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Chapter

New Discoveries on the Roles of "Other" HECT E3 Ubiquitin Ligases in Disease Development

Emma I. Kane and Donald E. Spratt

Abstract

HECT E3 ubiquitin ligases selectively recognize, bind, and ubiquitylate their substrate proteins to target them for 26S proteasomal degradation. There is increasing evidence that HECT E3 ubiquitin ligase dysfunction due to misfolding and/or the gene encoding the protein being mutated is responsible for the development of different diseases. Apart from the more prominent and well-characterized E6AP and members of the NEDD4 family, new studies have begun to reveal how other members of the HECT E3 ubiquitin ligase family function as well as their links to disease and developmental disorders. This chapter provides a comprehensive discussion on the more mysterious members of the HECT E3 ubiquitin ligase family and how they control intracellular processes. Specifically, AREL1, HACE1, HECTD1, HECTD4, G2E3, and TRIP12 will be examined as these enzymes have recently been identified as contributors to disease development.

Keywords: apoptosis, AREL1, cancer, HECT E3 ubiquitin ligase, G2E3, HACE1, HECT, HECTD1, HECTD4, neurodevelopment, proteasomal degradation, TRIP12, ubiquitin, ubiquitylation

1. Introduction

1.1 HECT E3 ubiquitin ligase-dependent ubiquitylation

Ubiquitylation is an essential post-translational modification that regulates numerous intracellular processes including protein localization and trafficking, DNA damage response, immune system and viral response, apoptosis and proteolysis [1, 2]. E3 ubiquitin ligases play an important role in recognizing, binding, and covalently attaching ubiquitin to their various substrates to elicit a specific cellular response [3]. The homologous to E6AP C-terminus (HECT) E3 ubiquitin ligases are a unique subfamily that use a multistep pathway to selectively target substrate proteins for ubiquitylation [4]. HECT-dependent ubiquitylation requires the recruitment of an E2 ubiquitin conjugating enzyme charged with ubiquitin to the N-terminal lobe of the HECT domain on the E3 ligase [5, 6]. The ubiquitin cargo is then transferred from the E2 enzyme to the conserved catalytic cysteine within the C-terminal lobe of the HECT domain *via* a transthiolation reaction to form a thioester bond. The HECT E3~ubiquitin complex will then bind to a substrate and

covalently attach ubiquitin on to a lysine residue of the substrate protein forming a stable isopeptide bond between the C-terminus of ubiquitin and the ε-amine of the substrate lysine [3, 5, 6]. This process can be repeated numerous times to form different polyubiquitin chain linkages with the specific HECT E3 ubiquitin ligase dictating the type(s) of ubiquitin linkages that are built [2, 7].

Chain types	Linker	Proposed function
Monoubiquitylation		
Monoubiquitylation/ multi-monoubiquitylation		Endocytosis [9] DNA damage repair [10–15] Histone regulation [10–15] Mitophagy [10–15] Protein localization [10–15] Protein interactions [10–15] Protein transportation [10–15] Transcription activation [10–15]
Polyubiquitylation		
Chain (homotypic)	M1	Innate immunity [2, 9, 16] Linear chain formation [9] NF-κB activation [9, 16] Signaling cascades [9, 16]
	K6	DNA damage response [14] NF-κB regulation [14] Mitophagy [14]
	K11	Cell cycle regulation [17] DNA damage response [18] Mitophagy [17] NF-κB activation [16] Protein degradation [17]
	K27	DNA damage response [18] Kinase activation [19] Protein degradation [20] Protein scaffolding [21] Protein trafficking [22]
	K29	DNA damage response [18] Kinase activation [19] Protein degradation [9]
	K33	DNA damage response [10–15, 18] Kinase activation [23] Post-golgi trafficking [24] T-cell signaling [23]
	K48	Protein degradation [1, 2, 25]
	K63	DNA damage response [9, 18] NF-κB activation [9, 16] Protein trafficking [9]
Chain (heterotypic; branched)	M1/K63	NF-κB activation [16]
	K11/K48	Protein degradation [26, 27]
	K29/K48	Protein degradation [26]
	K48/K63	Protein degradation [26]
	K11/K63	Endocytosis [28]

Table 1.
Ubiquitin conjugation determines the intracellular fate of a substrate protein.

1.2 Ubiquitin attachment site(s) and chain type linkages determine the fate of a substrate protein

The destiny of a ubiquitin-tagged protein is dependent on (i) the site(s) of ubiquitin attachment on the substrate, (ii) the number of ubiquitin moieties attached to the substrate (i.e. mono-, multi-mono-, or polyubiquitin), and (iii) the specific type(s) of linkages between the different ubiquitin molecules in a polyubiquitin chain (i.e. K48, K63, branched, etc.) [1, 2, 7]. Potential fates of a ubiquitin-tagged substrate include changes in cellular localization/trafficking, enhanced/inhibited protein activity, changes in protein–protein affinity/interactions, and proteolysis [1, 2, 6–8].

