

# Recent advances in the ARID family: focusing on roles in human cancer

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**Abstract:** The human AT-rich interaction domain (ARID) family contains seven subfamilies and 15 members characterized by having an ARID. Members of the ARID family have the ability to regulate transcription and are involved in cell differentiation and proliferation. Accumulating evidence suggests that ARID family members are involved in cancer-related signaling pathways, highly mutated or differentially expressed in tumor tissues, and act as predictive factors for cancer prognosis or therapeutic outcome. Here we review the molecular biology and clinical studies concerned with the role played by the ARID family in cancer. This may contribute to our understanding of the initiation and progression of cancer from a novel point of view, as well as providing potential targets for cancer therapy.

**Keywords:** AT-rich interaction domain, human cancer, cancer-related signaling pathway, therapy, potential targets

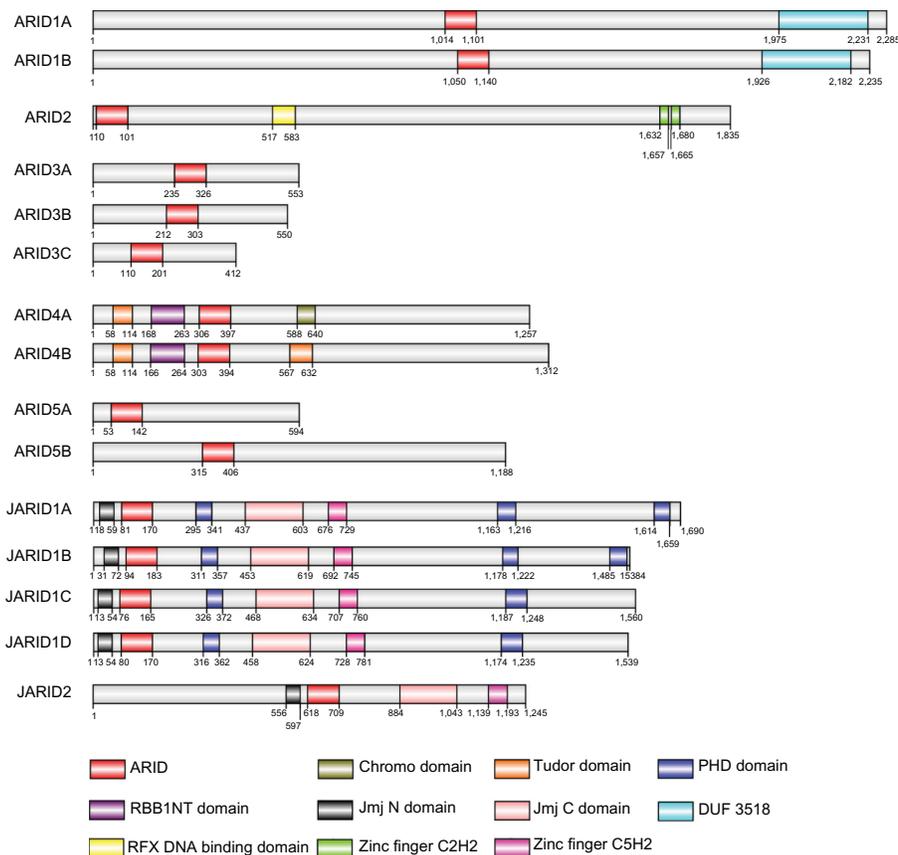
## Introduction

The human AT-rich interaction domain (ARID) family is a superfamily of 15 members. The family is divided into seven subfamilies based on the degree of sequence identity between individual members (Figure 1). Members of the ARID family all contain a DNA-binding domain that was initially found to interact with AT-rich DNA elements.<sup>1</sup> Further studies demonstrated that AT-rich binding was not an intrinsic property of ARID and that members of the ARID family might be involved in a wider range of DNA interactions.<sup>2</sup> As transcription regulators, the ARID family has been found to affect cell growth, differentiation, and development.<sup>3</sup> Recently, an increasing number of studies have suggested that the ARID family may play a role in human cancer. Our aim was to review the literature to date regarding the relationship between the ARID family and cancer (Table 1).

