family of proteins and their expression patterns make them potential candidates for neuro-developmental disorders, particularly those associated with intellectual disabilities and autism. Mutations in the gene encoding presenilin-1 have been identified in Alzheimer's disease. Both p120ctn, δ -catenin and p0071 directly bind presenilin-1 [115–118]. The functional significance of this association is less clear. It is worth exploring if members of the p120ctn family contribute to the initiation or progress of this devastating disorder.

In summary, components of the p120ctn family are critical mediators of cellular processes underlying dendrite arborization and synapse morphogenesis and plasticity in central neurons. These functional roles are likely mediated by their ability to transduce information from upstream sources to the cytoskeleton. Given their critical functional roles, these proteins are likely to be of great relevance for understanding the molecular and cellular aberrations associated with neurodevelopmental and neurodegenerative disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research in the Arikath Lab has been supported by Startup funds from the Munroe-Meyer Institute and grants from the Alzheimer's association, The Nebraska Research Initiative, an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number 5P20GM103471-10, the Nebraska EPSCoR (EPS-1004094) and RO3 from the National Institutes of Health (1R03MH110726-01). Li Yuan was partly supported by a graduate student fellowship from the University of Nebraska Medical Center.

References

1. Suzuki SC, Takeichi M. Cadherins in neuronal morphogenesis and function. *Dev Growth Differ*. 2008; 50:S119–S130. DOI: 10.1111/j.1440-169X.2008.01002.x [PubMed: 18430170]
2. Seong E, Yuan L, Arikath J. Cadherins and catenins in dendrite and synapse morphogenesis. *Cell Adh Migr*. 2015; 9:202–213. DOI: 10.4161/19336918.2014.994919 [PubMed: 25914083]
3. Arikath J. Molecular mechanisms of dendrite morphogenesis. *Front Cell Neurosci*. 2012; 6:61.doi: 10.3389/fncel.2012.00061 [PubMed: 23293584]

4. Mills F, Globa AK, Liu S, Cowan CM, Mobasser M, Phillips AG, Borgland SL, Bamji SX. Cadherins mediate cocaine-induced synaptic plasticity and behavioral conditioning. *Nat Neurosci*. 2017; doi: 10.1038/nn.4503
5. Maguschak KA, Ressler KJ. β -catenin is required for memory consolidation. *Nat Neurosci*. 2008; 11:1319–1326. DOI: 10.1038/nn.2198 [PubMed: 18820693]
6. Sun Y, Bamji SX. β -Pix Modulates Actin-Mediated Recruitment of Synaptic Vesicles to Synapses. *J Neurosci*. 2011; 31:17123–17133. DOI: 10.1523/JNEUROSCI.2359-11.2011 [PubMed: 22114281]
7. Bamji SX, Shimazu K, Kimes N, Huelsken J, Birchmeier W, Lu B, Reichardt LF. Role of β -catenin in synaptic vesicle localization and presynaptic assembly. *Neuron*. 2003; 40:719–31. <http://www.ncbi.nlm.nih.gov/pubmed/14622577> .accessed March 19, 2017. [PubMed: 14622577]
8. Yap AS, Niessen CM, Gumbiner BM. The juxtamembrane region of the cadherin cytoplasmic tail supports lateral clustering, adhesive strengthening, and interaction with p120ctn. *J Cell Biol*. 1998; 141:779–789. [PubMed: 9566976]
9. Paffenholz R, Franke WW. Identification and localization of a neurally expressed member of the plakoglobin/armadillo multigene family. *Differentiation*. 1997; 61:293–304. doi: S0301-4681(09)60682-4 [pii]. [PubMed: 9342840]
10. Carnahan RH, Rokas A, Gaucher EA, Reynolds AB. The molecular evolution of the p120-catenin subfamily and its functional associations. *PLoS One*. 2010; 5:e15747. doi: 10.1371/journal.pone.0015747 [PubMed: 21209830]
11. Keirsebilck A, Bonne S, Staes K, van Hengel J, Nollet F, Reynolds A, van Roy F. Molecular cloning of the human p120ctn catenin gene (CTNND1): expression of multiple alternatively spliced isoforms. *Genomics*. 1998; 50:129–146. doi: S0888-7543(98)95325-3 [pii]. [PubMed: 9653641]
12. Sirotkin H, Morrow B, Saint-Jore B, Puech A, Das Gupta R, Patanjali SR, Skoultschi A, Weissman SM, Kucherlapati R. Identification, characterization, and precise mapping of a human gene encoding a novel membrane-spanning protein from the 22q11 region deleted in velo-cardio-facial syndrome. *Genomics*. 1997; 42:245–251. doi: S0888754397947340 [pii]. [PubMed: 9192844]
13. Paulson AF, Mooney E, Fang X, Ji H, McCrea PD. Xarvcf, *Xenopus* member of the p120 catenin subfamily associating with cadherin juxtamembrane region. *J Biol Chem*. 2000; 275:30124–30131. DOI: 10.1074/jbc.M003048200 [PubMed: 10899158]
14. Hatzfeld M, Nachtseim C. Cloning and characterization of a new armadillo family member, p0071, associated with the junctional plaque: evidence for a subfamily of closely related proteins. *J Cell Sci*. 1996; 109(Pt 1):2767–2778. [PubMed: 8937994]
15. Lu Q, Aguilar BJ, Li M, Jiang Y, Chen YH. Genetic alterations of δ -catenin/NPRAP/Neurojungin (CTNND2): functional implications in complex human diseases. *Hum Genet*. 2016; 135:1107–1116. DOI: 10.1007/s00439-016-1705-3 [PubMed: 27380241]
16. Markham NO, Doll CA, Dohn MR, Miller RK, Yu H, Coffey RJ, McCrea PD, Gamse JT, Reynolds AB. DIPA-family coiled-coils bind conserved isoform-specific head domain of p120-catenin family: potential roles in hydrocephalus and heterotopia. *Mol Biol Cell*. 2014; 25:2592–2603. DOI: 10.1091/mbc.E13-08-0492 [PubMed: 25009281]
17. Chauvet N, Prieto M, Fabre C, Noren NK, Privat A. Distribution of p120 catenin during rat brain development: potential role in regulation of cadherin-mediated adhesion and actin cytoskeleton organization. *Mol Cell Neurosci*. 2003; 22:467–486. doi:S1044743103000307 [pii]. [PubMed: 12727444]
18. Ishiyama N, Lee SH, Liu S, Li GY, Smith MJ, Reichardt LF, Ikura M. Dynamic and static interactions between p120 catenin and E-cadherin regulate the stability of cell-cell adhesion. *Cell*. 2010; 141:117–128. DOI: 10.1016/j.cell.2010.01.017 [PubMed: 20371349]
19. Brigidi GS, Sun Y, Beccano-Kelly D, Pitman K, Mobasser M, Borgland SL, Milnerwood AJ, Bamji SX. Palmitoylation of delta-catenin by DHHC5 mediates activity-induced synapse plasticity. *Nat Neurosci*. 2014; 17:522–532. DOI: 10.1038/nn.3657 [PubMed: 24562000]
20. Gu D, Tonthat NK, Lee M, Ji H, Bhat KP, Hollingsworth F, Aldape KD, Schumacher MA, Zwaka TP, McCrea PD. Caspase-3 cleavage links delta-catenin to the novel nuclear protein ZIFCAT. *J Biol Chem*. 2011; 286:23178–23188. DOI: 10.1074/jbc.M110.167544 [PubMed: 21561870]

