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REVIEW

Advancements in the research of the structure, function, and disease-related roles of ARMC5

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Abstract **The armadillo repeat containing 5 (*ARMC5*) gene is part of a family of protein-coding genes that are rich in armadillo repeat sequences, are ubiquitously present in eukaryotes, and mediate interactions between proteins, playing roles in various cellular processes. Current research has demonstrated that reduced expression or absence of the *ARMC5* gene in various tumor tissues can lead to uncontrolled cell proliferation, thereby inducing a range of diseases. The *ARMC5* gene was initially extensively studied in the context of bilateral macronodular adrenocortical disease (BMAD), with harmful pathogenic variants in *ARMC5* identified in approximately 50% of BMAD patients. With advancing research, scientists have discovered that *ARMC5* pathogenic variants may also have potential effects on other diseases and could be associated with increased susceptibility to certain cancers. This review aims to present the latest research progress on how the *ARMC5* gene plays its role in tumors. It outlines the basic structure of *ARMC5* and the regions where it functions, as well as the diseases currently proven to be associated with *ARMC5*. Moreover, some evidence suggests its relation to embryonic development and the regulation of immune system activity. In conclusion, the *ARMC5* gene is a crucial focal point in genetic and medical research. Understanding its function and regulation is of great importance for the development of new therapeutic strategies related to diseases associated with its pathogenic variants.**

Keywords *ARMC5* gene; BMAD; meningioma; primary aldosteronism; renal cell carcinoma

Introduction

Armadillo repeat containing 5 (ARMC5) is a cytoplasmic protein devoid of enzymatic activity [1]. It is a member of the armadillo (ARM) repeat-containing family, characterized by the presence of multiple ARM repeats. These repeats are composed of 42 amino acids, forming a set of evolutionarily conserved proteins [2]. They play various roles within cells, such as in cell development, tissue integrity maintenance, and tumor formation [3]. The original study suggested that *ARMC5* is a tumor suppressor gene [4]. It is associated with the onset of various diseases. When mutated, it may lead to excessive cell proliferation and tumor formation. The disease primarily associated with pathogenic variants in the *ARMC5* gene is bilateral macronodular adrenocortical disease (BMAD, formerly known as primary bilateral macronodular adrenal cortical hyperplasia). *ARMC5* pathogenic variants are currently recognized as the main cause of BMAD [5]. This finding has transformed our understanding of the pathogenesis of BMAD, shifting from being considered a sporadic disease to a genetic disease, thereby improving the diagnosis, treatment, and screening processes for BMAD. However, subsequent studies have confirmed that inactivation of *ARMC5* function may also lead to increased apoptosis and decreased inactivation in different microenvironments [1,2,6]. In Table 1, we list the current studies on the role of *ARMC5* in different cell lines.

Escalating evidence suggests that *ARMC5* is also associated with several extra-adrenal diseases, such as meningioma, primary aldosteronism (PA), and renal cell

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carcinoma (RCC), although these connections require further research for confirmation. In addition, *ARMC5* plays a critical role in the embryonic development of T cell differentiation and apoptosis. Studies have shown that mice with *ARMC5* gene knockouts (KOs) die in early embryonic development, and obstacles are observed in T cell proliferation and differentiation into Th1 and Th17 [7]. Currently, research on *ARMC5* is increasingly gaining attention in the scientific community. Its functions are being delved into deeply, but many of its mechanisms of action have yet to be deciphered. To gain a systematic understanding of the current progress in *ARMC5* gene research, we used "ARMC5" as a keyword to search the PubMed database. We found that the relevant literature primarily spans from 2013 to the present, with a total of 107 results. We summarize the important research node of *ARMC5* gene to clarify the overall trend of research (Fig. 1).

Overview of the *ARMC5* gene

Genomic structure

The *ARMC5* gene is universally expressed in human tissues [8]. It is located on human chromosome 16 (16p11.2) [9], and its gene length is approximately 32 kilobase pairs, encoding a protein composed of 951 amino acid residues. At the mRNA level, the *ARMC5* gene has eight known isoforms. Among them, six encode proteins, except ARMC5-006 and ARMC5-007. The ARMC5-002 isoform is expressed in all 46 types of normal human tissues examined. The ARMC5-003 and ARMC5-001 isoforms appear to have more tissue-specific expression. The thymus, pancreas, adrenal glands, adipose tissue, trachea, and lungs have been found to express all four functional isoforms.

Table 1 Research on ARMC5 in various cell lines or cell types

Tissues/cell lines	*ARMC5* type	Proliferation	Apoptosis	References
H295R	*ARMC5* mutants	N/A	Antiapoptotic	[6]
HeLa cells	*ARMC5* mutants	N/A	Antiapoptotic	[6]
BMAD cells	*ARMC5* overexpression	Antiproliferative	Proapoptotic	[1]
HEK293 cells	*ARMC5* KO	Pro-proliferative	Antiapoptotic	[2]

BMAD, bilateral macronodular adrenocortical disease; N/A, not available.