## Members of the ARID family

### ARID I

The ARID1 subfamily has two members, ie, ARID1A and ARID1B.<sup>1</sup> *ARID1A* and *ARID1B* are located on 1p35.3 and 6q25.1, respectively. Their encoding proteins share 66% overall similarity and are two alternative, mutually exclusive subunits of BRG1-associated factor (BAF), a subclass of the human SWI/SNF complex involved in ligand-dependent transcriptional activation by nuclear receptors.<sup>4,5</sup> In addition to ARID, ARID1 proteins each bear a domain of unknown function 3518. Even though they are similar in structure, ARID1A and ARID1B containing complexes are functionally distinct from each other.<sup>6</sup>



**Figure 1** Brief overview of the ARID family proteins and the domains in each member. ARID family proteins share structure similarity within the subfamilies. The domains were identified through the SMART databases.

**Abbreviations:** ARID, AT-rich interaction domain; PHD, plant homeodomain; RBB1NT, N-terminal domain in retinoblastoma-binding protein-I family; Jmj, jumonji; DUF, domain of unknown function.

## ARID1A

ARID1A is found in both the cytoplasm and the nucleus. Nuclear ARID1A is less stable than cytoplasmic ARID1A because it is rapidly degraded by the ubiquitin-proteasome system in the nucleus. *ARID1A* mutation has been shown to affect the consensus nuclear export signal and reduce steady-state protein levels of ARID1A.<sup>7</sup> ARID1A is widely expressed in many normal human tissues, but is markedly reduced in human tumor tissues and cell lines.<sup>8</sup> Recent studies indicate that ARID1A is a tumor suppressor. ARID1A interacts with hypermethylated in cancer-1, a tumor suppressor that is epigenetically silenced in many human cancers, and represses transcription of E2F transcription factor-1 and E2F transcription factor-1-dependent cell survival and stress responses.<sup>9</sup> ARID1A is essential for cell cycle arrest, with ARID1A-depleted cells continuing synthesis of DNA and failing to show other characteristics typical of arrested cells, including upregulation of p21 and downregulation of cyclins.<sup>6</sup> ARID1A collaborates with p53 to regulate p21 and Smad family member 3 transcription

and alters tumor growth in gynecologic cancers.<sup>10</sup> Further, colony formation in breast and gastric cancer cell lines has been shown to be significantly inhibited after re-expression of ARID1A.<sup>11,12</sup>

Accumulating evidence shows that *ARID1A* is highly mutated in a number of different cancers (Table 2). Several studies have shown that decreased ARID1A expression is related to a variety of types of cancer. Loss of ARID1A expression has been found to be significantly more frequent in certain types of cancers, including Epstein-Barr virus-positive gastric carcinoma, informative ovarian clear-cell carcinoma, and aggressive phenotypes of breast cancer.<sup>11,13,14</sup> ARID1A has also been found to be related to the prognosis of some cancers. *ARID1A* and *ARID1B* mutations have been associated with early treatment failure and decreased survival in children with neuroblastoma.<sup>15</sup> Reduced ARID1A expression has been shown to be related to poor prognosis in ovarian clear-cell carcinoma and gastric cancer,<sup>12,13,16</sup> although other studies have suggested the opposite, eg, the level of ARID1A expression was not significantly associated with