21. Kim JS, Bareiss S, Kim KK, Tatum R, Han JR, Jin YH, Kim H, Lu Q, Kim K. Presenilin-1 inhibits delta-catenin-induced cellular branching and promotes delta-catenin processing and turnover. *Biochem Biophys Res Commun.* 2006; 351:903–908. doi: S0006-291X(06)02383-7 [pii]. [PubMed: 17097608]
22. Hong JY, Oh IH, McCrea PD. Phosphorylation and isoform use in p120-catenin during development and tumorigenesis. *Biochim Biophys Acta - Mol Cell Res.* 2016; 1863:102–114. DOI: 10.1016/j.bbamcr.2015.10.008
23. Aho S, Rothenberger K, Uitto J. Human p120ctn catenin: tissue-specific expression of isoforms and molecular interactions with BP180/type XVII collagen. *J Cell Biochem.* 1999; 73:390–9. <http://www.ncbi.nlm.nih.gov/pubmed/10321838>. accessed March 19, 2017. [PubMed: 10321838]
24. Kawamura Y, Fan QW, Hayashi H, Michikawa M, Yanagisawa K, Komano H. Expression of the mRNA for two isoforms of neural plakophilin-related arm-repeat protein/delta-catenin in rodent neurons and glial cells. *Neurosci Lett.* 1999; 277:185–188. doi: S0304394099008757 [pii]. [PubMed: 10626844]
25. Kelly KF, Spring CM, Otchere AA, Daniel JM. NLS-dependent nuclear localization of p120ctn is necessary to relieve Kaiso-mediated transcriptional repression. *J Cell Sci.* 2004; 117:2675–2686. DOI: 10.1242/jcs.01101 [PubMed: 15138284]
26. Duparc R-H, Boutemmine D, Champagne M-P, Tétreault N, Bernier G. Pax6 is required for delta-catenin/neurogenin expression during retinal, cerebellar and cortical development in mice. *Dev Biol.* 2006; 300:647–655. DOI: 10.1016/j.ydbio.2006.07.045 [PubMed: 16973151]
27. Foldy C, Darmanis S, Aoto J, Malenka RC, Quake SR, Sudhof TC. Single-cell RNAseq reveals cell adhesion molecule profiles in electrophysiologically defined neurons. *Proc Natl Acad Sci U S A.* 2016; 113:E5222–31. DOI: 10.1073/pnas.1610155113 [PubMed: 27531958]
28. Munton RP, Tweedie-Cullen R, Livingstone-Zatchej M, Weinandy F, Waidelich M, Longo D, Gehrig P, Potthast F, Rutishauser D, Gerrits B, Panse C, Schlappbach R, Mansuy IM. Qualitative and quantitative analyses of protein phosphorylation in naive and stimulated mouse synaptosomal preparations. *Mol Cell Proteomics.* 2007; 6:283–293. doi: M600046-MCP200 [pii]. [PubMed: 17114649]
29. Lee M, Ji H, Furuta Y, Park JI, McCrea PD. p120-catenin regulates REST and CoREST, and modulates mouse embryonic stem cell differentiation. *J Cell Sci.* 2014; 127:4037–4051. DOI: 10.1242/jcs.151944 [PubMed: 25074806]
30. Toyo-oka K, Wachi T, Hunt RF, Baraban SC, Taya S, Ramshaw H, Kaibuchi K, Schwarz QP, Lopez AF, Wynshaw-Boris A. 14-3-3epsilon and Zeta Regulate Neurogenesis and Differentiation of Neuronal Progenitor Cells in the Developing Brain. *J Neurosci.* 2014; 34:12168–12181. DOI: 10.1523/JNEUROSCI.2513-13.2014 [PubMed: 25186760]
31. Huttlin EL, Jedrychowski MP, Elias JE, Goswami T, Rad R, Beausoleil SA, Villen J, Haas W, Sowa ME, Gygi SP. A tissue-specific atlas of mouse protein phosphorylation and expression. *Cell.* 2010; 143:1174–1189. DOI: 10.1016/j.cell.2010.12.001 [PubMed: 21183079]
32. Erickson BK, Jedrychowski MP, McAlister GC, Everley RA, Kunz R, Gygi SP. Evaluating multiplexed quantitative phosphopeptide analysis on a hybrid quadrupole mass filter/linear ion trap/orbitrap mass spectrometer. *Anal Chem.* 2015; 87:1241–1249. DOI: 10.1021/ac503934f [PubMed: 25521595]
33. Tasic B, Menon V, Nguyen TNT, Kim TTK, Jarsky T, Yao Z, Levi BB, Gray LT, Sorensen SA, Dolbeare T, Bertagnolli D, Goldy J, Shapovalova N, Parry S, Lee CC, Smith K, Bernard A, Madisen L, Sunkin SM, Hawrylycz M, Koch C, Zeng H, Yao Z, Lee CC, Shapovalova N, Parry S, Madisen L, Sunkin SM, Hawrylycz M, Koch C, Zeng H. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat Neurosci.* 2016; 19:335–346. DOI: 10.1038/nn.4216 [PubMed: 26727548]
34. Allen Institute for Brain Science. Allen Brain Atlas Data Portal: Cell Taxonomy. (n.d.). <http://casestudies.brain-map.org/celltax> (accessed March 1, 2017)
35. Martinez MC, Ochiishi T, Majewski M, Kosik KS. Dual regulation of neuronal morphogenesis by a delta-catenin-cortactin complex and Rho. *J Cell Biol.* 2003; 162:99–111. DOI: 10.1083/jcb.200211025 [PubMed: 12835311]