Differences in ubiquitin lysine linkage specificity determine the destination and/or fate of the targeted protein in the cell (**Table 1**). For example, the well-established K48-polyubiquitylation chain, heterotypic K11/K48-polyubiquitin, K29/K48-polyubiquitin monoubiquitin tagged peptides and multiple monoubiquitin tagged proteins have also been found to signal for 26S proteasomal degradation [7, 8]. K63-polyubiquitin chains signal for protein degradation through the initiation of K48/K63 polyubiquitin branch formation [5] but cannot be recognized by the 26S proteosome [26]. To date, many different varieties of ubiquitin chain types have been identified, but their distinct biological functions remain unclear.

Monoubiquitylation can occur at one site or at multiple sites (multi-monoubiquitylation) on a substrate. Polyubiquitylation can build off of a mono-ubiquitin attachment site with a specific lysine linkage (homotypic) or have multiple chains with different lysine linkages (branch) at the end of a growing ubiquitin chain (heterotypic). These modifications can also influence signaling pathways, whether it is through enhancing or inhibiting participating proteins and processes.

2. The "other" HECT E3 ubiquitin ligases: important players in disease, yet poorly understood

The HECT E3 ubiquitin ligases can be categorized into three subfamilies – NEDD4, HERC, and "other" – based on their sequence/structure similarity and domain architecture [4, 5]. Of the 28 HECT E3 ubiquitin ligases identified in humans, there are 12 "other" HECT E3 ubiquitin ligases that do not fall under the well-studied NEDD4 or HERC subfamilies. Each member of the "other" HECTs have variable N-terminal domains that are thought to be involved in protein–protein interactions and/or intracellular localization [4, 5]. Having prominent responsibilities in cellular homeostasis would leave the impression there is ample research on the HECT E3 ubiquitin ligase family as a whole, however, there remain many unanswered questions about the biological functions and mechanisms of this important E3 ligase family, particularly for members of the more mysterious "other" subfamily. With new research and discoveries becoming available, there is mounting evidence that the lesser known HECT E3 ubiquitin ligases play critical roles in regulating intracellular processes and their dysfunction have been suggested to contribute to the onset of many diseases and disorders [4, 29–32]. Here we discuss the latest discoveries on these lesser known members of the HECT E3 ubiquitin ligases and on their emerging roles in developmental and neurological abnormalities, cancers, and embryogenesis.

### 2.1 AREL1, a key regulator of apoptosis and potential oncogenic drug target

Apoptosis resistant E3 ubiquitin protein ligase 1(AREL1; 823 residues) is a cytosolic enzyme responsible for regulating apoptosis through the inhibition of

proapoptotic proteins *via* ubiquitylation [33]. AREL1 contains two immunoglobin-like folds (IGF) near its N-terminus that potentially mediate substrate binding and recognition (**Figure 1**) [35, 36]. IGF domains assemble into a sandwich-like form consisting of antiparallel β-strands that allow for protein–protein interactions [36, 37].

Apoptosis (aka programmed cell death) is an important and highly regulated biological process that occurs during early embryonic development and the immune response [38, 39]. Once apoptosis is initiated the cell is committed to die, which is mediated by a caspase cascade [40]. Intrinsic apoptosis is turned on by the release of intermembrane mitochondrial proteins when cells are under oxidative stress [38, 39, 41]. In contrast, the extrinsic apoptotic pathway is activated by extracellular signaling at the cell membrane leading to the formation of the death-inducing signaling complex (DISC) [42–44].

AREL1 was first identified in 2013 and was immediately recognized as an oncogenic target due to its inhibitory role in apoptosis [33]. Identified substrates for AREL1 include second mitochondrial activator of caspase (SMAC), HtrA serine peptidase 2 (HtrA2) and septin 4 (ARTS), which are known antagonists of inhibitor of apoptosis proteins (IAPs) [45]. Studies have shown that AREL1 can build K48 and K63 polyubiquitin chains to target substrates for proteolysis, as well as atypical K33 polyubiquitin chains whose biological function is still being clarified [35, 46]. Various IAPs, including SMAC, HtrA1, and ARTS, are released from the mitochondrial intermembrane into the cytosol when the cell is triggered or stressed. AREL1 inhibits apoptosis by ubiquitylating these IAP antagonists with K48-linked polyubiquitin chains targeting the IAPs for proteasomal degradation [33].

