Morphological Features and Prognostic Significance of ARID1A-Deficient Esophageal Adenocarcinomas

Michael G. Drage, MD, PhD; Mingkhwan Tippayawong, MD; Agoston T. Agoston, MD, PhD; Yifan Zheng, MD; Raphael Bueno, MD; Jason L. Hornick, MD, PhD; Robert D. Odze, MD; Amitabh Srivastava, MD

• Context.—The clinicopathologic and prognostic significance of ARID1A mutation in esophageal adenocarcinoma (EAC) is unknown.

Objective.—To determine the morphological correlates and prognostic significance of ARID1A-deficient EAC.

Design.—One hundred twenty cases of primary EAC were evaluated for a predetermined set of histologic features and immunohistochemistry for ARID1A, p53, and MLH1 performed on EAC, as well as adjacent Barrett esophagus and Barrett esophagus–associated dysplasia, when feasible. Associations between categorical clinicopathologic variables were analyzed by Fisher exact test, and survival analysis was performed by a Cox proportional hazards analysis.

Results.—The study group included 97 men and 23 women (mean age, 66 years). Loss of ARID1A expression was seen in 12 of 120 EACs (10%). ARID1A-deficient tumors showed a strong correlation with a medullary and mucinous phenotype, and 8 of 12 (67%) had at least one feature reminiscent of high microsatellite instability colon carcinomas (mucinous or medullary differentiation, marked intratumoral or peritumoral lymphoid infiltrate). A mutant p53 pattern was present in 52 of 120 EACs (43%) and showed no correlation with ARID1A deficiency ($P > .05$). MLH1 loss was present in only 2 of 120 EACs (2%); both of which were also deficient in ARID1A. ARID1A-deficient EACs showed a trend toward increased risk of nodal metastasis but had no effect on overall patient survival.

Conclusions.—ARID1A-deficient EACs show a phenotype similar to colon cancer with high microsatellite instability but do not appear to have any prognostic significance. Concurrent MLH1 loss is not seen in most ARID1A-deficient tumors, suggesting that ARID1A may be a primary driver of carcinogenesis in a subset of EACs.

(Arch Pathol Lab Med. 2017;141:970–977; doi: 10.5858/arpa.2016-0318-OA)

Eosophageal adenocarcinomas (EACs) are morphologically heterogeneous tumors. This phenotypic diversity is reflected in the heterogeneous molecular pathways described in EACs. Mutations of tumor suppressor genes $TP53$ and $p16$, dysregulation of proto-oncogenes $EGF$, $EGFR$, $TGF$, and $HER2$, and loss of DNA mismatch repair function have all been described. There is also evidence of epigenetic alteration by promoter hypermethylation involving $APC$, $CDH1$, $CDKN2A$, $MGMT$, and $TMEFF2/HPPI$. Recently, whole exome analyses have revealed several novel, recurrent mutations in EACs, including loss-of-function mutations in $ARID1A$, with a prevalence of approximately 10%.

ARID1A (AT-rich interactive domain 1A), also known as BAF250A and SMARCF1, is a member of the switch/sucrose nonfermentable, ATP-dependent family of chromatin-restructuring genes that are involved in epigenetic regulation and are collectively mutated in approximately 20% of all malignancies. The chromatin-remodeling function of these switch/sucrose nonfermentable complexes is essential for the regulation of gene expression, cell proliferation, cell-fate determination, and DNA damage repair. The ARID-DNA interactions are essential for the tumor-suppressor function of $ARID1A$, and inactivation of the gene by somatic mutation or other epigenetic mechanisms leads to tumorigenesis.