36. Arikath J, Israely I, Tao Y, Mei L, Liu X, Reichardt LF. Erbin controls dendritic morphogenesis by regulating localization of delta-catenin. *J Neurosci*. 2008; 28:7047–7056. DOI: 10.1523/JNEUROSCI.0451-08.2008 [PubMed: 18614673]
37. Yuan L, Seong E, Beuscher JL, Arikath J. delta-Catenin Regulates Spine Architecture via Cadherin and PDZ-dependent Interactions. *J Biol Chem*. 2015; 290:10947–10957. DOI: 10.1074/jbc.M114.632679 [PubMed: 25724647]
38. Mariner DJ, Wang J, Reynolds AB. ARVCF localizes to the nucleus and adherens junction and is mutually exclusive with p120(ctn) in E-cadherin complexes. *J Cell Sci*. 2000; 113(Pt 8):1481–1490. [PubMed: 10725230]
39. Rappe U, Schlechter T, Aschoff M, Hotz-Wagenblatt A, Hofmann I. Nuclear ARVCF protein binds splicing factors and contributes to the regulation of alternative splicing. *J Biol Chem*. 2014; 289:12421–12434. DOI: 10.1074/jbc.M113.530717 [PubMed: 24644279]
40. Pieters T, Goossens S, Haenebalcke L, Andries V, Stryjewska A, De Rycke R, Lemeire K, Hochepeid T, Huylebroeck D, Berx G, Stemmler MP, Wirth D, Haigh JJ, van Hengel J, van Roy F. p120 Catenin-Mediated Stabilization of E-Cadherin Is Essential for Primitive Endoderm Specification. *PLOS Genet*. 2016; 12:e1006243.doi: 10.1371/journal.pgen.1006243 [PubMed: 27556156]
41. Lu Q, Paredes M, Medina M, Zhou J, Cavallo R, Peifer M, Orecchio L, Kosik KS. Delta-Catenin, an Adhesive Junction-Associated Protein which Promotes Cell Scattering. *J Cell Biol*. 1999; 144:519–532. [PubMed: 9971746]
42. Koutras C, Lessard CB, Levesque G. A nuclear function for the presenilin 1 neuronal partner NPRAP/delta-catenin. *J Alzheimers Dis*. 2011; 27:307–316. DOI: 10.3233/JAD-2011-110536 [PubMed: 21811021]
43. Elia LP, Yamamoto M, Zang K, Reichardt LF. p120 catenin regulates dendritic spine and synapse development through Rho-family GTPases and cadherins. *Neuron*. 2006; 51:43–56. doi: S0896-6273(06)00410-7 [pii]. [PubMed: 16815331]
44. Anastasiadis PZ, Moon SY, Thoreson MA, Mariner DJ, Crawford HC, Zheng Y, Reynolds AB. Inhibition of RhoA by p120 catenin. *Nat Cell Biol*. 2000; 2:637–644. DOI: 10.1038/35023588 [PubMed: 10980705]
45. Threadgill R, Bobb K, Ghosh A, Weinberg R, Hall A, Marshall C, Ellis C, Gutkind J. Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42. *Neuron*. 1997; 19:625–34. DOI: 10.1016/S0896-6273(00)80376-1 [PubMed: 9331353]
46. Israely I, Costa RM, Xie CW, Silva AJ, Kosik KS, Liu X. Deletion of the neuron-specific protein delta-catenin leads to severe cognitive and synaptic dysfunction. *Curr Biol*. 2004; 14:1657–1663. DOI: 10.1016/j.cub.2004.08.065 [PubMed: 15380068]
47. Matter C, Pribadi M, Liu X, Trachtenberg JT. Delta-catenin is required for the maintenance of neural structure and function in mature cortex in vivo. *Neuron*. 2009; 64:320–327. DOI: 10.1016/j.neuron.2009.09.026 [PubMed: 19914181]
48. Kim H, Han JR, Park J, Oh M, James SE, Chang S, Lu Q, Lee KY, Ki H, Song WJ, Kim K. Delta-catenin-induced dendritic morphogenesis. An essential role of p190RhoGEF interaction through Akt1-mediated phosphorylation. *J Biol Chem*. 2008; 283:977–987. doi: M707158200 [pii]. [PubMed: 17993462]
49. Edbauer D, Cheng D, Batterton MN, Wang CF, Duong DM, Yaffe MB, Peng J, Sheng M. Identification and characterization of neuronal mitogen-activated protein kinase substrates using a specific phosphomotif antibody. *Mol Cell Proteomics*. 2009; 8:681–695. DOI: 10.1074/mcp.M800233-MCP200 [PubMed: 19054758]
50. Laura RP, Witt AS, Held HA, Gerstner R, Deshayes K, Koehler MF, Kosik KS, Sidhu SS, Lasky LA. The Erbin PDZ domain binds with high affinity and specificity to the carboxyl termini of delta-catenin and ARVCF. *J Biol Chem*. 2002; 277:12906–12914. DOI: 10.1074/jbc.M200818200 [PubMed: 11821434]
51. Izawa I, Nishizawa M, Ohtakara K, Inagaki M. Densin-180 interacts with delta-catenin/neural plakophilin-related armadillo repeat protein at synapses. *J Biol Chem*. 2002; 277:5345–5350. DOI: 10.1074/jbc.M110052200 [PubMed: 11729199]