The induction of apoptosis is thought to require the release of numerous IAPs in the cytosol to allow different signaling pathways to initiate apoptosis depending on the cell's specific stress. For example, the release of SMAC into the cytosol allows it to bind cellular inhibitor of apoptosis protein 1/2 (cIAP1/2), which then targets cIAP1/2 for proteasomal degradation to initiate apoptosis. However, when AREL1 is present, SMAC is ubiquitylated by AREL1 and degraded, thus blocking SMAC-cIAP1/2 complex formation enabling cell survival [33]. Many cancer therapies are interested in specifically turning on apoptosis through IAPs in cancer cells [47–49],
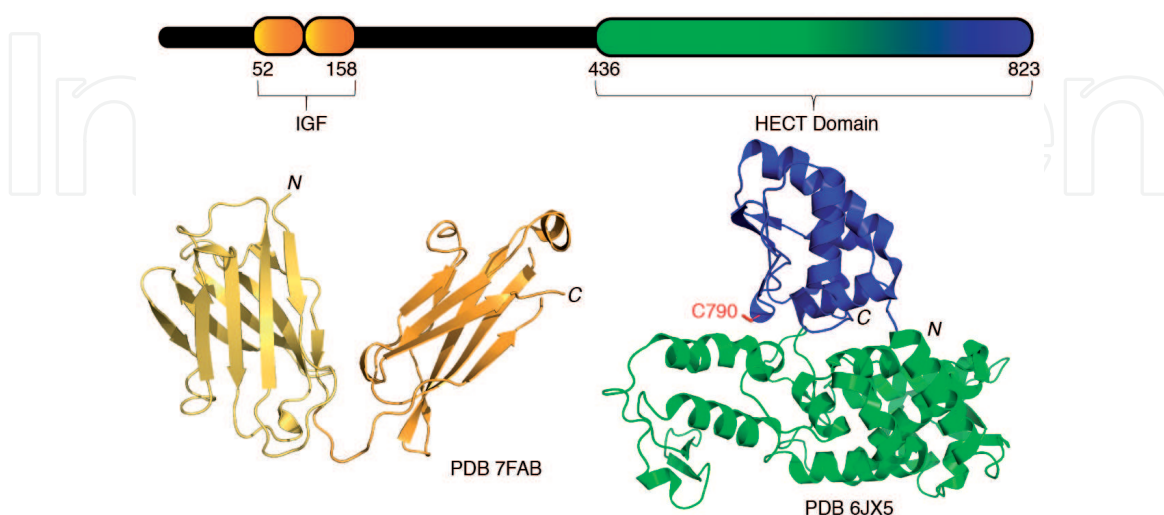
Figure 1.
AREL1 domain architecture. AREL1 contains a putative immunoglobulin fold domain (IGF, residues 52-158) and the canonical HECT domain (436-823) as annotated on UniProt and InterPro. Representative crystal structures of an IGF fold (human IGF FAB in yellow/orange; PDB 7FAB [34]), which is suggested to mediate AREL1 substrate binding and recognition, while the AREL1 HECT domain (HECT^{N-lobe} in green, HECT^{C-lobe} in blue, catalytic cysteine C790 in red; PDB 6JX5 [35]) is required for ubiquitylation activity. Structures were visualized using PyMol.

thus AREL1 could prove to be a novel enzyme in drug development. Continued studies on AREL1's mechanisms in controlling cell death are warranted.

2.2 HACE1, a prominent tumor suppressor with dual function

First identified in 2004, HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1; 909 residues) has been shown to take part in various cellular processes. For example, HACE1 is best known as a tumor suppressor as altered HACE1 expression levels have been observed in various cancers including colorectal, breast, liver, kidney, osteosarcoma, lymphoma and gastric cancer [50–54]. HACE1 contains six ankyrin repeats near its N-terminus that likely take part in HACE1-substrate recognition and protein–protein interactions (**Figure 2**). While it is not yet fully understood how the ankyrin repeats support HACE1 function, ankyrin repeats in other proteins have been shown to instigate the development of a wide array of diseases including cancer [56]. HACE1 also supports Golgi membrane biogenesis during cell division by ubiquitylating members of the Ras-related superfamily of small G proteins [57].