Loss-of-function somatic mutations in $ARID1A$ have been described in carcinomas from multiple sites, including the esophagus, stomach, colon, liver, biliary tract, endometrium, ovary, urinary bladder, and pancreas. $ARID1A$ mutations in ovarian cancer have been described in approximately 50% of ovarian clear cell carcinomas and 30% of endometrioid endometrial carcinomas. Moreover, loss of the $ARID1A$ protein expression in Mullerian adenocarcinomas correlates with DNA mismatch-repair enzyme deficiency and is mutually exclusive of $TP53$ mutations, suggesting a distinct pathway of carcinogenesis. The aims of our study were to analyze the morphological and immunophenotypic associations of $ARID1A$ loss in EAC and to determine the prognostic significance of $ARID1A$-deficient EACs.
MATERIALS AND METHODS

Study Group

We searched our archives for all esophagectomies and esophagogastrectomies performed between 1989 and 2011 for esophageal adenocarcinoma. Of the 863 resections, 521 (60%) had received neoadjuvant therapy and were excluded from the study. Of the remaining 342 primary resections, 164 tumors (48%) were centered in the esophagus with or without involvement of the gastroesophageal junction. Complete clinical information and archival slides and paraffin blocks were available for the final 120 tumors (73%) in the study group. Patient demographics and clinical outcome data were obtained by medical chart review, and overall survival was obtained by querying the social security death index. The study was approved by the institutional review board.

Morphological and Immunohistochemical Evaluation

All cases were evaluated for a predetermined set of parameters, including tumor location, tumor size and grade, maximum depth of invasion, lymphovascular and perineural invasion, presence of Barrett esophagus (BE), and the grade of any BE-associated dysplasia. In addition, the presence or absence of tumor-infiltrating lymphocytes and peritumoral lymphoid aggregates was noted. Tumors were classified according to the most recent World Health Organization classification1 and reviewed and restaged using the American Joint Committee on Cancer, 7th edition, staging criteria.24

Representative tumor tissue blocks were selected from each case for immunohistochemical analysis to include EAC as well as background BE and any BE-associated dysplasia, whenever possible. Immunoperoxidase studies were performed on 5-μm sections with antigen retrieval to assess expression of p53 (mouse monoclonal 1767, 1:1200; Beckman Coulter, Atlanta, Georgia), MLH1 (mouse monoclonal, MCL-L-MLH1; 1:75, Leica, Buffalo Grove, Illinois), and ARID1A (rabbit polyclonal, HPA 005456; 1:500, Sigma-Aldrich, St. Louis, Missouri) with automated immunostainers.

ARID1A and MLH1 expression in the tumor cells was scored as deficient when complete loss of expression was present in the entire tissue block. ARID1A-deficient tumors were defined as those having diffuse loss of ARID1A staining with intact nuclear positivity in the stromal cells (hematoxylin-eosin, original magnifications ×12 [A], ×100 [B and C], and ×200 [D]).
tumor with intact staining in adjacent stromal cells, or when a
discrete, confluent focus of complete loss, compatible with a distinct
tumor clone, was present anywhere in the tumor. Similarly, ARID1A
and MLH1 were scored as deficient in background BE and any BE-
associated dysplasia only when complete loss of staining involved
the entire crypt from the crypt base to the surface epithelium, with
retained nuclear staining in the adjacent stromal cells. P53
expression, in EAC and in BE-associated dysplasia, was scored as
a wild-type pattern when only scattered nuclei were positive and as a
mutant pattern when confluent, strong overexpression or complete
absence of staining (null pattern) was seen in the neoplastic cells.25,26

Data Analysis

Fisher exact test was used to compare differences in categorical
variables between ARID1A-deficient and -intact EAC. Differences
in overall survival were analyzed with a Kaplan Meier analysis and
a Cox proportional hazards model computed with the R statistical
programming language (version 2.15.1, R development core 2012;
R Foundation for Statistical Computing, Wien, Austria, http://cran.
r-project.org/). P < .05 was considered statistically significant.

RESULTS

Study Group

The final study group consisted of 97 men (81%) and 23
women (19%), with a mean age of 66 years (range, 30–87
years). The clinical and pathologic features of the study
group are summarized in Table 1. Barrett esophagus,
declared as columnar metaplasia in the distal esophagus
with goblet cells, was seen in 77 of 120 tumors (64%) and
BE-associated dysplasia adjacent to carcinoma was pre-
sent in 88 of 120 cases (73%). In the tumor tissue blocks