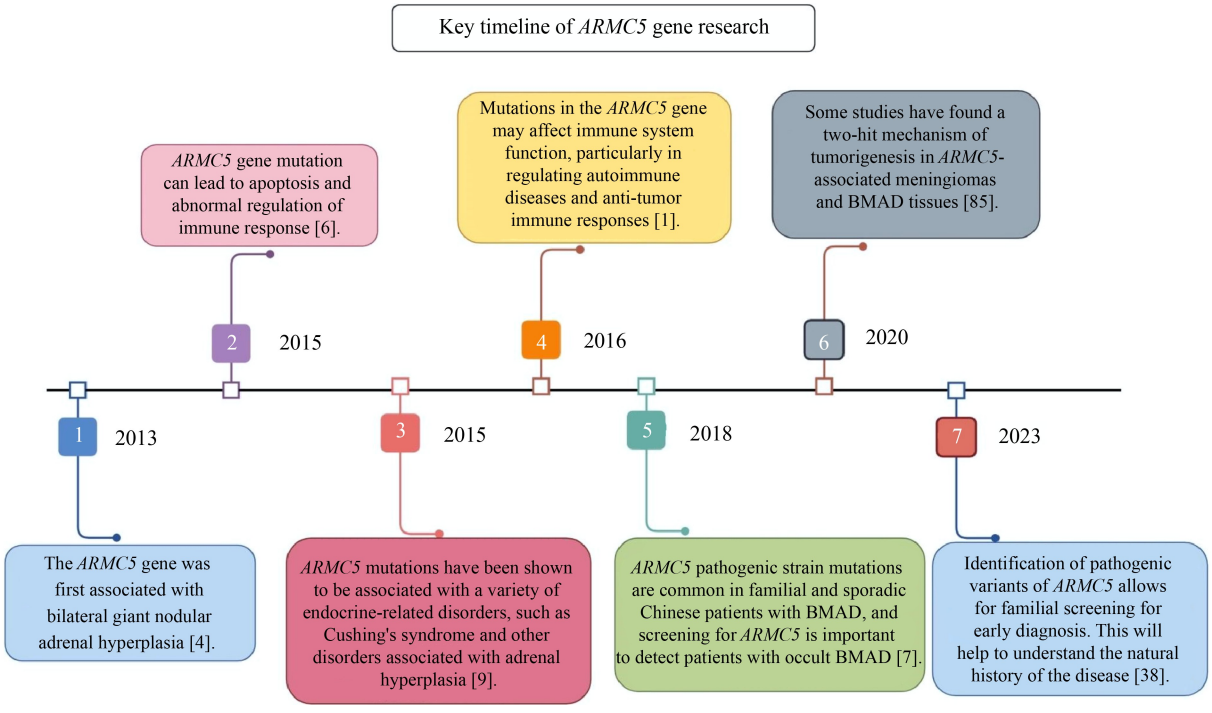

Fig. 1 Key timeline of *ARMC5* gene research: over the past decade, research on *ARMC5* has significantly advanced, particularly in the context of BMAD and meningioma. Studies have evolved from examining its roles in apoptosis and immune regulation to uncovering its critical involvement in tumorigenesis. These findings highlight the potential for future diagnostic approaches through early detection of *ARMC5* mutations.

Protein structure

ARMC5 consists of two structural domains: the ARM repeat domain at the N terminus and the Broad-Complex, Tramtrack, and Bric à brac (BTB)/Pox virus and Zinc finger (POZ) domain at the carboxyl terminus (Fig. 2A). These two domains are highly conserved from *Drosophila* to humans [10], and they can serve as docking platforms for many proteins, playing a crucial role in the function of their host proteins [8].

An ARM repeat consists of tandem repeats of about 42 amino acids, and the repeat region could take part in the formation of α-superhelix, which provides a substantial platform for protein binding. The ARM repeat-containing proteins (ARMCs) are widely distributed in eukaryotes. Composed of only a central ARM repeat (e.g., β-catenin) or combined with other domains (e.g., ARMC5), ARMCs can mediate conservative and unique protein–protein interactions [11]. The homology in the structure of ARMCs may suggest functional similarity. β-catenin is the prototypical ARM repeat protein, which plays an essential role as adhesion protein and signaling protein. Without Wnt signaling, β-catenin remains unstable and degraded by protein complexes. After Wnt signaling activation, β-catenin becomes stabilized and enters the nucleus, where it binds to transcription factors and regulates the target gene transcription [12]. Many β-catenin interaction partners, such as TCF3 and E-cadherin, bind to a positively charged groove in the ARM repeat region, which indicates the importance of ARM repeat in β-catenin functions [13]. The ARM repeat domain of ARMC5 shares structural similarity to that of β-catenin, suggesting that ARMC5 may serve as a key protein interaction hub to achieve specific cellular functions (Fig. 2B).

BTB domain was first described in *Drosophila* transcription factors and poxvirus proteins, and the canonical core BTB domain has five a-helices, with A1/2 and A4/5 forming α-helical hairpins and three b-strands (B1/B2/B3) forming a b-sheet; these two parts are connected by helix A3 and a variable linker region. Some BTB domains possess N- or C-terminal extension regions, which may contribute to protein-specific functions. Most of the conserved residues in BTB domains are hydrophobic residues that are buried within the scaffold and highly variable residues exposed to whose surface gives BTB domains enhanced potential for protein–protein interaction [14]. BTB domain-containing proteins can function as adaptor proteins in cullin-RING E3 ligase complexes, leading to protein degradation by the ubiquitin–proteasome system (UPS), and the BTB proteins themselves can become the substrate to be degraded [15]. Assuming that the BTB domain of ARMC5 endows it with the potential to function as an adaptor protein for E3 complex, regulating the degradation of intracellular proteins, is reasonable.

The ARMC5 protein does not contain any known conserved enzyme motifs or structural domains,

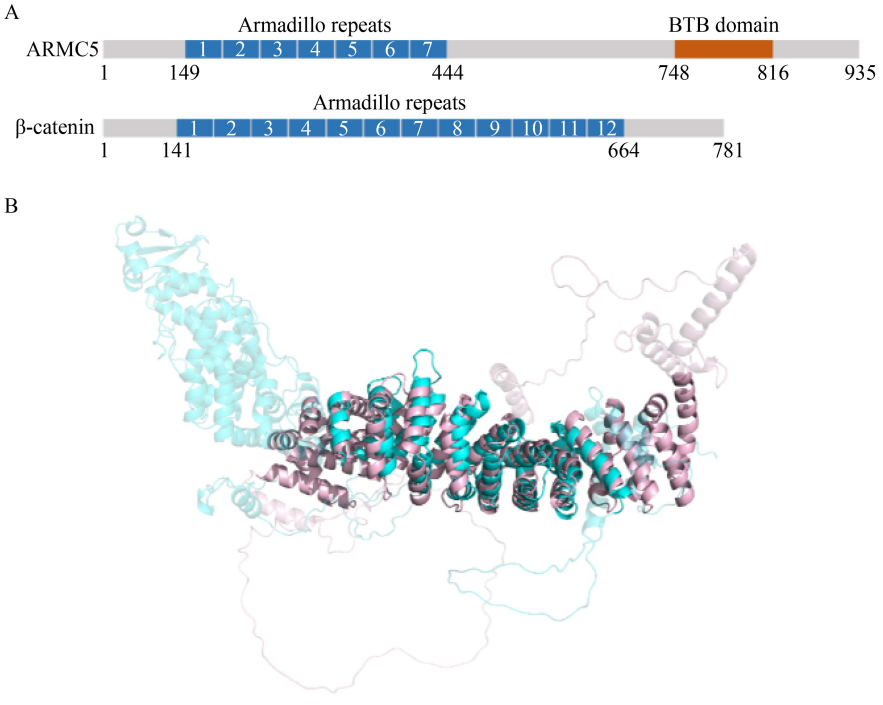

Fig. 2 Structure of ARMCs, ARMC5, and β-catenin. (A) Sketch of the structural domains of ARMC5 and β-catenin. (B) Alignment of the predicted structures of ARMC5 and β-catenin by AlphaFold.