52. Zitzer H, Hönck HH, Bächner D, Richter D, Kreienkamp HJ. Somatostatin receptor interacting protein defines a novel family of multidomain proteins present in human and rodent brain. *J Biol Chem*. 1999; 274:32997–3001. DOI: 10.1074/JBC.274.46.32997 [PubMed: 10551867]
53. Lee HB, He Y, Yang GS, Oh JA, Ha JS, Song OH, Lee DJ, Jung SC, Kim KK, Kim K, Kim H. Determination of C-Terminal δ -Catenin Responsible for Inducing Dendritic Morphogenesis. *J Nanosci Nanotechnol*. 2015; 15:5589–92. <http://www.ncbi.nlm.nih.gov/pubmed/26369122>. (accessed March 19, 2017). [PubMed: 26369122]
54. Gilbert J, Man HY. The X-Linked Autism Protein KIAA2022/KIDLIA Regulates Neurite Outgrowth via N-Cadherin and delta-Catenin Signaling. *eNeuro*. 2016; 3 ENEURO.0238-16.2016. eCollection 2016 Sep–Oct. doi:ENEURO.0238-16.2016 [pii].
55. Abu-Elneel K, Ochiishi T, Medina M, Remedi M, Gastaldi L, Caceres A, Kosik KS. A delta-catenin signaling pathway leading to dendritic protrusions. *J Biol Chem*. 2008; 283:32781–32791. DOI: 10.1074/jbc.M804688200 [PubMed: 18809680]
56. Gu D, Sater AK, Ji H, Cho K, Clark M, Stratton SA, Barton MC, Lu Q, McCrea PD. Xenopus δ -catenin is essential in early embryogenesis and is functionally linked to cadherins and small GTPases. *J Cell Sci*. 2009; 122:4049–4061. DOI: 10.1242/jcs.031948 [PubMed: 19843587]
57. Kim H, Oh M, Lu Q, Kim K. E-Cadherin negatively modulates δ -catenin-induced morphological changes and RhoA activity reduction by competing with p190RhoGEF for δ -catenin. *Biochem Biophys Res Commun*. 2008; 377:636–641. DOI: 10.1016/j.bbrc.2008.10.030 [PubMed: 18930028]
58. Ghose S, Min Y, Lin PC, Kreft B, Ochiishi T. δ -Catenin Activates Rho GTPase, Promotes Lymphangiogenesis and Growth of Tumor Metastases. *PLoS One*. 2015; 10:e0116338.doi: 10.1371/journal.pone.0116338 [PubMed: 25635825]
59. DeBusk LM, Boelte K, Min Y, Lin PC. Heterozygous deficiency of delta-catenin impairs pathological angiogenesis. *J Exp Med*. 2010; 207:77–84. DOI: 10.1084/jem.20091097 [PubMed: 20048286]
60. Fang X, Ji H, Kim SW, Park JI, Vaught TG, Anastasiadis PZ, Ciesiolka M, McCrea PD. Vertebrate development requires ARVCF and p120 catenins and their interplay with RhoA and Rac. *J Cell Biol*. 2004; 165:87–98. DOI: 10.1083/jcb.200307109 [PubMed: 15067024]
61. Cho K, Vaught TG, Ji H, Gu D, Papasakelariou-Yared C, Horstmann N, Jennings JM, Lee M, Sevilla LM, Kloc M, Reynolds AB, Watt FM, Brennan RG, Kowalczyk AP, McCrea PD. Xenopus Kazrin interacts with ARVCF-catenin, spectrin and p190B RhoGAP, and modulates RhoA activity and epithelial integrity. *J Cell Sci*. 2010; 123:4128–4144. DOI: 10.1242/jcs.072041 [PubMed: 21062899]
62. Zebda N, Tian Y, Tian X, Gawlak G, Higginbotham K, Reynolds AB, Birukova AA, Birukov KG. Interaction of p190RhoGAP with C-terminal Domain of p120-catenin Modulates Endothelial Cytoskeleton and Permeability. *J Biol Chem*. 2013; 288:18290–18299. DOI: 10.1074/jbc.M112.432757 [PubMed: 23653363]
63. Nolze A, Schneider J, Keil R, Lederer M, Hüttelmaier S, Kessels MM, Qualmann B, Hatzfeld M. FMRP regulates actin filament organization via the armadillo protein p0071. *RNA*. 2013; 19:1483–1496. DOI: 10.1261/rna.037945.112 [PubMed: 24062571]
64. Irwin SA, Galvez R, Greenough WT. Dendritic Spine Structural Anomalies in Fragile-X Mental Retardation Syndrome. *Cereb Cortex*. 2000; 10:1038–1044. DOI: 10.1093/cercor/10.10.1038 [PubMed: 11007554]
65. Berman RF, Murray KD, Arque G, Hunsaker MR, Wenzel HJ. Abnormal dendrite and spine morphology in primary visual cortex in the CGG knock-in mouse model of the fragile X premutation. *Epilepsia*. 2012; 53(Suppl 1):150–60. DOI: 10.1111/j.1528-1167.2012.03486.x [PubMed: 22612820]
66. Jaulin-Bastard F, Arsanto JP, Le Bivic A, Navarro C, Vely F, Saito H, Marchetto S, Hatzfeld M, Santoni MJ, Birnbaum D, Borg JP. Interaction between Erbin and a Catenin-related protein in epithelial cells. *J Biol Chem*. 2002; 277:2869–2875. DOI: 10.1074/jbc.M109652200 [PubMed: 11711544]
67. Wolf A, Keil R, Götzl O, Mun A, Schwarze K, Lederer M, Hüttelmaier S, Hatzfeld M. The armadillo protein p0071 regulates Rho signalling during cytokinesis. *Nat Cell Biol*. 2006; 8:1432–1440. DOI: 10.1038/ncb1504 [PubMed: 17115030]