| Table 1. Patient Demographics and Tumor Characteristics of Study Group, n = 120 |
|-----------------------------|-----------------------------|
| Characteristic              | Result                      |
| Age, y, mean (range)        | 66 (30–87)                  |
| M:F ratio                   | 4.2                         |
| Tumor size, cm, mean (range)| 3.1 (0.2–18)                |
| Histologic type, No. (%)    |                             |
| NOS                         | 108 (90.0)                  |
| Mucinous                    | 7 (5.8)                     |
| Medullary                   | 7 (5.8)                     |
| Signet ring cell            | 2 (1.7)                     |
| Histologic grade, No. (%)   |                             |
| Low                         | 41 (34.2)                   |
| High                        | 79 (65.8)                   |
| Other features, No. (%)     |                             |
| IELs, >3/HPF                | 20 (16.7)                   |
| LVI                         | 46 (38.3)                   |
| PNI                         | 34 (28.3)                   |
| Tumor stage, No. (%)        |                             |
| 1a                          | 31 (25.8)                   |
| 1b                          | 39 (32.5)                   |
| 2                           | 12 (10.0)                   |
| 3                           | 38 (31.7)                   |
| Lymph node stage, No. (%)   |                             |
| 0                           | 80 (66.7)                   |
| 1                           | 22 (18.3)                   |
| 2                           | 12 (10.0)                   |
| 3                           | 6 (5.0)                     |
| Duration of follow-up, y, mean (range)| 5.2 (<1–22.4) |
| Overall mortality, No. (%)  | 67 (55.8)                   |

Abbreviations: HPF, high-power field; IEL, intraepithelial lymphocyte;
LVI, lymphovascular invasion; NOS, not otherwise specified; PNI, perineural invasion.
selected for immunohistochemical analysis, 43 of 120 (36%) contained adjacent, nondysplastic BE, and 17 of 120 (14%) and 47 of 120 (39%) contained foci of adjacent BE-associated low- and high-grade dysplasia, respectively.

**Morphological and Immunohistochemical Data**

Loss of ARID1A staining was seen in 12 of 120 EACs (10%), with complete loss of staining in the entire tumor in 10 of 12 cases (83%) and in a discrete, confluent focus in 2 of 12 (17%) cases. In 1 of these latter 2 cases, loss of ARID1A staining was restricted to the poorly differentiated component, with intact staining in the conventional glandular component. Loss of ARID1A in EAC was associated with a distinctive morphology reminiscent of microsatellite instability high (MSI-H) colorectal adenocarcinomas. A medullary phenotype, with solid architecture and increased tumor-infiltrating lymphocytes; a conventional gland-forming carcinoma, with increased tumor-infiltrating lymphocytes or an exophytic, tubulovillous growth pattern with copious, extracellular mucin, consistent with mucinous adenocarcinoma; or prominent, peritumoral, lymphoid aggregates (Figure 1, A through C) were characteristic of ARID1A-deficient EAC. At least one of those features was present in 6 of 12 ARID1A-deficient tumors (50%), with loss of staining throughout the tumor, compared with only 5 of 108 of the ARID1A-intact tumors (5%; \( P < .001 \)). The remaining 4 tumors with complete ARID1A loss were conventional gland-forming adenocarcinomas (Figure 1, D), with no tumor-infiltrating lymphocytes or peritumoral lymphoid aggregates.

Loss of MLH1 expression was present in 2 of 12 cases (17%) with ARID1A loss but in none of the ARID1A-intact tumors. Interestingly, in one case, the MLH1 loss was noted in both the carcinoma and in the adjacent dysplasia, whereas the ARID1A loss was seen in the carcinoma component only (Figure 2). The other case with concordant MLH1 and ARID1A loss showed diffuse loss of MLH1 in the entire tumor and a discrete, confluent focus of ARID1A-deficient tumor cells.