**Table 1** ARID family and related cancers

ARID subfamilies	ARID members	Other names	Cancers studied	Potential roles
ARID1	ARID1A	BAF250, BAF250a, P270, OSA1, hOSA1, RPI1-50O24.1, B120, BM029, C1orf4, MRD14, SMARCF1, ELD, hELD	Gastric cancer, colon cancer, hepatocellular cancer, lung cancer, breast cancer, ovarian cancer, cervix cancer, endometrial carcinoma, prostate cancer, neuroblastoma, glioblastoma	Tumor suppressor
	ARID1B	BAF250B, BRIGHT, OSA2, ELD/O SA1, RPI1-419L10.1, 6A3-5, DAN15, MRD12, P250R	Pancreatic cancer	Tumor suppressor
ARID2	ARID2	BAF200, p200	Lung cancer, hepatocellular carcinoma, pancreatic cancer	Tumor suppressor
ARID3	ARID3A	BRIGHT, DRIL1, DRIL3, E2FBP1	Leukemia	Tumor promoter
	ARID3B	BDP, DRIL2	Ovarian cancer, breast cancer	Both roles were mentioned
ARID4	ARID3C	BRIGHT-like	Not mentioned	
	ARID4A	RBBP1, RBPI	Breast cancer, leukemia	Both roles were mentioned
ARID5	ARID4B	BCAA, BRCAA1, RBBP1L1, RBP1L1, SAPI80	Breast cancer, lung cancer, colon cancer, pancreatic cancer, ovarian cancer	Tumor promoter
	ARID5A	MRF1, UNQ5814, RPI1-363D14	Not mentioned	
JARID1	ARID5B	MRF2, RPI1-341A19.1, DESRT,	Leukemia	Unclear
	JARID1A	KDM5A, RBP2, RBBP2,	Leukemia and endocrine neoplasia	Tumor promoter
	JARID1B	KDM5B, PLUI, PUT1, CT31, RBBP2H1A	Breast cancer, prostate cancer, bladder cancer, lung cancer, esophageal cancer, malignant melanoma	Both roles were mentioned
JARID2	JARID1C	KDM5C, SMCX, MRXJ, XE169	Clear cell renal cell carcinoma	Tumor suppressor
	JARID1D	KDM5D, SMCY, HY, HYA	Prostate cancer	No significant association
	JARID2	JMJ	Leukemia	Tumor suppressor

**Abbreviations:** ARID, AT-rich interaction domain; JARID, Jumonji AT-rich interaction domain.

survival in endometrial carcinoma<sup>17,18</sup> and was not related to the prognosis of uterine cervix cancer.<sup>19</sup>

### ARID1B

Like ARID1A, ARID1B is widely distributed in tissues. Although structurally similar, ARID1B appears to play an opposite role to that of ARID1A. ARID1B-containing BAF complexes have been shown to activate the cell cycle.<sup>20</sup> In contrast with its role as a cell cycle activator, ARID1B seems to be a tumor suppressor in pancreatic cancer. It is also less expressed in advanced-stage pancreatic cancer tissues and was found to inhibit colony formation in a pancreatic cancer cell line.<sup>21</sup> The role of ARID1B protein remains unclear and needs further study.

Within the ARID1 subfamily, ARID1A and ARID1B play opposite roles in the cell cycle and are two mutually exclusive subunits of BAF complex. The roles played by the BAF complex in human cancer may be decided by the dominant subunit. Studies focused on both members are needed in the future to clarify how the same

ARID1A status can have different clinicopathological characteristics.

### ARID2

The ARID2 subfamily has only one member. *ARID2* is located on 12q12. As with the other members of the ARID1 subfamily, its encoding proteins also comprise a subunit of the human SWI/SNF complex, but in an alternative subclass containing complex polybromo-associated BAF (PBAF).<sup>22</sup> ARID2 protein contains an ARID, another DNA-binding domain known as RFX DNA, and two conservative C-terminal C2H2 Zn fingers. Among these domains, mutations have been found to disrupt the Zn finger motifs only, suggesting the importance of these motifs in the biological activity of ARID2.<sup>23</sup>

ARID2 is widely expressed. Gene sequencing results show that *ARID2* is highly mutated in certain types of cancers, including non-small-cell lung cancer, hepatocellular carcinoma (HCC), and pancreatic cancer.<sup>24–27</sup> Interestingly, *ARID2* has been shown to be highly mutated in cases of hepatitis C

**Table 2** Gene sequencing of ARID1A in different cancers

Type of cancer	Subtype of cancer	No of ARID1A mutated cases/cases studied	Reference
Ovarian cancer	Clear cell carcinoma	24/42	Jones et al <sup>10</sup>
		55/119	Wiegand et al <sup>11</sup>
	Endometrioid carcinomas	10/33	
	High-grade serous carcinomas	0/76	
	Serous carcinoma	0/51	Guan et al <sup>7</sup>
Uterine cancer	Mucinous carcinoma	0/5	
	Uterine endometrioid carcinoma	10/25	Guan et al <sup>7</sup>
Gastric cancer	Uterine serous carcinoma	0/12	
		9/110	Zang et al <sup>112</sup>
Hepatocellular cancer		6/22	Wang et al <sup>113</sup>
		10/100	Jones et al <sup>114</sup>
Cholangiocarcinomas		10/120	Fujimoto et al <sup>26</sup>
Colon cancer		3/32	Jiao et al <sup>107</sup>
Pancreatic cancer		12/119	Jones et al <sup>114</sup>
Breast cancer		10/119	
Lung cancer		4/114	
Prostate cancer		2/36	
Glioblastoma		2/23	
Leukemia		3/125	
Medulloblastoma		0/89	
Neuroblastoma		0/34	
		4/71	Sausen et al <sup>15</sup>