68. Lee SH, Peng IF, Ng YG, Yanagisawa M, Bamji SX, Elia LP, Balsamo J, Lilien J, Anastasiadis PZ, Ullian EM, Reichardt LF. Synapses are regulated by the cytoplasmic tyrosine kinase Fer in a pathway mediated by p120catenin, Fer, SHP-2, and β -catenin. *J Cell Biol.* 2008; 183:893–908. DOI: 10.1083/jcb.200807188 [PubMed: 19047464]
69. Turner TN, Sharma K, Oh EC, Liu YP, Collins RL, Sosa MX, Auer DR, Brand H, Sanders SJ, Moreno-De-Luca D, Pihur V, Plona T, Pike K, Soppet DR, Smith MW, Cheung SW, Martin CL, State MW, Talkowski ME, Cook E, Huganir R, Katsanis N, Chakravarti A. Loss of delta-catenin function in severe autism. *Nature.* 2015; 520:51–56. DOI: 10.1038/nature14186 [PubMed: 25807484]
70. Arikath J, Peng IF, Ng YG, Israely I, Liu X, Ullian EM, Reichardt LF. Delta-catenin regulates spine and synapse morphogenesis and function in hippocampal neurons during development. *J Neurosci.* 2009; 29:5435–5442. DOI: 10.1523/JNEUROSCI.0835-09.2009 [PubMed: 19403811]
71. Murakoshi H, Wang H, Yasuda R. Local persistent activation of Rho GTPases during plasticity of single dendritic spines. *Nature.* 2011; 472:100–4. DOI: 10.1038/nature09823 [PubMed: 21423166]
72. Harnett MT, Makara JK, Spruston N, Kath WL, Magee JC. Synaptic amplification by dendritic spines enhances input cooperativity. *Nature.* 2012; 491:599–602. DOI: 10.1038/nature11554 [PubMed: 23103868]
73. Silverman JB, Restituto S, Lu W, Lee-Edwards L, Khatri L, Ziff EB. Synaptic anchorage of AMPA receptors by cadherins through neural plakophilin-related arm protein AMPA receptor-binding protein complexes. *J Neurosci.* 2007; 27:8505–8516. doi:27/32/8505 [pii]. [PubMed: 17687028]
74. Ochiishi T, Futai K, Okamoto K, Kameyama K, Kosik KS. Regulation of AMPA receptor trafficking by δ -catenin. *Mol Cell Neurosci.* 2008; 39:499–507. DOI: 10.1016/j.mcn.2008.06.002 [PubMed: 18602475]
75. Poore CP, Sundaram JR, Pareek TK, Fu A, Amin N, Mohamed NE, Zheng YL, Goh AX, Lai MK, Ip NY, Pant HC, Kesavapany S. Cdk5-mediated phosphorylation of delta-catenin regulates its localization and GluR2-mediated synaptic activity. *J Neurosci.* 2010; 30:8457–8467. DOI: 10.1523/JNEUROSCI.6062-09.2010 [PubMed: 20573893]
76. Ide N, Hata Y, Deguchi M, Hirao K, Yao I, Takai Y. Interaction of S-SCAM with Neural Plakophilin-Related Armadillo-Repeat Protein/ δ -Catenin. *Biochem Biophys Res Commun.* 1999; 256:456–461. DOI: 10.1006/bbrc.1999.0364 [PubMed: 10080919]
77. Yudowski GA, Olsen O, Adesnik H, Marek KW, Brecht DS. Acute Inactivation of PSD-95 Destabilizes AMPA Receptors at Hippocampal Synapses. *PLoS One.* 2013; 8:e53965. doi: 10.1371/journal.pone.0053965 [PubMed: 23342049]
78. Danielson E, Zhang N, Metallo J, Kaleka K, Shin SM, Gerges N, Lee SH. S-SCAM/MAGI-2 Is an Essential Synaptic Scaffolding Molecule for the GluA2-Containing Maintenance Pool of AMPA Receptors. *J Neurosci.* 2012; 32:6967–6980. DOI: 10.1523/JNEUROSCI.0025-12.2012 [PubMed: 22593065]
79. Kang R, Wan J, Arstikaitis P, Takahashi H, Huang K, Bailey AO, Thompson JX, Roth AF, Drisdell RC, Mastro R, Green WN, Yates JR III, Davis NG, El-Husseini A. Neural palmitoyl-proteomics reveals dynamic synaptic palmitoylation. *Nature.* 2008; 456:904–909. DOI: 10.1038/nature07605 [PubMed: 19092927]
80. Wan J, Savas JN, Roth AF, Sanders SS, Singaraja RR, Hayden MR, Yates JR, Davis NG. Tracking Brain Palmitoylation Change: Predominance of Glial Change in a Mouse Model of Huntington's Disease. *Chem Biol.* 2013; 20:1421–1434. DOI: 10.1016/j.chembiol.2013.09.018 [PubMed: 24211138]
81. Oh M, Kim H, Yang I, Park JH, Cong WT, Baek MC, Bareiss S, Ki H, Lu Q, No J, Kwon I, Choi JK, Kim K. GSK-3 phosphorylates delta-catenin and negatively regulates its stability via ubiquitination/proteasome-mediated proteolysis. *J Biol Chem.* 2009; 284:28579–28589. DOI: 10.1074/jbc.M109.002659 [PubMed: 19706605]
82. Hong JY, Oh IH, McCrea PD. Phosphorylation and isoform use in p120-catenin during development and tumorigenesis. *Biochim Biophys Acta - Mol Cell Res.* 2016; 1863:102–114. DOI: 10.1016/j.bbamcr.2015.10.008