ARID1A and MLH1 staining was patchy in nondysplastic and dysplastic BE, and negative surface epithelial staining was quite frequently associated with intact staining in the

---

**Figure 3.** A and B, ARID1A expression in nondysplastic Barrett esophagus is typically heterogeneous with consistent staining of the crypt bases and reduced or absent expression toward the surface epithelium. C and D, Loss of ARID1A staining was not seen in any focus of nondysplastic Barrett esophagus in our study and in only one focus of low-grade dysplasia (hematoxylin-eosin, original magnification \( \times 100 \) [A and C]; ARID1A, original magnification \( \times 100 \) [B and D]).
crypt base (Figure 3, A and B). Loss of ARID1A staining was not seen in any of the 43 foci of nondysplastic BE adjacent to the carcinoma. In the 64 cases (53%) with BE-associated low- or high-grade dysplasia, loss of ARID1A was seen in only one focus (1.5%) of low-grade dysplasia (Figure 3, C and D) separate from the main tumor mass. Thus, in most cases, loss of ARID1A was restricted to the carcinoma component only.

A mutant p53 staining pattern was seen in 52 of 120 EACs (43%), as well as in 3 of 17 foci (18%) of low-grade and 15 of 47 foci (32%) of high-grade dysplasia. A mutant p53 pattern of staining was not seen in any focus of nondysplastic BE. Six of 12 (50%) of the ARID1A-deficient tumors also showed a mutant staining pattern for p53 (Figure 4, A through D).

**Clinicopathologic Correlates and Prognostic Significance of ARID1A Loss in EAC**

As mentioned above, loss of ARID1A expression in EAC showed a significant association with a medullary and mucinous histology. All 3 EACs with a medullary phenotype and 3 of 7 mucinous EACs (43%) were ARID1A-deficient compared with only 6 of 110 conventional gland-forming adenocarcinomas (5.4%; Table 2). A trend was noted for increased risk of nodal metastasis in ARID1A-deficient tumors but was not statistically significant ($P = .06$). The overall survival of patients with ARID1A-deficient EAC was similar to that of those with intact ARID1A expression on both a Kaplan Meier (Figure 5; $P = .10$) and Cox proportional hazards analysis (Table 3).

**DISCUSSION**

ARID1A functions as a tumor suppressor and has an important role in carcinogenesis in many organs. There is a strong correlation between loss of ARID1A expression and DNA mismatch repair deficiency in carcinomas involving the stomach and colon, suggesting that ARID1A loss may be a secondary phenomenon related to impaired DNA repair and not a primary driver of carcinogenesis. In our study, loss of ARID1A expression was present in 10% (12 of 120) of EACs and the majority of ARID1A-deficient EACs showed morphologic features similar to microsatellite

![Figure 4](https://example.com/image4.jpg)

**Figure 4.** Loss of ARID1A expression is not exclusive to the p53 mutant pattern of staining in esophageal adenocarcinomas. A poorly differentiated adenocarcinoma with tumor infiltrating lymphocytes (A) shows loss of ARID1A expression (B), retained MLH1 expression (C), and diffuse, strong positivity for p53 immunohistochemistry (D) (original magnification ×40 [A through D]).
unstable colorectal adenocarcinomas. Only 2 of 12 tumors (17%) with ARID1A loss showed a concurrent loss of MLH1, whereas a mutant p53 pattern was seen in 6 of 12 (50%) of the ARID1A-deficient tumors. These findings suggest that ARID1A is a primary driver of carcinogenesis in a subset of EACs and, unlike Müllerian carcinomas, abnormal ARID1A and p53 expression are not mutually exclusive in EAC.

Loss of DNA mismatch repair proteins with MSI-H occurs in only 3% to 6% of all EACs. The MSI-H esophageal adenocarcinomas are morphologically heterogeneous but may show medullary or mucinous differentiation or marked tumor-infiltrating lymphocytes, similar to their colorectal counterparts. The association between ARID1A loss and DNA mismatch repair protein deficiency has been reported in gastric, colorectal, and Müllerian adenocarcinomas and shows some interesting site-specific correlations. ARID1A mutation or loss of protein expression in gastric cancer shows a strong correlation with Epstein-Barr virus infection and microsatellite instability. ARID1A is predominantly mutated by indels involving short mononucleotide repeats in MSI-H gastric carcinomas, but ARID1A mutations in microsatellite-stable gastric cancer seldom involve similar indels and are most often single-nucleotide variations, comprising nonsense or missense mutations. Similar findings have