Studies have shown that HACE1 expression levels are altered when comparing normal and cancerous tissue. Specifically, in the Wilms' tumor cell line, HACE1 expression was essentially nonexistent, whereas in other cancer cell lines expression levels were lower than average [50]. This study concluded that HACE1 was essential in repressing cancer development as the lowered expression levels of HACE1 were not mutation dependent. Low expression levels of HACE1 have also been observed in other cancer cell lines. For instance, it was found that the methylation of the HACE1 promoter resulted in decreased HACE1 expression in liver cancer cells, which in turn decreased HACE1's ability to ubiquitylate its identified substrates optineurin (OPTN) and microtubule-associated proteins 1A/1B light chain 3B protein [53]. Many different substrates of HACE1 have been identified to date (summarized in [4]), including β2-adrenergic receptor (ß2AR) [58], OPTN [59], retinoic acid receptor beta (RAR-β) [57], tumor necrosis factor receptor-2 (TNFR2) [60], and various Ras-related
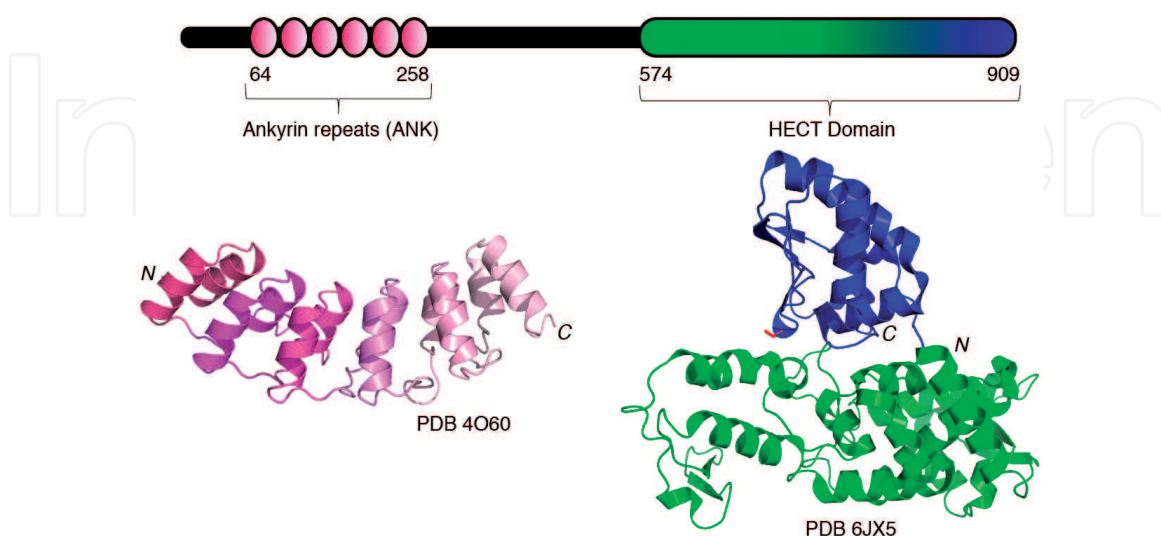
Figure 2.
Predicted domain architecture of HACE1. HACE1 contains six putative ankyrin-repeats (ANK; residues 64-258) and a HECT domain (574-909) as annotated on UniProt and InterPro. Representative crystal structures of an ANK repeat fold (in shades of pink, PDB 4O6o [55]), which is likely involved in HACE1 substrate binding and recognition, and a HECT domain (HECTN-lobe in green, HECTC-lobe in blue; PDB 6JX5 [35]) found at HACE1's C-terminus that is required of ubiquitylation activity. Structures were visualized using PyMol.

proteins [57, 58, 61–65]. Expanded studies on how HACE1 binds and recognizes its substrates are needed to further clarify the role of HACE1 in cancer development.

HACE1 also plays an essential role in neurodevelopment as it was recently shown to be involved in the spastic paraplegia and psychomotor retardation with or without seizures (SPPRS) phenotype [66]. HACE1 also has cardiac protection function during hemodynamic stress when it was shown in mice with *HACE1* deficiency, their susceptibility to accelerated heart failure greatly increased [67]. This suggests that HACE1 has a critical role in protecting the heart from various stresses, thus making it a potential cardiac drug target.

2.3 HECTD1, an important regulator in neurodevelopment

HECT domain containing E3 ubiquitin protein ligase 1 (HECTD1; 2610 residues) was discovered in 2007 as a novel and important regulator of neurodevelopment [68]. HECTD1 has similar domain architecture to HACE1 with four ankyrin repeats near its N-terminus and a C-terminal HECT domain (**Figure 3**). HECTD1 plays an important role in pulmonary fibrosis during endothelial-mesenchymal transition (EndMT) with reports of increased circular RNA HECTD1 (circHECTD1) transcription, which causes decreased HECTD1 protein expression in lung tissue [72, 73]. Elevated circHECTD1 gene expression has also been found in patients with acute ischemic stroke (AIS) [74]. HECTD1 also contains a Smad4 activation SAD1/UNC (SUN) domain and a mind bomb (MIB) domain, with each having unique roles in intracellular signaling due to Smad-DNA complex formation and cellular interactions through the Notch pathway, respectively [75, 76].