suggesting that its function may be contingent upon its interactions with other molecules. Some studies have explored the mechanisms of action and metabolism of ARMC5. Some researchers have proven through the yeast two-hybrid test [16] that ARMC5 can bind to 16 types of proteins [1]. Among these proteins, the highest-scoring interactions were identified with RPB1, the largest subunit of RNA polymerase II (Pol II), and Cullin3 (CUL3). Despite these findings, the specific signaling pathways wherein ARMC5 is involved remain unclear.

UPS plays a critical role in controlling protein homeostasis within cells, and it serves as an essential regulatory factor for ARMC5 [17]. Before degradation within the proteasome, proteins must be ubiquitinated, a process that relies on a cascade of three types of enzymes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases [18]. E3 ligases are critical because they determine substrate specificity. Cul3 and the RING-finger protein RBX1 both belong to the E3 ligase family and can interact with each other to form a multi-subunit RING-finger E3 complex, serving as the substrate recognition subunit and playing a pivotal role in UPS [19]. Two extensive protein–protein interaction screenings [20,21] have demonstrated that ARMC5 can interact with Cul3 through its BTB domain, leading to the ubiquitination of ARMC5 and its further degradation via the proteasome pathway [17]. The discovery of these structures and mechanisms has laid the groundwork for subsequent exploration of the pathogenic mechanisms of *ARMC5* pathogenic variants.

Function

Since the link between *ARMC5* and BMAD was reported, the functionality of *ARMC5* has been further explored, yet much remains unknown. *ARMC5* is universally expressed in human tissues [22], participating in T cell development [23], lung morphogenesis [24], neural tube development [25], osteoblast/chondrocyte conversion [26], adrenal cortex development [27], and tumor suppression [28], among other processes. Pathogenic variants surrounding or within the ARM repeat domain and the BTB/POZ domain, which are key components of this gene, affect *ARMC5*'s function. Dysregulation of the protein kinase A (PKA) pathway is one of the most common alterations implicated in the pathogenesis of bilateral adrenal diseases. Recent findings have identified that pathogenic variants in the *ARMC5* gene also play a role in this pathway, thereby influencing the onset and progression of BMAD [29]. However, the precise role of *ARMC5* within this pathway has not been fully elucidated because of its complex involvement in various biological processes, including cell cycle regulation, proteasome-mediated protein degradation, and interactions with other pathways, such as the PKA pathway (Fig. 3).

Previous *in vitro* studies found that overexpression of wild-type *ARMC5* stimulates rapid apoptosis in H295R and HeLa cells. Conversely, lineage missense pathogenic variants of *ARMC5* do not stimulate cell apoptosis [4]. Therefore, the intrinsic function of wild-type *ARMC5* appears to be the suppression of cell proliferation or the promotion of apoptosis. Missense pathogenic variants in *ARMC5* may abolish its direct or indirect proapoptotic functions. The mechanism of gene inactivation, which involves a germline event followed by another at the somatic level, is consistent with Knudson's two-hit hypothesis [30]. While patients with a single germline allele pathogenic variant may still produce sufficient *ARMC5*, a second allele may incur somatic damage later in life, hence not manifesting an obvious phenotype as seen in heterozygous KO mice. The randomness of somatic pathogenic variants and the time needed for critical nucleotide changes to occur may explain the delayed onset of diseases, such as BMAD [31]. *ARMC5* also regulates the cell cycle, participating in the G1-S cell cycle process. Studies have shown that *ARMC5* silencing reduces the percentage of cells in the G1 phase and increases the percentage of cells in the S phase [32]. In 2020 [33], Berthon *et al.* tested the interaction of ARMC5 with CUL3 in human embryonic kidney (HEK293) cell protein extracts. They found a specific interaction between ARMC5 and CUL3, with ARMC5 serving as a substrate of CUL3 and being degraded by UPS. However, this interaction can be disrupted by pathogenic genetic variants in the sequence encoding the ARMC5 BTB domain, thus relieving the regulation of ARMC5 protein turnover and promoting cell development. This mechanism could be one of the important mechanisms by which *ARMC5* pathogenic variants lead to tumorigenesis. Previous studies have identified CUL3 and RPB1 (the largest subunit of RNA Pol II) as potential interacting partners of ARMC5. ARMC5 forms a specific active E3 ubiquitin ligase complex with CUL3 and RBX1, targeting RPB1. The absence of *ARMC5* leads to a significant reduction in the ubiquitination of RPB1 and an increase in RPB1 accumulation, thereby expanding the Pol II pool in normal tissues and organs. This expanded Pol II pool regulates the expression of several genes, resulting in altered cell proliferation and steroidogenesis. The enlargement of the Pol II pool and the associated gene dysregulation have been correlated with adrenal hyperplasia in humans and KO mice [31].