| Variable                  | Total, No. (%), (n = 120) | ARID1A Deficient, No. (%), (n = 12) | ARID1A Retained, No. (%), (n = 108) | OR*  | P*  |
|---------------------------|---------------------------|-------------------------------------|-------------------------------------|------|-----|
| Age ≥65 y                 | 72 (60)                   | 65 (60)                             | 0.93                                | >.99 |
| Male                      | 97 (81)                   | 86 (80)                             | 2.81                                | .46  |
| Mid/proximal location     | 4 (3)                     | 2 (2)                               | 9.8                                 | .06  |
| Tumor size, ≥2.0 cm       | 68 (57)                   | 61 (56)                             | 1.1                                 | .24  |
| High tumor grade          | 79 (66)                   | 68 (63)                             | 5.34                                | .10  |
| Histologic type           |                           |                                     |                                     |      |
| NOS                       | 110 (92)                  | 6 (50)                              | 0.04                                | <.001|
| Medullary                 | 3 (3)                     | 0                                   | >99                                 | .001 |
| Signet ring cell          | 2 (2)                     | 2 (2)                               |                                     | .81  |
| IELs, >3/HPF              | 19 (16)                   | 3 (25)                              | 1.92                                | .40  |
| PTL                       | 28 (23)                   | 23 (21)                             | 2.64                                | .15  |
| LVI                       | 45 (38)                   | 42 (39)                             | 0.47                                | .36  |
| PNI                       | 33 (28)                   | 29 (27)                             | 1.22                                | .75  |
| pT stage, ≥1b             | 88 (73)                   | 78 (72)                             | 1.92                                | .51  |
| pN stage, ≥1              | 39 (33)                   | 32 (30)                             | 3.33                                | .06  |
| High stage, ≥II B         | 52 (43)                   | 44 (41)                             | 2.91                                | .12  |
| MLH1 deficient            | 2 (2)                     | 0                                   | >99                                 | .10  |
| p53 mutant pattern        | 52 (43)                   | 46 (43)                             | 1.35                                | .76  |
| Overall mortality         | 66 (55)                   | 57 (53)                             | 2.68                                | .22  |

Abbreviations: HPF, high-power field; IEL, intraepithelial lymphocytes; LVI, lymphovascular invasion; NOS, not otherwise specified; OR, odds ratio; PNI, perineural invasion; PTL, peritumoral lymphoid aggregates.

* Fisher exact test for univariate comparison between ARID1A-deficient and -intact esophageal adenocarcinoma.

Figure 5. Kaplan-Meier analysis of overall survival among patients with esophageal adenocarcinoma with retained or deficient ARID1A expression shows no difference in prognosis.
also been reported in colorectal carcinoma.22 Knockdown of ARID1A leads to inhibition of Fas-mediated apoptosis,22 and it has been speculated that selection for ARID1A mutations in MSI-H tumors may be due to its ability to inhibit apoptosis and thereby promote immune evasion from the abundant tumor-infiltrating lymphocytes that are a feature of microsatellite-unstable gastric carcinomas.31 In contrast, MSI-H endometrial carcinomas do not show indels of short repeats within ARID1A of MSI-H gastric cancer is 12- to 60-fold higher than the global background somatic indel rate in mononucleotide repeats of similar length in other genes.31 This finding indicates preferential selection of a driver gene in MSI-H gastric carcinomas and is similar to other genes, such as TGFBR2, which are selected in MSI-H colon cancer.34 In addition, mutations in the switch/sucrose nonfermentable family of chromatin-remodeling genes ARID1A, SMARCA4, and ARID2 also occur in about 20% of microsatellite-stable EACs, supporting the role of ARID1A as an independent tumor-suppressor pathway in esophageal carcinogenesis.13 This is further supported by the reports of ARID1A mutations not only in EACs but also in a subset of nondysplastic BE and BE-associated dysplasia.35