**Abbreviation:** ARID, AT-rich interaction domain.

virus (HCV)-associated HCC, while some studies indicate that ARID2 might play a role in infection with the virus. ARID2 is essential for regulation of interferon-induced gene expression, especially *IFITM1*, a tight junction protein that inhibits entry of HCV.<sup>22,28</sup> Viral hepatitis is important in the tumorigenesis of HCC. We can hypothesize that ARID2 prevents HCV infection, leading to its tumor suppressor role in HCV-associated HCC. Further studies should focus in more detail on ARID2 in the pathways of viral carcinogenesis.

## ARID3

The ARID3 subfamily contains three members, ie, ARID3A, ARID3B, and ARID3C.<sup>1</sup> Their genes are located on 19p13.3, 15q24, and 9p13.3, respectively. Their encoding proteins are similar in their amino acid sequences and characterized by extended ARID (with additional alpha-helices at the N- and C-termini of the core ARID).<sup>1,29</sup> The members of this subfamily play a role in embryonic patterning, cell lineage gene regulation, and cell cycle control.

### ARID3A

ARID3A protein is mainly expressed in B-lymphocytes and the testes.<sup>30</sup> Studies have related ARID3A to the p53 tumor suppressor to some degree. A potential p53 binding site was found in the second intron of the *ARID3A* gene.<sup>31</sup> A further study by the same group of investigators found a cooperative

role for ARID3A and p53 in the transcriptional activation of p21, a p53 target gene important in cell cycle arrest.<sup>32</sup> Another study found ARID3A to disrupt cellular protection against RAS<sup>V12</sup>-induced proliferation downstream of the p19/p53 pathway.<sup>33</sup>

There is some evidence that ARID3A can block cell differentiation and promote proliferation, indicating a tumor promoter role for ARID3A. One study found that ARID3A was required to maintain cell survival potential by downregulation of promyelocytic leukemia nuclear bodies.<sup>34</sup> Further research revealed ARID3A to act as a critical antagonist of the p16 retinoblastoma protein (RB) tumor suppressor machinery by regulating the stability of promyelocytic leukemia.<sup>35</sup> However, direct knockdown of human ARID3A resulted in colonies expressing multiple lineage markers, suggesting that repression of ARID3A promoted developmental plasticity.<sup>36</sup> Repression of ARID3A by miR-125b blocked cell differentiation and apoptosis, and increased cell proliferation in B-cell acute lymphoblastic leukemia.<sup>37</sup>

### ARID3B

The testes and leukocytes show the highest levels of ARID3B.<sup>38</sup> The role of ARID3B in cancer remains controversial. Some studies suggest that *ARID3B* tends to act as an oncogene. ARID3B is a target of miR-125a, promoting invasion of ovarian cancer and migration of breast cancer.<sup>39,40</sup>

Coexpression of ARID3B and Mycn has been observed in a proportion of germ cell tumors. ARID3B and Mycn have been shown to cooperate in proliferation of mouse stem cells, with ARID3B avoiding cell death and Mycn driving progression of the cell cycle.<sup>41</sup> Another study reported the opposite, ie, overexpression of full-length ARID3B increased tumor necrosis factor alpha (TNF- $\alpha$ ) levels and TNF-related apoptosis inducing ligand (TRAIL)-induced cell death in ovarian cancer cells.<sup>42</sup>

There might be some factors contributing to this discrepancy. First, ARID3B Sh, a splice form of ARID3B has been demonstrated, overexpression of which did not induce cell apoptosis.<sup>42</sup> The expression levels of full-length ARID3B and ARID3B Sh may together contribute to the effect of ARID3B in human cancer. Second, there has been a study suggesting that cellular localization of ARID3B is required for its function.<sup>43</sup> Different cellular localization of endogenous and exogenous ARID3B may result in different roles in human cancer. Further study is needed to understand the underlying mechanisms of ARID3B in carcinogenesis. Increasing the expression of full-length ARID3B and altering its cellular location may become a novel treatment strategy for cancer.