HECTD1 supports fetal growth and proper placenta development. Specifically, HECTD1 aids in the development of the labyrinthine and junctional zones of the placenta, regions where the fetus acquires nutrients and disposes of waste, as well as a bilayer between the labyrinthine and decidual cells, respectively [77, 78]. HECTD1 ensures the proper size development of the labyrinthine, yet the mechanisms to ensure this are still not fully understood. Mutations within HECTD1 lead to the onset of irregular labyrinthine development, which in turn depletes nutrients for the fetus. Fetal fatality can occur without proper maintenance of these placental regions, suggesting
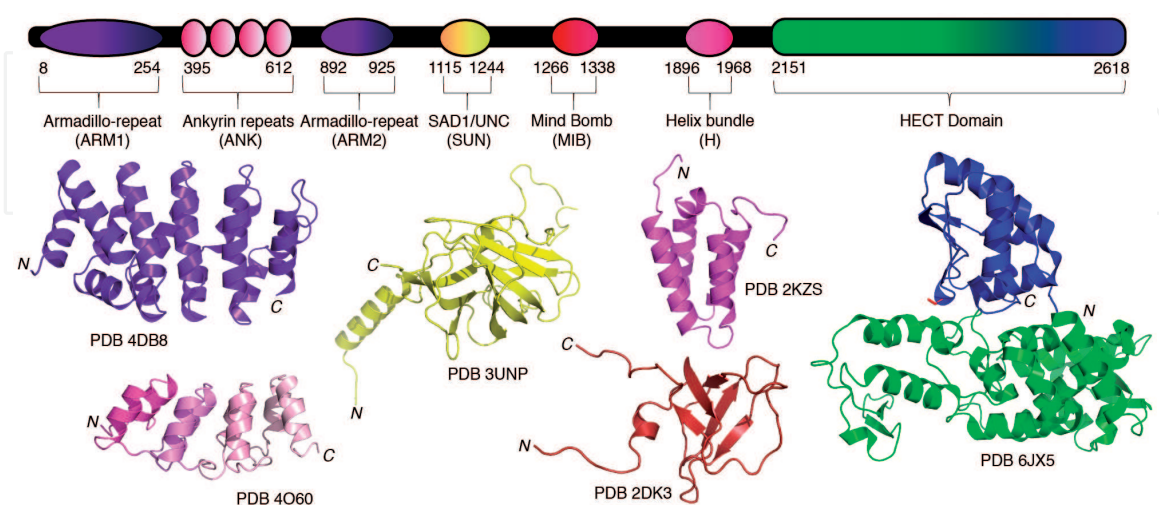
Figure 3.
HECTD1 domain architecture. HECTD1 contains putative protein-protein interaction domains including two armadillo-repeat containing domains (ARM1, residues 8-254; ARM2 residues 892-925 in purple; PDB 4DB8 [69]), four ankyrin-repeats (residues 395-612 in shades of pink; PDB 4O60 [56]), a SAD1/UNC domain (SUN, residues 1115-1244 in yellow; PDB 3UNP [70]), a mind bomb domain (MIB, residues 1266–1338 in red; PDB 2DK3), a helix-bundle domain (H, residues 1896–1968 in magenta; PDB 2KZS [71]) and a HECT domain (HECT^{N−lobe} in green, HECT^{C−lobe} in blue; PDB 6JX5 [35]). Domain boundaries are denoted according to UniProt and InterPro. Structures were visualized using PyMol.

that HECTD1 expression is essential for the proper development and survival of fetuses *in utero*. HECTD1 also plays a role in proper neural tube closure. Anencephaly occurs when the neural tube does not close properly, which has been linked to HECTD1 control of heat shock protein 90 (Hsp90) levels [79]. When Hsp90 secretion levels are not properly regulated by HECTD1 ubiquitylation, abnormal neural tube development can occur. The continued examination of this important enzyme will hopefully clarify the molecular basis for HECTD1's role in neurodevelopment.

2.4 HECTD4, a genetically linked precursor to cancer and cardiovascular disease

HECT domain containing E3 ubiquitin protein ligase 4 (HECTD4; 3996 residues) was recently discovered in 2014. A pleiotropic gene screen showed that there were links between metabolic syndromes and inflammation, specifically with single nucleotide polymorphisms (SNPs) in the *HECTD4* gene [80]. Since 2014, HECTD4 has also been found to be associated with diabetes, hypertension and cardiovascular disease, lung adenocarcinoma, urothelial carcinoma and ovarian endometriosis [81–84].

Being one of the larger enzymes within the "other" HECT E3 ubiquitin ligase subfamily, it is intriguing that there have been no putative domains annotated for HECTD4 except the C-terminal HECT domain (residues 3627–3996). There are likely different domains located in the N-terminal region of the HECTD4 protein that need to be identified and functionally examined.