Recent research has found that *ARMC5* also plays a crucial role in embryonic development [34] and in the proliferation and differentiation of T cells [1]. However, the same *ARMC5* gene pathogenic variant, while promoting cell proliferation in the adrenal cortex, can also promote T cell apoptosis. This finding suggests that the function of *ARMC5* exhibits tissue and environmental specificity, generating different phenotypes by binding to

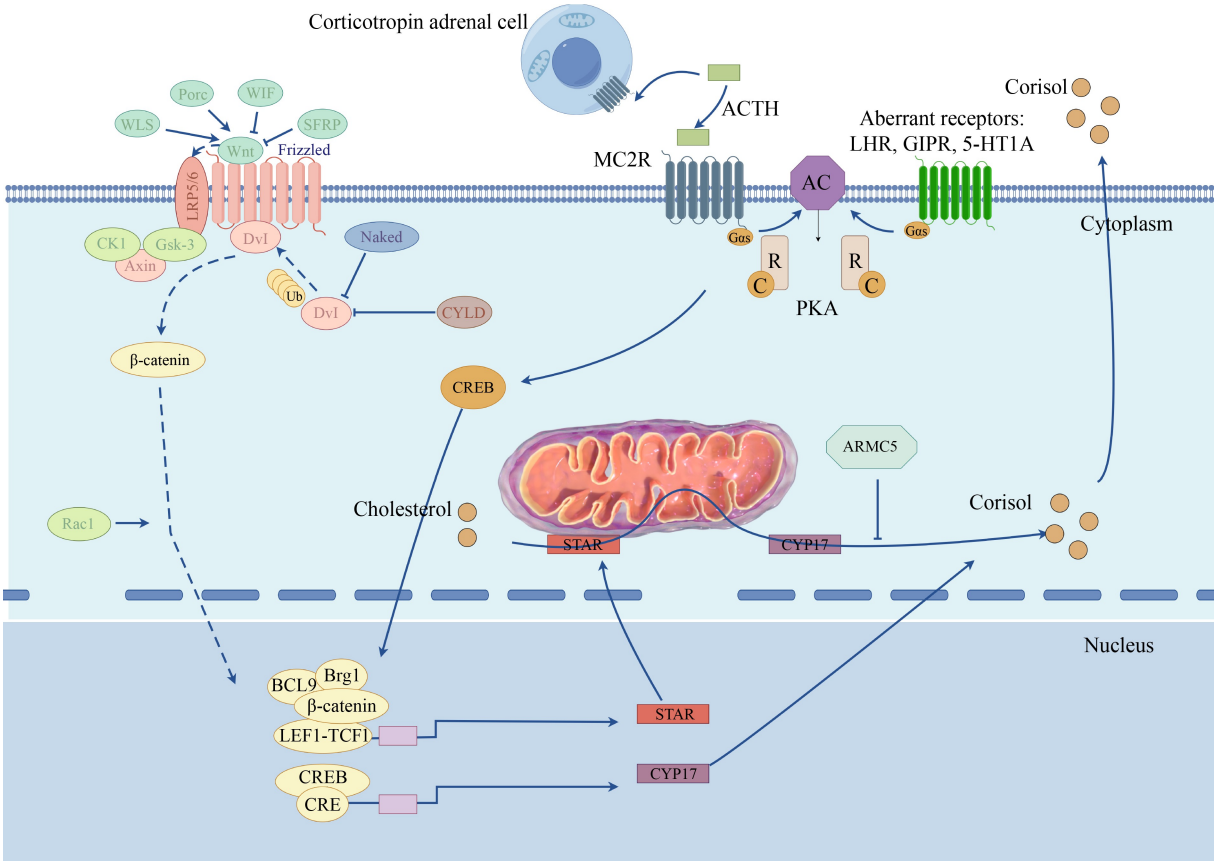

Fig. 3 Pathophysiology of BMAD. Corticotropin adrenal cells: a cluster of gonadal-like adrenal cells secreting local ACTH responsible for an autocrine or paracrine stimulation of the PKA pathway. PKA pathway: mechanisms leading to an activation of the PKA signaling pathway have been described. Mutations of APC in PBMAH lead to dissociation of the β-catenin from the destruction complex. The β-catenin protein accumulates in the cytoplasm and in the nucleus, where it stimulates target gene expression. The mutations of ARMC5 lead to a decreased apoptosis of the cortical cells and probably to their accumulation, explaining the increase in cortisol secretion despite a reduction in cortisol production at the cell level.

different partners in various cells.

ARMC5 gene pathogenic variants and diseases

BMAD

BMAD is morphologically defined as bilateral adrenal enlargement, accompanied with nodules larger than 1 cm or widespread thickening on computed tomography scans [35]. This disease can lead to an overproduction of corticosteroids, resulting in symptoms such as hypertension, diabetes, and obesity. It is a rare cause of hypercortisolism, accounting for less than 2% of all endogenous cases of Cushing's syndrome (CS) [36,37]. Abnormal expression of various G-protein-coupled receptors can lead to abnormal autocrine/paracrine regulation of steroid production, resulting in increased steroid production [38–41]. Although CS is the most common clinical manifestation of this disease, reports of hyperaldosteronism, feminization, or virilization caused by concurrent secretion of aldosterone, estrone, or androgens also exist [42–44]. Another characteristic of this disease is that patients often present with insidious onset and slow progression, leading to a high proportion of mild autonomous cortisol secretion and late diagnosis after the age of 40 [45,46].

BMAD was initially thought to be sporadic, but many features suggest that it is primarily a genetic disease. First, the characteristic bilateral adrenal cortical hyperplasia implies that gene pathogenic variants behind tumor occurrence may exist in early embryogenesis, thus affecting both adrenal glands [22]. Second, recent reports of familial clustering cases [35,47–54] have indicated that the disease's segregation pattern conforms to the characteristics of autosomal dominant inheritance. Lastly, in 2013, Assié *et al.* discovered *ARMC5* gene pathogenic variants in BMAD patients [4]. They used a combination of SNP arrays and whole-genome sequencing methods to genotype the DNA in the blood and tumor samples of 33 BMAD patients who underwent surgery, eventually detecting *ARMC5* pathogenic variants in 18 (55%) of the