### ARID3C

ARID3C is a newly discovered member of the ARID3 subfamily. It is expressed preferentially in B lineage lymphocytes. *ARID3C* encodes two isoforms, ie, Brightlike and Brightlike delta 6, that include and exclude the REKLES-encoding exon 6, respectively.<sup>44</sup> No study has focused on the relationship between ARID3C and cancer as yet. Further research is needed to understand ARID3C better.

### ARID4

The ARID4 subfamily has two members, ie, ARID4A and ARID4B.<sup>1</sup> *ARID4A* and *ARID4B* are located on 14q23.1 and 1q42.1-q43, respectively. Their encoding proteins are 40%–50% identical in sequence. They contain ARIDs, Tudor domains, and N-terminal domain in retinoblastoma-binding protein-1 family domains. ARID4A contains an additional LXCXE motif, which is an RB binding motif.<sup>45</sup>

### ARID4A

ARID4A has been found to play a role in cell growth and migration via interaction with pRB and the mSIN3-histone deacetylase (mSIN3-HDAC) complex. ARID4A represses E2F-dependent transcription by recruiting the mSIN3-HDAC complex to pRB family members and plays a central role in

arresting cell growth.<sup>46</sup> Breast cancer metastasis suppressor 1, which suppresses the metastasis of multiple types of human cancer cells, complexes with ARID4A and mSIN3-HDAC, thereby repressing transcription.<sup>47</sup>

However, the role of ARID4A in cancer remains controversial. KASIFLK, a peptide epitope identical to ARID4A, was found to be expressed preferentially in breast cancer cell lines and tissues, indicating that *ARID4A* may be an oncogene.<sup>48</sup> However, another study found *ARID4A* to be a leukemia suppressor gene, with ARID4A-deficient mice showing ineffective hematopoiesis followed by transition to leukemia.<sup>49</sup> In this study, ten of twelve ARID4A<sup>-/-</sup> ARID4B<sup>+/-</sup> mice progressed to acute myeloid leukemia, while only five of 42 ARID4A<sup>-/-</sup> mice did so, indicating that ARID4B might influence the role of ARID4A in carcinogenesis. However, this study was based on an animal model of leukemia, in which the mechanisms may be different from those in solid tumors in humans.

### ARID4B

Like ARID4A, ARID4B has been found to be an mSIN3-HDAC complex-associated protein. The *ARID4B* gene is also known as *breast cancer-associated antigen 1 (BRCAAI)* and is highly expressed in human breast, lung, colon, pancreatic, and ovarian cancers, and in normal testes, but has limited expression in other normal tissues.<sup>50</sup> There is some evidence to suggest its involvement in breast cancer. A causative role of ARID4B in progression of metastatic breast cancer has been observed in cell lines and animal models, as well as in patients.<sup>51</sup> SSKKQKRSHK, a peptide epitope identical to ARID4B, was shown to be associated with prognosis in patients with breast cancer, in whom its serum titer was significantly elevated.<sup>52</sup>

### ARID5

The ARID5 subfamily contains two members, ie, ARID5A and ARID5B. Their genes are located on 2q11.2 and 10q21.2, respectively. ARID5A and ARID5B share more than 70% identity within the ARID domain, but outside this domain their amino acid sequences are not similar.<sup>3</sup>

### ARID5A

ARID5A is widely distributed in human tissue. Its DNA binding activity has been found to be significantly reduced in differentiated cells and it acts as a trans-acting factor in repressing enhancer activity.<sup>53</sup> Studies had found ARID5A to be involved in the inflammatory process.<sup>54,55</sup> An association between ARID5A and cancer has not been reported as yet.

## ARID5B

ARID5B is also widely expressed in human tissue. Histone deacetylase-1, which plays a role in cell proliferation, differentiation, and apoptosis, was found to be associated with ARID5B.<sup>56</sup> Of all the malignant diseases, leukemia is the one most closely linked with ARID5B. Mounting evidence shows that mutations and single nucleotide polymorphisms of *ARID5B* are associated with the development of acute lymphoblastic leukemia and the treatment outcome, and may be associated with acute myeloblastic leukemia in childhood.<sup>57–62</sup>