Genetic screening has identified various mutations in *HECTD4* in cancer cells. For example, *HECTD4* was recently identified as one of nine genes that correlated with the onset of lung adenocarcinoma [83]. Tumor genetic screens have revealed in patients with urothelial carcinoma in the bladder (UCB) that mutations in *HECTD4*, Fibrillin-3 Precursor (*FBN3*) and Citron Rho-Interacting Kinase (*CIT*) were correlated to UCB disease progression [81]. *HECTD4* may also be linked to the development of ovarian endometriosis (OEM) [82]. However, future studies are still needed to verify this relationship.

Already having various genetic links to cancers and cardiovascular disease, HECTD4 deserves more attention by the research community to further clarify its biological and functional roles in the cell. Currently very little is known about HECTD4, therefore it will be imperative to first identify potential similarities in protein sequence and/or domain architecture. To better clarify HECTD4's role in ubiquitin biology, it will also be important to discover HECTD4 substrates and annotate the sites of HECTD4-dependent ubiquitylation to answer how this mysterious HECT E3 ubiquitin ligase contributes to disease development.

2.5 G2E3, a unique multifunctional HECT E3 ubiquitin ligase with RING-like features

G2/M-phase specific E3 ubiquitin protein ligase (G2E3; 706 residues) was first identified in 2006 and named for its role during the G2/M phase of cell division and for having a conserved C-terminal HECT domain [85]. Knockout studies of G2E3 in mice demonstrated that this enzyme is essential in preventing apoptotic cell death during early embryonic development [86]. Expression levels in G2E3 were also observed to increase during early embryogenesis, specifically during central nervous system development. This enzyme is also implicated in cell cycle progression and DNA damage response [85, 87, 88].

G2E3 contains three plant homeodomain (PHD)-type zinc finger repeats, a domain typically known to bind to modified histones and act as epigenetic readers [89], making it the only known HECT E3 ubiquitin ligase to possess "RING"-like
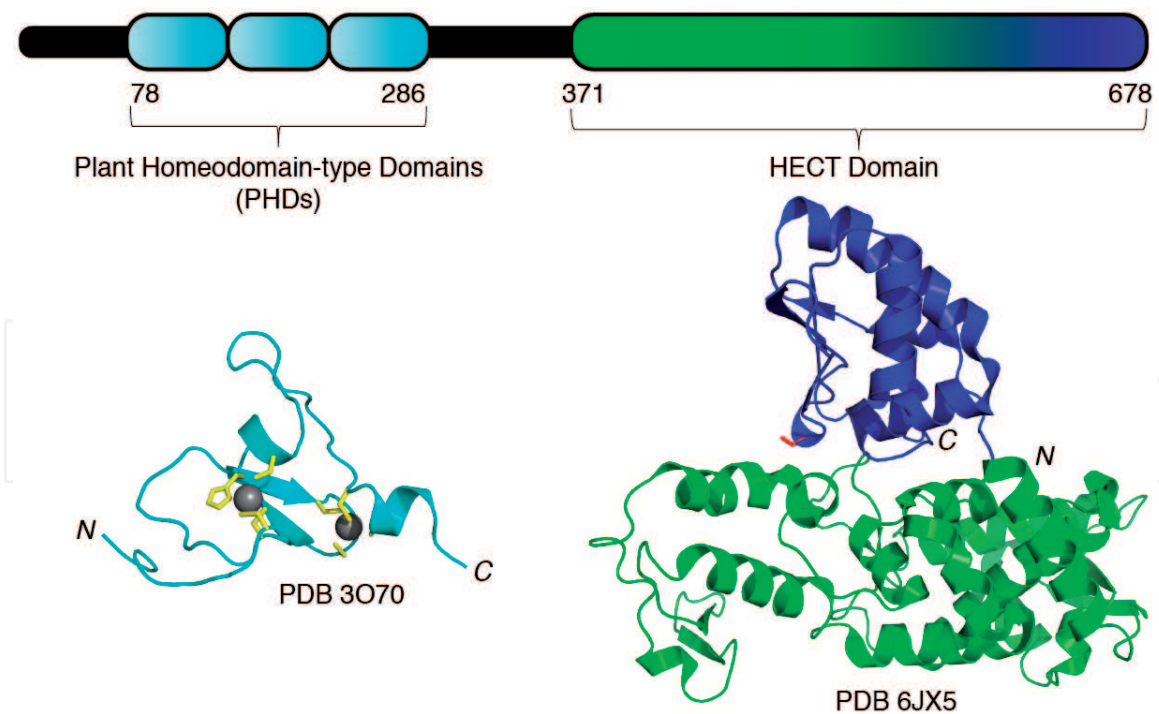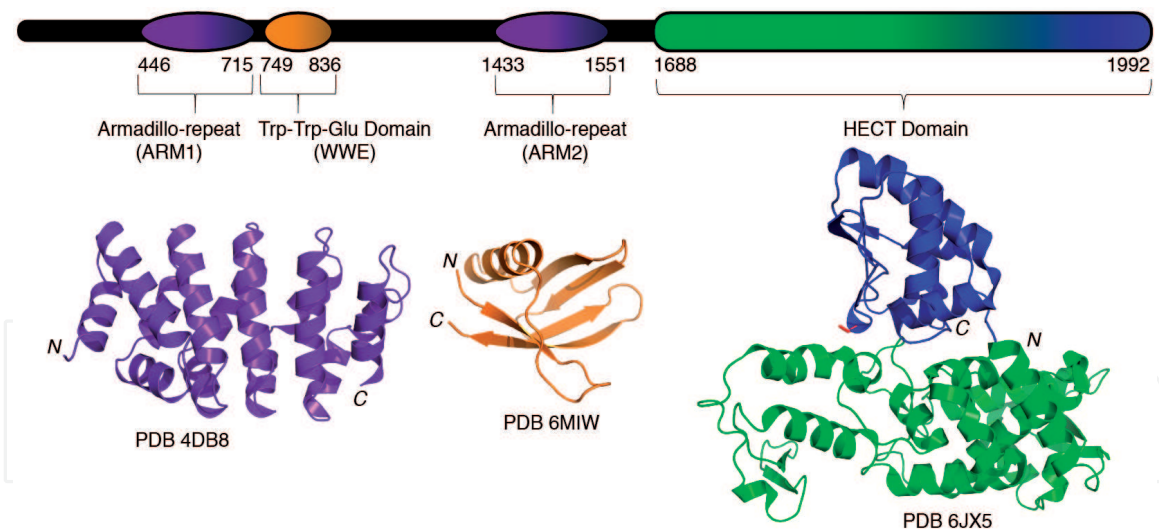
Figure 4.
Domain architecture of G2E3. G2E3 contains three putative plant homeodomain (PHD)-type domains (residues 78-128) and a unique HECT-like domain (371-678) as annotated on UniProt and InterPro. Representative crystal structures of a PHD domain (human PHD finger protein 13 in cyan with Zn-coordinating residues in yellow; PDB 3O70 [90]), which is suggested to interact with DNA and/or proteins in the nucleus, while the G2E3 HECT domain (HECT^{N-lobe} in green, HECT^{C-lobe} in blue; PDB 6JX5 [35]) may have lost its ability to catalyze the transfer of ubiquitin. Structures were visualized using PyMol.