83. Wisniewski JR, Nagaraj N, Zougman A, Gnäd F, Mann M. Brain phosphoproteome obtained by a FASP-based method reveals plasma membrane protein topology. *J Proteome Res.* 2010; 9:3280–3289. DOI: 10.1021/pr1002214 [PubMed: 20415495]
84. Ballif BA, Carey GR, Sunyaev SR, Gygi SP. Large-scale identification and evolution indexing of tyrosine phosphorylation sites from murine brain. *J Proteome Res.* 2008; 7:311–318. DOI: 10.1021/pr0701254 [PubMed: 18034455]
85. Lundby A, Secher A, Lage K, Nordsborg NB, Dmytriiev A, Lundby C, Olsen JV. Quantitative maps of protein phosphorylation sites across 14 different rat organs and tissues. *Nat Commun.* 2012; 3:876.doi: 10.1038/ncomms1871 [PubMed: 22673903]
86. Mackie S, Aitken A. Novel brain 14-3-3 interacting proteins involved in neurodegenerative disease. *FEBS J.* 2005; 272:4202–4210. doi: EJB4832 [pii]. [PubMed: 16098201]
87. Wagner SA, Beli P, Weinert BT, Scholz C, Kelstrup CD, Young C, Nielsen ML, Olsen JV, Brakebusch C, Choudhary C. Proteomic analyses reveal divergent ubiquitylation site patterns in murine tissues. *Mol Cell Proteomics.* 2012; 11:1578–1585. DOI: 10.1074/mcp.M112.017905 [PubMed: 22790023]
88. Na CH, Jones DR, Yang Y, Wang X, Xu Y, Peng J. Synaptic Protein Ubiquitination in Rat Brain Revealed by Antibody-based Ubiquitome Analysis. *J Proteome Res.* 2012; 11:4722–4732. DOI: 10.1021/pr300536k [PubMed: 22871113]
89. Kim W, Bennett EJ, Huttlin EL, Guo A, Li J, Possemato A, Sowa ME, Rad R, Rush J, Comb MJ, Harper JW, Gygi SP. Systematic and quantitative assessment of the ubiquitin-modified proteome. *Mol Cell.* 2011; 44:325–40. DOI: 10.1016/j.molcel.2011.08.025 [PubMed: 21906983]
90. Miyashita Y, Ozawa M. Increased internalization of p120-uncoupled E-cadherin and a requirement for a dileucine motif in the cytoplasmic domain for endocytosis of the protein. *J Biol Chem.* 2007; 282:11540–8. DOI: 10.1074/jbc.M608351200 [PubMed: 17298950]
91. McCrea PD, Maher MT, Gottardi CJ. Nuclear Signaling from Cadherin Adhesion Complexes. *Curr Top Dev Biol.* 2015; :129–196. DOI: 10.1016/bs.ctdb.2014.11.018 [PubMed: 25733140]
92. McCrea PD, Gottardi CJ. Beyond β -catenin: prospects for a larger catenin network in the nucleus. *Nat Rev Mol Cell Biol.* 2015; 17:55–64. DOI: 10.1038/nrm.2015.3 [PubMed: 26580716]
93. Daniel JM, Reynolds AB. The catenin p120(ctn) interacts with Kaiso, a novel BTB/POZ domain zinc finger transcription factor. *Mol Cell Biol.* 1999; 19:3614–23. <http://www.ncbi.nlm.nih.gov/pubmed/10207085> (accessed May 12, 2017). [PubMed: 10207085]
94. Park J, Ji H, Jun S, Gu D, Hikasa H, Li L, Sokol SY, McCrea PD. Frd1 Links Dishevelled to the p120-Catenin/Kaiso Pathway: Distinct Catenin Subfamilies Promote Wnt Signals. *Dev Cell.* 2006; 11:683–695. DOI: 10.1016/j.devcel.2006.09.022 [PubMed: 17084360]
95. Kulikov AV, Korostina VS, Kulikova EA, Fursenko DV, Akulov AE, Moshkin MP, Prokhorchouk EB. Knockout Zbtb33 gene results in an increased locomotion, exploration and pre-pulse inhibition in mice. *Behav Brain Res.* 2016; 297:76–83. DOI: 10.1016/j.bbr.2015.10.003 [PubMed: 26454239]
96. Hosking CR, Ulloa F, Hogan C, Ferber EC, Figueroa A, Gevaert K, Birchmeier W, Briscoe J, Fujita Y. The transcriptional repressor Glis2 is a novel binding partner for p120 catenin. *Mol Biol Cell.* 2007; 18:1918–1927. doi: E06-10-0941 [pii]. [PubMed: 17344476]
97. Rodova M, Kelly KF, VanSaun M, Daniel JM, Werle MJ. Regulation of the rapsyn promoter by kaiso and delta-catenin. *Mol Cell Biol.* 2004; 24:7188–7196. DOI: 10.1128/MCB.24.16.7188-7196.2004 [PubMed: 15282317]
98. Kim K, Oh M, Ki H, Wang T, Bareiss S, Fini ME, Li D, Lu Q. Identification of E2F1 as a positive transcriptional regulator for δ -catenin. *Biochem Biophys Res Commun.* 2008; 369:414–420. DOI: 10.1016/j.bbrc.2008.02.069 [PubMed: 18302937]
99. Mainardi, P Cerruti. Cri du Chat syndrome. *Orphanet J Rare Dis.* 2006; 1:33.doi: 10.1186/1750-1172-1-33 [PubMed: 16953888]
100. Medina M, Marinescu RC, Overhauser J, Kosik KS. Hemizygosity of delta-catenin (CTNND2) is associated with severe mental retardation in cri-du-chat syndrome. *Genomics.* 2000; 63:157–164. DOI: 10.1006/geno.1999.6090 [PubMed: 10673328]
101. Asadollahi R, Oneda B, Joset P, Azzarello-Burri S, Bartholdi D, Steindl K, Vincent M, Cobilanschi J, Sticht H, Baldinger R, Reissmann R, Sudholt I, Thiel CT, Ekici AB, Reis A,