## JARID1

Jumonji ARID1 (JARID1) is the biggest subfamily, with four members previously named JARID1A through D and now known as lysine (K)-specific demethylase (KDM) 5A through D.<sup>63</sup> Their genes are located on 4q42, 1q32.1, Xp11.22–p11.21, and Yq11, respectively. The name Jumonji (meaning “cross” in Japanese) comes from the morphology produced by the normal neural groove and abnormal grooves on the neural plates of Jumonji mutant mice.<sup>64</sup> The subfamily members contain ARID, Jumonji N, and Jumonji C domains, as well as plant homeodomain and Zf-C5HC2 Zn fingers. Plant homeodomains can bind methylated lysine residues,<sup>65</sup> and all members have been found to be histone demethylases.<sup>66,67</sup> An increasing number of studies have found the JARID1 subfamily to be associated with cancer, especially JARID1A and JARID1B.

## JARID1A

Like ARID4A, JARID1A is also a pRB-binding protein, and binding of JARID1A to pRB promotes cell differentiation.<sup>68</sup> JARID1A interacts physically with RBP-J, which activates transcription of Notch target genes and is crucial for Notch-induced growth and tumorigenic responses.<sup>69</sup> JARID1A protein was found to regulate demethylation of histone H3 lysine 4,<sup>70</sup> and since then, a number of studies have indicated that the demethylase activity of JARID1A is associated with cancer-related signaling pathways. JARID1A protein-mediated demethylation of H3 lysine 4 has been associated with silencing of target genes for retinoblastoma and the Myc/Max/Mad network.<sup>71,72</sup> The histone demethylase activity of JARID1A was also found to be related to tumorigenesis in hematopoietic malignancies and endocrine neoplasia.<sup>73,74</sup> *JARID1A* was identified as the fusion partner of *NUP98* in samples from leukemia patients, and this gene fusion induced acute myeloid leukemia in animal models requiring its demethylase activity.<sup>73,75</sup> Other studies have found that

chronic drug exposure causing an alteration in the chromatin state is associated with JARID1A in drug-tolerant cancer cells.<sup>76,77</sup>

## JARID1B

Sharing 56% overall similarity to JARID1A, JARID1B is a histone demethylase that interacts with several proteins.<sup>78</sup> Unlike other JARID1 subfamily members, JARID1B has limited expression in normal tissue. It has been found to be upregulated in primary breast, prostate, bladder, lung, and esophageal cancers, but downregulated in malignant melanoma.<sup>79–83</sup> JARID1B may promote proliferation of breast cancer cell lines by demethylation of histone H3 lysine 4.<sup>84</sup> JARID1B downregulates breast cancer-1 (BRCA1), which is a tumor suppressor gene.<sup>85</sup> JARID1B downregulates chemokine (C-C motif) ligand 14 (CCL14) which suppresses the angiogenic and metastatic potential of breast cancer cells.<sup>86</sup> It also downregulates genes involved in regulating the M phase of the mitotic cell cycle which induces cells to fail to arrest in G2/M in breast cancer.<sup>85</sup> A dramatic decrease in E2-stimulated tumor growth was observed in nude mice with downregulated JARID1B.<sup>87</sup> In bladder cancer, knock-down of JARID1B suppresses the proliferation of cancer cells and increases the number of cells in sub-G1 phase via the E2F/RB pathway.<sup>81,88</sup> In colorectal cancer, JARID1B-positive cells showed greater tumorigenicity and depletion of JARID1B-induced cellular senescence.<sup>89</sup> However, in melanoma, JARID1B tends to be a tumor suppressor. It has been shown to inhibit proliferation, increase caspase activity, and induce partial cell cycle arrest in G1/0 phase by modulation of pRB.<sup>90</sup> Expression of a set of melanoma-relevant genes was altered after increasing the levels of JARID1B.<sup>91</sup> Interestingly, expression of JARID1B was found to be dynamically regulated in melanoma cells without following a hierarchical cancer stem cell model.<sup>92</sup>

JARID1B seems to play different roles in different malignant tumors. As a histone demethylase, JARID1B is a transcription regulator, but its exact role may depend on the different genes it regulates.