Our findings support the role of switch/sucrose nonfermentable chromatin regulators as important tumor suppressor genes36 and highlight some features that distinguish ARID1A-deficient carcinomas in the esophagus from similar tumors at other sites. An inverse relationship has been reported between ARID1A and TP53 mutations in gastric and colorectal carcinomas.22,30,31 Similarly, TP53 mutations are uncommon in ovarian clear cell carcinomas and endometrioid endometrial carcinomas that carry ARID1A mutations, whereas ovarian serous carcinomas that typically harbor TP53 mutations seldom show concurrent mutations in ARID1A.23 Interestingly, there was no difference in prevalence of a mutant p53 pattern in ARID1A-proficient (52 of 108; 48%) and ARID1A-deficient (6 of 12; 50%) tumors (P = .55). Similar findings were reported in a prior small series of EACs using next-generation sequencing, in which 10 of 13 ARID1A-mutant EACs (77%) demonstrated concurrent TP53 mutations.13

Loss of ARID1A has been shown in precursor lesions adjacent to carcinomas at various sites,37,38 suggesting that it is an early event in carcinogenesis. Similarly, loss of ARID1A expression was previously reported in 5% of nondysplastic BE, with increasing prevalence in BE with low- and high-grade dysplasia.30 However, in our study, loss of ARID1A was restricted to foci of carcinoma, and only one focus of low-grade dysplasia showed complete, confluent loss of ARID1A staining. The reason for this discrepancy may be the strict definition used in our study to define ARID1A loss in nondysplastic and dysplastic epithelium. As illustrated in Figure 4, ARID1A staining in nondysplastic and dysplastic BE consistently shows a heterogeneous pattern and a significant reduction in the intensity of staining toward the surface epithelium. The latter finding is similar to that seen in DNA mismatch repair immunohistochemistry in healthy colonic mucosa. The similarity in reported prevalence of ARID1A mutations13,14 and the loss of protein expression in our cohort suggests that the strict criteria used in our study to define ARID1A loss were appropriate. A precise correlation of ARID1A mutational status and protein expression in metaplastic and dysplastic background epithelium was beyond the scope of this study in which our primary aim was to determine the morphological correlates and prognostic significance of ARID1A loss in EAC.

| Risk Factor | Dead, No./Risk Factor | Present, No. (%) | HR | 95% CI | P |
|-------------|-----------------------|------------------|----|--------|---|
| Age, ≥65 y  | 43/72 (60)            | 1.75             | 1.043–2.930 | .03 |
| Male        | 52/97 (54)            | 0.75             | 0.418–1.334 | .32 |
| Location (mid/proximal) | 2/3 (67) | 1.16 | 0.283–4.761 | .84 |
| Tumor size, ≥2.0 cm | 48/66 (73) | 3.31 | 1.93–5.70 | <.001 |
| Poor differentiation | 27/36 (75) | 2.56 | 1.560–4.209 | <.001 |
| ARID1A deficient | 9/12 (75) | 1.82 | 0.893–3.686 | .10 |
| ARID1A proficient | 53/72 (73) | 1.75 | 1.043–2.930 | .03 |

Abbreviations: HPF, high-power field; HR, hazard ratio; IELs, intraepithelial lymphocytes; LVI, lymphovascular invasion; PNI, perineural invasion; PTL, peritumoral lymphoid aggregates.
tional consequences. Secondly, we used primary resections to ensure we had adequate tissue material to evaluate ARID1A expression in EAC and in background columnar mucosa. The lack of prognostic significance for ARID1A-deficient tumors may be due to the small number of EACs with ARID1A loss in our study. Moreover, the prognostic findings may not be applicable to all patients with EAC because most cases are now treated with neoadjuvant therapy followed by surgery.

In summary, loss of ARID1A expression is seen in about 10% (12 of 120) of EACs, and most of those tumors show features similar to those described in MSI-H colorectal carcinomas. The ARID1A-deficient EACs are also more likely to show loss of MLH1 compared with ARID1A-intact tumors. The prevalence of a mutant p53 pattern is similar in EAC with and without the loss of ARID1A. Finally, in primary resections for EAC, loss of ARID1A expression carries no prognostic significance.

References

1. Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO classification of Tumours of the Digestive System, 4th ed. Lyon, France: IARC Press; 2010. 

2. Farris AB III, Demicco EG, Le, LP, et al. Clinicopathologic and molecular profiles of microsatellite unstable Barrett esophagus-associated adenocarcinoma. 