characteristics (**Figure 4**). G2E3 is primarily found within the nucleus due to its N-terminal nucleolar localization signal sequence, while the PHD domains have been suggested to cause the translocation of G2E3 to the cytoplasm [85, 86]. Previous biochemical studies showed that the ubiquitin ligase activity of G2E3 was exclusively found in two of the putative N-terminal PHD domains while the C-terminal HECT domain of G2E3 had apparently lost its ubiquitylation activity [86]. Since the PHD domains of G2E3 appear to be capable of recruiting E2 enzymes to build K48-linked polyubiquitin chains [86], this suggests that the HECT domain of G2E3 may have become vestigial through evolutionary pressure. Intriguingly, G2E3 has aspects of the RING and HECT E3 ubiquitin ligase families, analogous to members of the RING-between-RING (aka RING-BRcat-Rcat) E3 ubiquitin ligases that includes parkin and HOIL-interacting protein (HOIP) of the LUBAC complex [91, 92].

G2E3 was recently identified as a potential drug target to increase the efficacy of chemotherapy drugs, specifically with Cisplatin [88]. Since Cisplatin is the most common chemotherapy drug, much research has been dedicated to increasing Cisplatin's ability to specifically trigger the DNA damage response in cancer cells to initiate apoptosis while limiting its exposure time and prescribed duration for patients [93]. Clearly, G2E3 is an important nuclear protein whose mechanism is currently unresolved. Further studies are needed to clarify how this divergent HECT-domain containing E3 ubiquitin ligase works in the cell.

2.6 TRIP12, the multifunctioning E3 ubiquitin ligase essential for embryogenesis and DNA damage repair

Thyroid hormone receptor interactor 12 (TRIP12; 2040 residues), was first identified in 2001 for containing a unique tryptophan-tryptophan-glutamate (WWE) domain that is predicted to be involved in ubiquitylation and ADP-ribosylation [94] (**Figure 5**). It also contains two N-terminal ARM domains, similar to HECTD1, and

Figure 5.
TRIP12 domain architecture. TRIP12 contains two putative armadillo-repeat containing domains (ARM1, residues 437-713; ARM2, residues 826-938), a tryptophan-tryptophan-glutamate (WWE)-domain (residues 749-836) and a conserved HECT domain (1885-1992) as annotated on UniProt and InterPro. Representative crystal structures of an ARM domain (in purple; PDB 4DB8 [69]) and WWE domain (in orange; PDB 6MIW), both of which are suggested to be involved in protein-protein and substrate interactions, as well as a HECT domain (HECT^{N-lobe} in green, HECT^{C-lobe} in blue; PDB 6JX5 [35]) required for ubiquitylation activity. Structures were visualized using PyMol.

a conserved HECT domain at its C-terminus. TRIP12 is a novel HECT E3 ubiquitin ligase that has been shown to take part in various cellular pathways and processes including embryogenesis, DNA damage response and the neddylation pathway [95–97]. It has been reported that TRIP12 preferentially builds mono- as well as K48 and K63 polyubiquitin chains to tag its substrates for degradation and for DNA damage site recruitment, respectively [96].