## JARID1C

*JARID1C* mutation has been widely studied in X-linked mental retardation.<sup>93–95</sup> In addition to mental disorders, JARID1C has also been associated with cancer. JARID1C might contribute to tumorigenesis via the transforming growth factor-beta/Smad family member 3 signaling pathway.<sup>96</sup> Inactivating mutations of *JARID1C* have been found in clear-cell renal cell carcinoma specimens;<sup>97</sup>

von Hippel–Lindau<sup>-/-</sup> clear-cell renal cell carcinoma cells with suppressed JARID1C were found to form much larger tumors in a xenograft model, suggesting a tumor suppressor role for JARID1C in clear-cell renal cell carcinoma.<sup>98</sup>

## JARID1D

The evidence presently available suggests that JARID1D contributes to rejection of male tissues by female transplant recipients.<sup>99</sup> There is limited research on the association between JARID1D and cancer. JARID1D is expressed to a similar extent in prostate cancer and benign prostatic hypertrophy tissues.<sup>100</sup> Even though JARID1D is similar to JARID1C in its amino acid sequence, no significant relationship between JARID1D and cancer has been identified as yet.

## JARID2

The JARID2 subfamily contains only one member, which is located on 6p24p23. Its encoding protein has an ARID domain, JmjN and JmjC domains, and a Zf-C5HC2 Zn finger domain.<sup>101</sup> Unlike members of the JARID1 subfamily, JARID2 has histone methyltransferase activity.<sup>102</sup>

Recent studies suggest that JARID2 has a tumor suppressor role. JARID2 protein was found to regulate cell proliferation in a negative manner<sup>103</sup> and to suppress transcription of cyclin D1 by methylation of histone H3-K9.<sup>102</sup> Deletions of *JARID2* have been detected in leukemic transformation of chronic myeloid malignancies.<sup>104</sup> Reticuloendotheliosis virus strain T, an oncogenic retrovirus, promotes cell survival by downregulation of targets that include JARID2.<sup>105</sup>

## Summary

Members of the ARID family have DNA binding ability, are likely to be involved in modification of chromatin structure, and regulate targeted gene transcription positively or negatively.<sup>106</sup> A number of the members of this family have been found to be altered in cancer tissues, at both the DNA and protein levels. Accumulating evidence suggests an important role for the ARID family in the development, progression, and treatment of cancer. Members of this family may play either a tumor promoter or a tumor suppressor role. Interestingly, ARID3B, ARID4A, and JARID1B seem to have conflicting roles in different types of cancer. Their transcription-regulating role may be specific to particular types of cancer and depend on the target gene they regulate. Their signaling pathways remain unclear, and clarifying their biological function may lead to an answer.

The ARID family is divided into subfamilies according to the protein structure of its members. Similar in structure, their roles in human cancer may be influenced by other members of the same subfamily. Members of the ARID1 and ARID2 subfamily are all components of a chromatin regulation complex. ARID1A and ARID2 were both found to be mutated in a study of cholangiocarcinoma.<sup>107</sup> Another study of a series of genes in HCC, including *ARID1A*, *ARID1B*, and *ARID2*, showed that loss-of-function mutations were more enriched in these chromatin-regulating genes than in genes from other areas of the HCC genome.<sup>26</sup> Members of the JARID1 subfamily are all histone demethylases, while JARID2 is a histone methyltransferase, and may have an opposite role to that of members of the JARID1 subfamily. The evidence indicates that these members may be involved in the same cancer-related pathways within ARID1, ARID2, JARID1 and JARID2 subfamilies.

There is little evidence to suggest that members of the ARID3 and ARID4 subfamilies interact with each other in human cancer. However, current research suggests that members of these two subfamilies may interact in pathways other than those for carcinogenesis. ARID3C significantly co-activates ARID3A-mediated immunoglobulin gene transcription.<sup>44</sup> ARID4A and ARID4B both function as transcriptional coactivators for the androgen receptor and RB involved in male fertility.<sup>108</sup> Currently, most of the published studies focus on individual members of the ARID family, and have sometimes yielded conflicting results. Studying subfamily members together may give us a more complete picture of the ARID family.

Recently, several small molecules were found to be JARID1B inhibitors and to inhibit proliferation of cells overexpressing JARID1B.<sup>109</sup> This suggests that the ARID family could be a potential therapeutic target in the treatment of cancer. More studies focusing on the relationship between the ARID family and cancer are needed in the future, and may lead to a new understanding of the prevention, diagnosis, and treatment of cancer.

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## Disclosure

The authors report no conflicts of interest in this work.

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