- Bijlsma EK, Andrieux J, Dieux A, FitzPatrick D, Ritter S, Baumer A, Latal B, Plecko B, Jenni OG, Rauch A. The clinical significance of small copy number variants in neurodevelopmental disorders. *J Med Genet.* 2014; 51:677–688. DOI: 10.1136/jmedgenet-2014-102588 [PubMed: 25106414]
102. Belcaro C, Dipresa S, Morini G, Pecile V, Skabar A, Fabretto A. CTNND2 deletion and intellectual disability. *Gene.* 2015; 565:146–149. DOI: 10.1016/j.gene.2015.03.054 [PubMed: 25839933]
103. Sardina JM, Walters AR, Singh KE, Owen RX, Kimonis VE. Amelioration of the typical cognitive phenotype in a patient with the 5pter deletion associated with Cri-du-chat syndrome in addition to a partial duplication of *CTNND2*. *Am J Med Genet Part A.* 2014; 164:1761–1764. DOI: 10.1002/ajmg.a.36494
104. Zhang B, Willing M, Grange DK, Shinawi M, Manwaring L, Vineyard M, Kulkarni S, Cottrell CE. Multigenerational autosomal dominant inheritance of 5p chromosomal deletions. *Am J Med Genet A.* 2016; 170:583–93. DOI: 10.1002/ajmg.a.37445 [PubMed: 26601658]
105. McMichael G, Girirajan S, Moreno-De-Luca A, Gecz J, Shard C, Nguyen LS, Nicholl J, Gibson C, Haan E, Eichler E, Martin CL, MacLennan A. Rare copy number variation in cerebral palsy. *Eur J Hum Genet.* 2014; 22:40–5. DOI: 10.1038/ejhg.2013.93 [PubMed: 23695280]
106. Vrijenhoek T, Buizer-Voskamp JE, van der Stelt I, Strengman E, Genetic Risk and Outcome in Psychosis (GROU) Consortium. Sabatti C, Kessel A Geurts van, Brunner HG, Ophoff RA, Veltman JA. Recurrent CNVs disrupt three candidate genes in schizophrenia patients. *Am J Hum Genet.* 2008; 83:504–10. DOI: 10.1016/j.ajhg.2008.09.011 [PubMed: 18940311]
107. Nivard MG, Mbarek H, Hottenga JJ, Smit JH, Jansen R, Penninx BW, Middeldorp CM, Boomsma DI. Further confirmation of the association between anxiety and CTNND2: replication in humans. *Genes Brain Behav.* 2014; 13:195–201. DOI: 10.1111/gbb.12095 [PubMed: 24256404]
108. Jun G, Moncaster JA, Koutras C, Seshadri S, Buros J, McKee AC, Levesque G, Wolf PA, St George-Hyslop P, Goldstein LE, Farrer LA. δ -Catenin is genetically and biologically associated with cortical cataract and future Alzheimer-related structural and functional brain changes. *PLoS One.* 2012; 7:e43728.doi: 10.1371/journal.pone.0043728 [PubMed: 22984439]
109. Xie L, Ju GZ, Liu SZ, Shi JP, Yu YQ, Wei J. Searching for a schizophrenia susceptibility gene in the 22q11 region. *Biomed Environ Sci.* 2005; 18:31–5. <http://www.ncbi.nlm.nih.gov/pubmed/15861775> accessed March 20, 2017. [PubMed: 15861775]
110. Henry JC, van Amelsvoort T, Morris RG, Owen MJ, Murphy DGM, Murphy KC. An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). *Neuropsychologia.* 2002; 40:471–8. <http://www.ncbi.nlm.nih.gov/pubmed/11749977> (accessed March 20, 2017). [PubMed: 11749977]
111. Mas S, Bernardo M, Gassó P, Alvarez S, Garcia-Rizo C, Bioque M, Kirkpatrick B, Lafuente A. A functional variant provided further evidence for the association of ARVCF with schizophrenia. *Am J Med Genet B Neuropsychiatr Genet.* 2010; 153B:1052–9. DOI: 10.1002/ajmg.b.31073 [PubMed: 20333729]
112. Mas S, Bernardo M, Parellada E, Garcia-Rizo C, Gassó P, Álvarez S, Lafuente A. ARVCF single marker and haplotypic association with schizophrenia. *Prog Neuro-Psychopharmacology Biol Psychiatry.* 2009; 33:1064–1069. DOI: 10.1016/j.pnpbp.2009.06.001
113. Sanders AR, Rusu I, Duan J, Vander Molen JE, Hou C, Schwab SG, Wildenauer DB, Martinez M, Gejman PV. Haplotypic association spanning the 22q11.21 genes COMT and ARVCF with schizophrenia. *Mol Psychiatry.* 2005; 10:353–65. DOI: 10.1038/sj.mp.4001586 [PubMed: 15340358]
114. Williams ME, Wilke SA, Daggett A, Davis E, Otto S, Ravi D, Ripley B, Bushong EA, Ellisman MH, Klein G, Ghosh A. Cadherin-9 Regulates Synapse-Specific Differentiation in the Developing Hippocampus. *Neuron.* 2011; 71:640–655. DOI: 10.1016/j.neuron.2011.06.019 [PubMed: 21867881]
115. Kouchi Z, Barthet G, Serban G, Georgakopoulos A, Shioi J, Robakis NK. p120 catenin recruits cadherins to gamma-secretase and inhibits production of Abeta peptide. *J Biol Chem.* 2009; 284:1954–61. DOI: 10.1074/jbc.M806250200 [PubMed: 19008223]
116. Tanahashi H, Tabira T. Isolation of human delta-catenin and its binding specificity with presenilin 1. *Neuroreport.* 1999; 10:563–568. [PubMed: 10208590]

117. Levesque G, Yu G, Nishimura M, Zhang DM, Levesque L, Yu H, Xu D, Liang Y, Rogaeva E, Ikeda M, Duthie M, Murgolo N, Wang L, VanderVere P, Bayne ML, Strader CD, Rommens JM, Fraser PE, St George-Hyslop P. Presenilins interact with armadillo proteins including neural-specific plakophilin-related protein and beta-catenin. *J Neurochem.* 1999; 72:999–1008. [PubMed: 10037471]
118. Zhou J, Liyanage U, Medina M, Ho C, Simmons AD, Lovett M, Kosik KS. Presenilin 1 interaction in the brain with a novel member of the Armadillo family. *Neuroreport.* 1997; 8:2085–2090. [PubMed: 9223106]

Fig. 1. Schematic of Protein structures of p120ctn family members in the central nervous system