patient samples. They found that *ARMC5* inactivation affects steroid production and *in vitro* cell survival, and patients with *ARMC5* pathogenic variants have an earlier age of diagnosis (average age of diagnosis: 49 versus 55) and a higher clinical CS prevalence (71% versus 35%). Subsequent studies have reported pathogenic variant rates of ARMC5 in BMAD patients. In 2014, Gagliardi *et al.* detected *ARMC5* pathogenic variants in four out of five BMAD families [22], Alencar *et al.* evaluated 47 individuals from a Brazilian primary macronodular adrenal hyperplasia (PMAH) family and confirmed identical heterozygous germline variants in the *ARMC5* gene by routine sequencing in all 16 affected family members [55], and Faucz *et al.* found that 44%–55% of their study subjects with isolated BMAD had germline variations in *ARMC5* [56]. A study conducted in the Chinese population in 2018 [7] by Yu *et al.* collected clinical data and performed *ARMC5* sequencing on three BMAD families and 23 sporadic BMAD patients, ultimately discovering pathogenic germline *ARMC5* pathogenic variants in all three BMAD families. They found the secondary *ARMC5* somatic pathogenic variants in two adrenal nodules in two BMAD family members with *ARMC5* germline pathogenic variants. *In vitro* inactivation of *ARMC5* reduces the expression of genes involved in steroid and cortisol synthesis [4,57]. Loss of *ARMC5* function leads to increased apoptosis and decreased cell proliferation, as well as reduced expression of the adrenocorticotropic hormone receptor (MC2R) and several steroidogenic enzymes [58], elucidating the observed relative inefficiency in steroidogenesis [59]. However, the elevation in cortisol levels is attributed not to the hyperactivity of individual cells but to a substantial increase in the total mass of adrenal cells. Consequently, CS emerges only when the adrenal mass enlarges sufficiently to compensate for the reduced steroidogenesis observed at the cellular level [10]. This finding aligns with recent research findings that in patients carrying pathogenic variants of *ARMC5*, the size of the adrenal gland correlates with the levels of 17-hydroxycorticosteroids [60].

Currently, more than 100 pathogenic variants of the *ARMC5* gene (we list the known genetic variants and their sources in Table 2), including germline and somatic levels, have been identified in BMAD patients [4,7,9,22,45,55,56,61–67], spanning the coding sequence of the gene at the germline and somatic levels. However, only a few regions have been explicitly identified as hotspots for these pathogenic variants [10]. Most *ARMC5* pathogenic variants are nonsense (22%, 12 out of 54) and frameshift (38%, 21 out of 54) [68]. A significant proportion of these pathogenic variants in sporadic BMAD patients—four-fifths—are located within or near the ARM repeat domain of ARMC5, whereas two-thirds of the pathogenic variants in familial BMAD are in or near the BTB/POZ domain. An existing challenge is to determine the pathogenic potential of compound heterozygous variants in BMAD patients [17], given that the development of functional tests for these variants is limited by our incomplete understanding of *ARMC5* function. Notably, one study reported up to 14 different somatic *ARMC5* pathogenic variant events in a single BMAD patient [61], with each nodule of BMAD having specific somatic changes, implying instability at the *ARMC5* gene locus.

Based on current research, *ARMC5* pathogenic variants are recognized as the most common cause of BMAD, present in approximately 20%–25% of unselected patient cohorts with BMAD and in 40%–45% of those who have undergone surgical intervention [69]. However, a recent series of studies from Japan reported that 71% of the patients, in a cohort of 14, carried *ARMC5* pathogenic variants, suggesting a potentially higher prevalence of *ARMC5* pathogenic variants in the Japanese population, although the surgical status of these patients was not specified [67]. Moreover, patients with pathogenic variants of *ARMC5* exhibit a more severe phenotype than those without *ARMC5* pathogenic variants [4,45,56], characterized by a greater number of adrenal cortical nodules, earlier diagnosis [48], and more frequent metabolic complications, such as diabetes and arterial hypertension. Furthermore, they are more often subjected to therapeutic interventions, either through bilateral adrenalectomy or pharmacological treatments [45,69].

In clinical screening of apparently unaffected relatives of BMAD patients, affected individuals have also been identified [22,54]. Given that the onset of BMAD typically occurs after age 40 and that a high proportion of BMAD patients present with insidious onset, only manifesting subclinical hypercortisolism or mild suppression of ACTH levels [9,45,55,56,63], delayed diagnosis could arise [70]. Consequently, BMAD patients may be at risk of long-term exposure to the harmful catabolic effects of excessive cortisol before diagnosis. All BMAD patients who have confirmed germline pathogenic variants are recommended to encourage their first-degree relatives to actively undergo genetic screening and counseling [55]. Genetic testing revealing hereditary autosomal dominant pathogenic variants in the *ARMC5* gene can identify high-risk individuals early in the disease's insidious progression [71], even before clinical symptoms manifest. These carriers may exhibit severe manifestations upon disease onset.

Meningioma

Meningiomas are benign tumors originating from the meninges, a thin envelope surrounding the brain and spinal cord. While the majority (approximately 85%) of meningiomas are benign, a small percentage (around