TRIP12 has been shown to be directly and/or indirectly involved in cancer progression. For example, TRIP12 may serve as an oncogenic drug target for patients with acute myeloid leukemia (AML) by blocking a TRIP12 alternative splicing event, specifically excising exon3 from the mature TRIP12 mRNA [98]. TRIP12 also targets pancreas transcription factor 1a (PTF1a) for proteasomal degradation, a protein essential for pancreatic cancer development [99]. TRIP12 forms a ternary complex with deubiquitylase ubiquitin-specific protease 7 (USP7) that aids in hepatocellular carcinoma (HCC) proliferation; when USP7 expression levels are heightened, TRIP12 cannot tag ARF tumor suppressor (p14ARF) for ubiquitylation [100]. Furthermore, TRIP12 is associated with human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HNSCC) due to its mediation of p16-related radiation efficacy [101].

Members of the HECT E3 ubiquitin ligase family play important roles in neurodevelopment and their malfunction may be causative in different neurological diseases and disorders (reviewed in [4]). Recent genetic screens have been looking to identify genetic markers for autism spectrum disorder (ASD) and intellectual disability (ID). Interestingly, a *de novo* mutation in *TRIP12* was found in patients with or without ASD and displaying characteristics of ID [102]. Further studies to clarify the specific mechanism(s) for how mutations in the *TRIP12* gene contribute to ASD and ID phenotypes are needed.

3. Conclusion

Although much research has and continues to be performed for E6AP and members of the NEDD4 family, greater attention on the mysterious "other"

HECT E3 ubiquitin ligases is warranted due to their emerging involvement in various diseases and neurological disorders. Combining genetic, cell biology, biochemical, and biophysical approaches to study these unique HECT E3 ubiquitin ligases will help to decipher their specific roles and/or functions in the cell as well as potentially aid in novel therapy development to treat rare conditions caused by the dysfunction of these lesser known members of the HECT E3 ubiquitin ligase family.

Acknowledgements

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this chapter.

Abbreviations

AIS	acute ischemic stroke
AML	acute myeloid leukemia
ANK	ankyrin repeat
AREL1	apoptosis resistant E3 ubiquitin protein ligase 1
ARM	armadillo-repeat domain
ARTS	septin 4
ASD	autism spectrum disorder
β2AR	adrenergic receptor β2AR
cIAP1/2	cellular inhibitor of apoptosis protein 1/2
circHECTD1	circular RNA HECTD1
CIT	citron rho-interacting kinase
EndMT	endothelial-mesenchymal transition
FBN3	fibrillin-3 precursor
G2E3	G2/M-phase specific E3 ubiquitin protein ligase
H	helix-bundle domain
HACE1	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1
HCC	hepatocellular carcinoma
HECT	hmologous to E6AP C-terminus
HECTD1	HECT domain containing E3 ubiquitin protein ligase 1
HECTD4	HECT domain containing E3 ubiquitin protein ligase 4
HERC	HECT and RLD domain-containing
HNSCC	head and neck squamous cell carcinoma
HOIP	HOIL-interacting protein
HPV	human papillomavirus
Hsp90	heat shock protein 90
HtrA2	HtrA serine peptidase 2
ID	intellectual disability
IGF	immunoglobulin-like fold
MIB	mind bomb domain

NEDD4	neuronal precursor cell-expressed developmentally down-regulated 4
SMAC	second mitochondrial activator of caspase
OEM	ovarian endometriosis
OPTN	optineurin
p14ARF	ARF tumor suppressor
PHD	plant homeodomain-type zinc finger
PTF1a	pancreas transcription factor 1a
RAR-β	retinoic acid receptor beta
RING	really interesting new gene
TNFR2	tumor necrosis factor receptor-2
SNPs	single nucleotide polymorphisms
SPPRS	spastic paraplegia and psychomotor retardation with or without seizures
SUN	Smad4 activation SAD1/UNC domain
TRIP12	thyroid hormone receptor interactor 12
UCB	urothelial carcinoma in the bladder
USP7	deubiquitylase ubiquitin-specific protease 7
WWE	tryptophan-tryptophan-glutamate domain

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