A schematic of the protein structures of the four members of the p120ctn family, namely p0071, δ -catenin, p120ctn and ARVCF. The structures include an N-terminal domain, including a coiled-coiled domain, a series of ARM repeats and a C-terminal region. The ARM repeats are separated by an insert region as indicated. The polyK sequence is located within the insert region as indicated in purple. For p120ctn and ARVCF, an alternative splicing insert, exon C, is located within the polyK sequence as indicated by $\vee$. For δ -catenin, an alternative splicing insert of 25 amino acid is localized within the 7th ARM repeat (shadow region). The PDZ-binding motif is localized at the C-terminus of p0071, δ -catenin and ARVCF as indicated by an arrow. Protein structures were mapped according to the mouse protein sequences from UniProtKB with identifiers as follows: p0071 (Q68FH0), δ -catenin (O35927), p120ctn (P30999) and ARVCF (P98203). The number of amino acids for each protein is indicated right above each protein. The ARM repeats for each protein were defined by comparison to the ARM repeats of p120ctn [18] after protein sequence alignment.

Fig. 2. Schematic of posttranslational modification sites in p120ctn family members in the central nervous system

Schematic representing of the four members of the p120ctn family with sites of phosphorylation (black), ubiquitination (red) and palmitoylation (blue) indicated. The map for each family member is shown in a raster plot as indicated. The x-axis represents the length of the protein; the y-axis represents the ID of the references. Each modification site is plotted as a vertical line, with its position in the x-axis and referred from the reference with its ID in the y-axis. The thick black line represents the location of the ARM repeats. The grey regions indicate phosphorylation enriched regions before (region A) and after the ARM domains (region B) in each protein. Reference ID: 1, [30]; 2, [82]; 3, [27]; 4, [83]; 5, [84]; 6, [31]; 7, [53]; 8, combination of [29,54,75,81,85]; Ub, [87]; Palm: [19]. The reference protein sequences and region of the ARM repeats are as in Fig. 1. The detailed information of this figure, including modified positions, is in the supplementary material. This image was generated by MATLAB and modified in Adobe Photoshop for optimal visualization.

Fig. 3. Model of the functional roles of p120ctn family in central neurons

Members of the p120ctn family are localized in membrane, cytosolic or nuclear pools. The membrane association is mediated by interaction with cadherin via its JMD and other membrane proteins, including components of the synaptic scaffolding complex. The p120ctn family of proteins likely serve as a node for transmitting information from upstream regulators in a cadherin-dependent or -independent manner and transducing this information to the cytoskeleton and nucleus to mediate functional roles in dendritic and synapse architecture and function and nuclear signaling.

Table 1

Summary of the observations of the functional roles of p120ctn family on dendritic and synaptic development.

Protein	Biological context	Conditions	Observations
<i>Dendritic morphology</i>			
p120ctn	Knockout	<i>In vitro</i>	Decrease dendritic arborization [43]
	Knockdown	<i>In vitro</i>	Decrease dendritic length and arborization [36]
	N-term mice	<i>In vitro</i>	Decrease dendritic length and arborization [36]
δ-catenin	N-term mice	<i>In vivo</i>	No alterations in the dendritic arbor at 5 weeks of age Increase retraction after 5 weeks [47]
	Overexpression	<i>In vitro</i>	Increase dendritic branching [48,49]
p0071	Overexpression	<i>In vitro</i>	Increase dendritic arborization [63]
<i>Synaptic density, morphology and function</i>			
p120ctn	Knockout	<i>In vitro</i>	Decrease spine density [43] Decrease spine length [43] Decrease spine head width [43] Mislocalization of presynaptic vesicles [68]
	Knockout	<i>In vivo</i>	Decrease spine density [68] Decrease synapse density [68]
δ-catenin	Knockdown	<i>In vitro</i>	Decrease spine density [55] Increase spine density [19,70] Increase mEPSCs frequency [70] No change on mEPSCs frequency [19] Decrease dendritic protrusion head width [19,37] Increase dendritic protrusion length [19] Decrease dendritic protrusion length [37] Decrease surface AMPAR [74] No change on mEPSCs amplitude [19,70]
	N-term mice	<i>In vitro</i>	Increase spine density [70] Increase mEPSCs frequency [70] Decrease dendritic protrusion head width [37] Decrease dendritic protrusion length [37] No change on mEPSCs amplitude [70]
	Overexpression	<i>In vitro</i>	Increase dendritic protrusion density [19,48,55] Increase mEPSCs frequency [19] Increase spine length [19,48] Increase surface AMPAR [73,74] Increase mEPSCs amplitude [19]

Table 2
Posttranslational modifications of δ -catenin and their functional consequences in central neurons

Please note that data is described for δ -catenin only. While the posttranslational modifications for the other members of the family are known as indicated in Fig. 2, their functional consequences remain incompletely explored.

Modification	Amino acid	Enzyme	Function	Ref
Phosphorylation	T454	Akt	Sequester p120RhoGEF and inhibit RhoA activity Regulates dendritic arborization, spine density and length	[48]
Phosphorylation	S300, S357	CDK5	Inhibit δ -catenin localize to the membrane Inhibit δ -catenin associate with N-cadherin, GRIP and PSD95 Decrease membrane AMPA receptor level Decrease density of dendritic protrusion	[75]
Phosphorylation	S447	JNK	Facilitate proteasome-dependent degradation of δ -catenin Regulates dendritic arborization	[49]
Phosphorylation	S693, S1063, T1064, S1098, S1242	–	mGluR-mediated phosphorylation	[55]
Phosphorylation	T1078	GSK-3	Facilitate ubiquitination and proteasome-dependent degradation of δ -catenin	[81]
Phosphorylation	S1094	PKA	Binding to 14-3-3 ϵ/ζ Facilitate ubiquitination and proteasome-dependent degradation of δ -catenin	[30, 86]
Palmitoylation	C960, C961	DHHC5	Enhance δ -catenin-cadherin interaction Activity-dependent recruit δ -catenin to cadherin	[19]
Palmitoylation	C960, C961	DHHC20	Enhance δ -catenin-cadherin interaction	[19]