Table 2 ARMC5 mutations identified in patients with BMAD

cDNA	Protein	Mutation type	Reference
/	p.(R267X)	Germline	[4]
/	p.(Q86X)	Germline	
/	p.(L548P)	Germline	
/	p.(G57Efs*79)	Germline	
/	p.(R619X)	Germline	
/	p.(R898W)	Germline	
/	p.(A702_S706del)	Germline	
/	p.(A104Gfs*6)	Germline	
c.1214delG	c.1214delG p.(Gly405Alafs*56)	Germline	[7]
c.523delG	p.(Ala175Profs*7)	Germline	
c.318delG	p.(Ser107Argfs*30)	Germline	
c.2564delT	p.(Val855Glyfs*62)	Germline	
c.622_623insC	p.(Gln208Profs*15)	Germline	
c.1855C>T	p.(Arg619*)	Germline	
c.2290C>T	p.(Arg764*)	Germline	
c.2189C>A	p.(Ser730*)	Germline	
c.2599G>T	p.(Glu867*)	Somatic	
c.1851delG	p.(His618Thrfs*12)	Somatic	
c.323_324insC	p.(A110fs*9)	Germline	[9]
c.1084C>T	p.R362W	Somatic	
LOH	p.(A110fs*9)	Somatic	
c.305_341del	p.S102fs	Somatic	
c.311delC	p.A104fs	Somatic	
c.164_165insG	p.A55fs	Somatic	
c.1960C_x0005_>T	p.R654*	Somatic	
c.1297G>T	p.E433*	Somatic	
c.315_316insG	p.A106fs	Somatic	
c.1777C>T	p.(Arg593Trp)	Germline	[22]
c.2139del	p.(Thr715Leufs*1)	Germline	
c.943C>T	p.(Arg315Trp)	Germline	
c.799C>T	p.(Arg267*)	Germline	
/	p.(Q86X)	Germline	[6]
/	p.(R267X)	Germline	
/	p.(L548P)	Germline	
/	p.(R267X)	Germline	
/	p.(G57Efs*80)	Germline	
/	p.(R267X)	Germline	
/	p.(A702_S706del)	Germline	
/	p.(R898W)	Germline	
/	p.(F700del)	Germline	
/	p.(A296Cfs*34)	Germline	
/	p.(R619X)	Germline	
/	p.(C657R)	Germline	
c.1094T>C	p.(Leu365Pro)	Germline	[55]
c.1971C>G	p.(Cys657Trp)	Somatic	
c.2423A>C	p.(His808Pro)	Germline	
c.247_256del	p.(Ala83Argfs*51)	Somatic	
c. (164_171)insG	p.(Ile58Asnfs*45)	Germline	
c.2336C>G	p.(Ser779*)	Germline	
c.290_294del	p.(Ala97Glyfs*4)	Somatic	
c.952C>G	p.(Leu318Val)	Germline	
c.1181T>C	p.(Leu394Pro)	Germline	
c.1158G3A	p.(Trp386*)	Germline	
c.1428G>A	p.(Trp476*)	Germline	[61]
c.247G>C	p.(Ala83Pro)	Somatic	
c.327delC	p.(Ala110Profs*27)	Somatic	
c.346delT	p.(Ser116Argfs*21)	Somatic	
c.476-1G>A	Splice	Somatic	
c.608delG	p.(Ser203Thrfs*2)	Somatic	
c.789_808del20	p.(Glu264Profs*5)	Somatic	
c.807C>A	p.(Cys269*)	Somatic	
c.1033C>T	p.(Gln345*)	Somatic	
c.1059C>A	p.(Cys353*)	Somatic	
c.1059_1080del22	p.(Cys353*)	Somatic	
c.1751T>A	p.(Val584Glu)	Somatic	
c.2228C>T	p.(Ala743Val)	Somatic	
c.2405C>G	p.(Pro802Arg)	Somatic	
c.2444delG	p.(Ala815Leufs*102)	Somatic	
c.-117 A>C	/	Germline	[62]
c.167G>C	p.(Gly56Ala)	Somatic	
c.174dupC	p.(Glu59Argfs44*)	Somatic	
c.194delG	p.(Gly65Alafs72*)	Somatic	
c.220_222delinsTT	p.(Leu74Phefs63*)	Somatic	
c.325_326delinsTd	p.(Pro109Serfs28*)	Somatic	
c.438 G>A	p.(Arg146Arg)	Germline	
c.1042delCd	p.(L348Wfs27*)	Somatic	
c.1084 C>T	p.(Arg362Trp)	Somatic	
c.1090 C>T	p.Arg364Ter	Somatic	
c.1448 C>T	p.(Pro483Leu)	Germline	
c.1739 T>C	p.(Leu580Pro)	Somatic	
c.1975 C>T	p.(Arg659Cys)	Germline	
c.2192 C>G	p.Pro731Arg	Germline	
c.2290 C>T	p.(Arg764Ter)	Somatic	
c.*234_*238dup	/	Germline	
c.327_328insC	p.(A110Rfs*9)	Germline	[63]
c.288COG	p.(A96 A)	Somatic	

(*Continued*)

cDNA	Protein	Mutation type	Reference	cDNA	Protein	Mutation type	Reference
/	p.(E430X) or p.(A110Pfs*26)	Germline	[6]	c.2029GOT	p.(E677X)	Somatic	[63]
/	micro DEL	Germline		c. 2114COT	p.(A705V)	Germline	
/	p.(A104Gfs*7)	Germline		c.1855C.T	p.(R619*)	N/A	[67]
/	p.(I664S)	Germline		c.2692C.T	p.(R898W)	N/A	
/	p.(L754P)	Germline		c.1855C.T	p.(R654*)	N/A	
/	p.(R764X)	Germline		c.1085G.A	p.(R362Q)	N/A	
/	p.(A106Rfs*31)	Germline		c.427_454del	p.(G143Sfs*8)	N/A	
/	p.(A104Gfs*7)	Germline		c.1960C.T	p.(R654*)	N/A	
				c.327_328insC	p.(Ala110Argfs*9)	Germline	[31]

BMAD, bilateral micronodular adrenal cortical disease; N/A, not available.

15%) may be malignant or invasive [72]. They can appear anywhere in the brain, including the surface of the brain, intracranial nerve passages, or the spinal cord [73]. According to data from the American Brain Tumor Association [74], meningiomas represent about 36.6% of all primary brain and central nervous system tumors, making them the most common type. The incidence of meningiomas increases with age, particularly common among individuals aged 40 to 70, and the rate is typically twice as high in females than males. Although the cause of most meningiomas remains unknown, several risk factors have been identified [73,75], including exposure to radiation, a history of neurofibromatosis type II, and long-term use of certain hormonal medications. However, most patients do not have these risk factors. Among the general population, only 0.9% are diagnosed with meningiomas by chance after their fourth decade of life [76].

Since the late 1920s, when Cushing and Eisenhardt first described cases of rapid progression of meningiomas during pregnancy, the impact of hormones on the development, progression, and recurrence of meningiomas has gained growing recognition [75,77]. Previous studies have confirmed the expression of sex hormones and somatostatin receptors in meningiomas [78–82]. In recent years, researchers have discovered that a "second hit" to *ARMC5* can lead to the development of meningiomas in patients with *ARMC5* pathogenic variants associated with BMAD. In addition to genetic predisposition, the aberrant circulating steroid milieu caused by adrenal tumors is hypothesized to contribute to the growth and development of meningiomas [83,84]. Meningiomas have been reported in siblings with familial BMAD, but no studies of *ARMC5* pathogenic variants were conducted in these cases [35]. In 2014, Elbelt *et al.* [9] discovered somatic pathogenic variants in *ARMC5* in the DNA of meningioma tissue from a patient with BMAD, suggesting that biallelic inactivation of *ARMC5* might be a cause of intracranial meningiomas. Alencar *et al.* [55] reported that three out of seven family members in a single Brazilian family (43%) had adrenocortical nodular hyperplasia and meningiomas due to *ARMC5* pathogenic variants. In 2020, Jojima and colleagues studied a case of a 65 year-old woman with BMAD and a meningioma, who, contrary to previous reports, initially presented with neurological symptoms caused by the meningioma and was later diagnosed with BMAD [85]. These findings provide evidence for the potential involvement of *ARMC5* in the development of meningiomas. However, to better delineate the association between *ARMC5* pathogenic variants and meningiomas, further analyses on larger cohorts are warranted, with systematic brain imaging included in the initial screening, at least for patients diagnosed with pathogenic *ARMC5* variants.

PA

PA is an endocrine disorder caused by excessive aldosterone secretion from the adrenal glands. The overabundance of aldosterone leads to increased reabsorption of sodium and water and elevated potassium excretion, resulting in hypertension and hypokalemia [86]. It is the most common cause of secondary hypertension, with an incidence rate of about 5%–10% among all hypertensive patients. However, this percentage may be higher in patients with resistant hypertension, i.e., those poorly responsive to standard treatment [87]. Moreover, patients with PA warrant attention given their higher cardiovascular morbidity and mortality rates compared with age and gender-matched individuals with the same degree of primary hypertension [88–90].

Previous research data have shown that hypertension is more prevalent in African Americans than in Caucasians [68,91–93]. The susceptibility of African Americans to hypertension is associated with the retention of salt and water in the body, which may be due to an

overproduction of aldosterone, heightened sensitivity to aldosterone, or genetic variations that lead to hyperactivity of the epithelial sodium channels [94]. Recent studies have suggested that this discrepancy may be linked to *ARMC5* gene pathogenic variants causing PA in African Americans. In 2015, Zilbermint *et al.* identified destructive germline *ARMC5* gene pathogenic variants in 10.7% of patients with PA (6 out of 56 patients) [95]. Notably, all subjects predicted to have destructive *ARMC5* pathogenic variants were African Americans. In 2018, another pathogenic germline pathogenic variant of *ARMC5* was identified in patients with CS and PA [7]. In 2019, Zilbermint *et al.* built upon previous research to identify a common variant in the *ARMC5* gene (rs116201073) that is associated with a reduced risk of hypertension in Black populations, along with a set of 16 rare variants linked to hypertension [96]. However, the currently available data do not allow for a definitive connection to be established between *ARMC5* pathogenic variants and PA, suggesting the need for further research. *ARMC5* variants have also been found to correlate with higher fasting blood glucose and HbA1c levels in African Americans [95,97]. Therefore, screening for *ARMC5* sequence variations should be considered in cohorts of patients with PA, particularly African Americans. Whether this conclusion applies to other populations remains uncertain.

Additionally, the mechanism by which *ARMC5* participates in PA is unclear. The known pathogenic gene for PA, CTNNB1, encodes β-catenin and potentially regulates aldosterone synthesis through the WNT/β-catenin signaling pathway [98]. ARMC5 contains tandem ARM repeat sequences similar to CRNNB1, but it is unclear whether ARMC5 is related to the WNT pathway. Recent studies have identified a cluster of cells expressing high levels of aldosterone synthase (CYP11B2), known as aldosterone-producing cell clusters (APCCs), within the adrenal tissue of normal individuals and those with PA [99]. Considering the association between germline *ARMC5* pathogenic variants and PA, researchers hypothesized that germline variants in *ARMC5* might predispose to the accumulation of APCCs. However, sequencing of the five adrenal samples with the highest APCC scores only identified a single benign *ARMC5* variant, suggesting that *ARMC5* pathogenic variants are unlikely to significantly contribute to the accumulation of APCCs. Therefore, the consequences of *ARMC5* pathogenic variants may differ between functional zones of the adrenal gland, such as the zona glomerulosa (responsible for aldosterone production) and the zona fasciculata (responsible for cortisol production). Further research is required to elucidate how *ARMC5* pathogenic variants affect aldosterone secretion.

RCC

RCC, originating from renal tubular epithelial cells, is the most common type among all primary malignant kidney tumors, accounting for approximately 90% [100]. It typically occurs in individuals over the age of 40, with a male-to-female incidence ratio of about 2:1. The causes of RCC are not entirely understood, but smoking, overweight and obesity, and specific germline pathogenic variants of certain genes are considered risk factors [101]. Surgery is the primary treatment method, and patients with distant metastases have a very poor prognosis [102]. Therefore, early diagnosis and treatment are crucial to improving survival rates for kidney cancer patients. However, patients usually have no obvious symptoms in the early stages [103], making the study of RCC proliferation mechanisms critical for early disease diagnosis and treatment.

ARMC5 pathogenic variants have been confirmed as a primary cause of BMAD, with *ARMC5* modulating the cell cycle by altering the G1/S phase [32]. UPS is an important regulator of this process. In 2020 [17], researchers found that the protein levels of ARMC5 were reduced in renal cancer cell tissues and cell lines. Subsequent screening identified USP7 as a deubiquitinating enzyme related to ARMC5, which can stabilize the protein by inhibiting ARMC5 degradation and play a vital role in regulating RCC proliferation by modulating ARMC5 stability. This finding suggests a possible connection between *ARMC5* and the pathogenesis of RCC.

However, current evidence linking *ARMC5* and RCC remains limited, and further research is needed to clarify the role of *ARMC5* in the pathogenesis of RCC. This gap could lead to the exploration of new treatment methods to improve the prognosis of patients with RCC.

Embryonic development and immune system

Human and mouse ARMC5 proteins exhibit 90% amino acid sequence homology and share similar tertiary structures. On the basis of this biological similarity, Berthon *et al.* established a novel *ARMC5* KO mouse model in 2017 [34]. Their research revealed that the majority of *ARMC5*$^{-/-}$ mice succumbed during early embryonic development, powerfully indicating the crucial role of *ARMC5* during the gastrulation phase of embryogenesis. The survival of *ARMC5*$^{-/-}$ mice was marked by a reduced size compared with wild-type mice, highlighting the potential for grave developmental abnormalities stemming from the absence of the *ARMC5* gene. Nonetheless, the precise role of the *ARMC5* gene in human embryonic development remains to be elucidated. The development of *ARMC5* heterozygous mice (*ARMC5*$^{+/-}$) proceeded normally, but they exhibited

hypoadrenocorticism at the age of 12 months. This finding is in line with *in vitro* findings showing that ARMC5 deficiency leads to decreased expression of steroidogenic enzymes, thereby reducing steroidogenesis. However, this condition of hypoadrenocorticism was temporary, with about one-third of the mice developing CS later in life, without the presence of adrenal hyperplasia or nodules.

Some research suggests that *ARMC5* may play a role in modulating T cell activity. In 2016, Hu *et al.* [1] found that *ARMC5* mRNA is highly expressed in the thymus. They established an *ARMC5* gene KO mouse model and found that this deletion impaired T cell proliferation and differentiation into Th1 and Th17 cells, increased T cell apoptosis, and resulted in developmental defects and impaired T cell immune responses in the KO mice. Additionally, they observed decreased severity of experimental autoimmune encephalomyelitis and defects in the immune response to lymphocytic choriomeningitis virus infection in the KO mice. Similar to the pathogenesis of human BMAD, these mice displayed adrenal hyperplasia in old age.

The proliferation and differentiation impediments in T cells and the occurrence of dwarfism in *ARMC5* KO cells suggest a general phenotype of reduced proliferation. Paradoxically, patients with *ARMC5* pathogenic variants suffering from BMAD demonstrate adrenal hyperplasia and meningiomas. This observation of a dichotomous function of *ARMC5* has led researchers to hypothesize that *ARMC5* may exert different functions in various cell types, which implies a tissue or context specificity that allows it to bind to different partners. This condition could result in a spectrum of functions, ranging from pro-proliferative to antiproliferative, pro-apoptotic to antiapoptotic, or even neutral effects. These findings significantly enhance our understanding of the functional complexity of *ARMC5*. There is a pressing need for further research to clarify the role of *ARMC5* in the immune system, which in turn could inform the development of immunotherapeutic strategies for disease mechanisms.

Conclusions

The *ARMC5* gene family plays a significant role in maintaining normal cellular functions and preventing disease onset. As research advances, our understanding of the role of the *ARMC5* gene in human diseases is gradually increasing. However, to date, research progress on this gene is still in the early stages. Our understanding of the normal functions of the *ARMC5* gene and how its pathogenic variants lead to diseases remains limited, particularly concerning the study of interactions between ARMC5 protein and other proteins, as well as its involvement in cell signaling pathways. Moreover, the effects of *ARMC5* loss or pathogenic variant, which may be either antiproliferative or pro-proliferative and antiapoptotic or proapoptotic, depending on the microenvironment or disease context, do not align with the initial simplistic definition of *ARMC5* as a tumor suppressor gene. A more comprehensive assessment of *ARMC5*'s interaction with different targets is required to understand the downstream indirect effects.

The role of *ARMC5* gene pathogenic variants in BMAD has been established, providing a new genetic tool for the diagnosis of BMAD. Understanding how the *ARMC5* gene affects the growth and hormone secretion of the adrenal cortex at the molecular level could also help in identifying potential therapeutic targets. A current belief is that genetic screening for *ARMC5* should be offered to most patients with BMAD. Identifying pathogenic germline pathogenic variants allows for early diagnosis and treatment of the disease in the carrier's family members, thus preventing the harmful comorbidities associated with hypercortisolism. However, further work is required to better describe the genotype/phenotype correlations in larger cohorts of BMAD patients and to expand the spectrum of pathogenic germline pathogenic variants in BMAD. Nonsense mutations in *ARMC5* typically introduce early-stop codons, resulting in truncated proteins. Most nonsense mutations lead to loss of function (LOF). Frameshift mutations, caused by insertions or deletions that alter the reading frame, also usually result in truncated or dysfunctional proteins, leading to LOF. Missense mutations involve the substitution of one amino acid for another, which can induce either LOF or gain of function, depending on the mutation's location and impact. Germline mutations require analysis of individuals in the family who carry the germline mutation to determine if they exhibit related diseases. If the germline mutation results in the widespread appearance of disease symptoms among family members and follows Mendelian inheritance patterns, it is likely an LOF mutation.

Some studies suggest that *ARMC5* gene pathogenic variants may pose risks for potential extra-adrenal phenotypes, such as meningiomas, RCC, and effects on embryonic development and the immune system [1,9,17,34,55,85]. Therefore, in addition to adrenal investigations, conducting screenings based on the identified genetic causes is recommended, although their occurrence rates have not yet been well established. Future research should strive to further reveal the role of *ARMC5* in different diseases, providing new insights for treating related diseases.

Based on the aforementioned knowledge and our existing research, assuming that ARMC5 plays a crucial role in a signaling pathway similar to WNT signaling, leading to the occurrence of BMAD and other diseases, is reasonable. First, ARMC5 shares structural similarity

with β-catenin, and the ARM repeats endow it with the function of being a hub protein for protein–protein interaction. Second, ARMC5 has been shown to interact with many key proteins, such as RBP1 and CUL3, which play critical roles in regulating signal transduction and determining cell fate. Mutations in *ARMC5*, especially pathogenic variants of residues in its two structural domains, have been reported in several diseases mentioned in our article, such as BMAD, RCC, and meningioma [8,16,51,81], highlighting the importance of functional protein complexes that contain ARMC5. Although structural studies of ARMC5 with its binding partners are currently lacking, we still hypothesize that ARMC5 mediates the formation of important functional complexes, altering the gene expression pattern and affecting the biological functions of cells, and is thus responsible for the occurrence of diseases. Research on the structure and function of *ARMC5* will contribute to further understanding of the significance of molecular biology and epigenetic research in elucidating disease mechanisms and translational applications. Overall, the role of the *ARMC5* gene and its pathogenic variants in adrenal cortical hyperplasia and other related diseases has become an active area of research. With technological advancements and a deeper understanding of this gene, there may be more innovative research about *ARMC5* in the future.

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Compliance with ethics guidelines

Conflicts of interest Yang Qu, Fan Yang, Yafang Deng, Haitao Li, Yidong Zhou, and Xuebin Zhang declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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