3. Falkenback D, Johansson I, Halvarsson B, Nilbert M. Defective mismatch repair as a minor tumorigenic pathway in Barrett esophagus-associated adenocarcinoma. Cancer Genet Cytogenet. 2005;157(1):82–86.

4. Bian YS, Osterheld MC, Bosman FT, Benhattar J, Fontelet C. p53 gene mutation and protein accumulation during neoplastic progression in Barrett's esophagus. Mod Pathol. 2001;14(5):397–403.

5. Mokrowiecka A, Wierzchniewska-Lawska A, Smolarz B, Romanowicz-Makowska H, Malecka-Panas E, p16 gene mutations in Barrett's esophagus in adenocarcinoma. 

6. Menke V, Pot RG, Moons LM, et al. Functional single-nucleotide polymorphism of epidermal growth factor is associated with the development of Barrett's esophagus and esophageal adenocarcinoma. J Hum Genet. 2012; 57(1):26–32.

7. Marx AH, Zielinski M, Kowitz CM, et al. Homogeneous EGFR amplification defines a subset of aggressive Barrett's adenocarcinomas with poor prognosis. Histopathology. 2010;57(3):418–426.

8. Lagarde SM, ten Kate FJ, Richel DJ, Offerhaus GJ, van Lanschot JJ. Human cancers. 

9. Prins MJ, Ruurda JP, ten Diest PJ, van Hillegersberg R, ten Kate FJ. Evaluation of the HER2 amplification status in esophageal adenocarcinoma by conventional and automated FISH: a tissue microarray study. J Clin Pathol. 2014; 67(1):26–32.

10. Kulke MH, Thakore KS, Thomas G, et al. Microsatellite instability and hMLH1/hMSH2 expression in Barrett esophagus-associated adenocarcinoma. Cancer. 2001;91(8):1451–1457.

11. Muzeau F, Fløjou JF, Belghiti J, Thomas G, Hamelin R. Infrequent microsatellite instability in oesophageal cancers. Br J Cancer. 1997;75(9):1336–1339.

12. Sato F, Meltzer SJ. CpG island hypermethylation in progression of esophageal and gastric cancer. Cancer 2006;107(3):483–493.

13. Dunlop CG, Stojanov P, Peng S, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nat Genet. 2013;45(5):478–486.

14. Chong IY, Cunningham D, Barber LJ, et al. The genomic landscape of oesophageogastric junctional adenocarcinoma. J Pathol. 2013;231(3):301–310.

15. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS One. 2013;8(11):e75119.

16. Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and swi/swi complexes during oncogenic transformation [published correction appears in Cancer Cell. 2011;19(1):153]. Cancer Cell. 2010;18(4): 316–328.

17. Zhang X, Sun Q, Shan M, et al. Promoter hypermethylation of ARID1A gene is responsible for its low mRNA expression in many invasive breast cancers. PloS One 2013;8(1):e53931.

18. Shain AH, Giacomini CP, Matsukuma K, et al. Convergent structural alterations define switch/sucrose nonfermentable (SWI/SNF) chromatin remodeler as a central tumor suppressive complex in pancreatic cancer. Proc Natl Acad Sci U S A. 2012;109(5):E522–E529.

19. Jones S, Wang TL, Shih IeM, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science. 2010; 330(6001):228–231.

20. Guan B, Mao TL, Panagantiki PK, et al. Mutation and loss of expression of ARID1A in uterine low-grade endometroid carcinoma. Am J Surg Pathol. 2011; 35(5):625–632.

21. Allo G, Bernardini MQ, Wu RC, et al. ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas. Mod Pathol. 2014;27(2):255–261.

22. Chou A, Toon CW, Clarkson A, et al. Loss of ARID1A expression in colorectal carcinoma is strongly associated with mismatch repair deficiency. Hum Pathol. 2014;45(8):1697–1703.

23. Bosse T, Ter Haar NT, Seeger LM, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. Mod Pathol. 2013;26(11):1532–1535.

24. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Troisi A, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

25. Lassus H, Lemenen A, Lundin J, Lehtovirta P, Butzow R. Distinct subtypes of serous ovarian carcinoma identified by p53 determination. Gynecol Oncol. 2003;91(3):504–512.

26. Yemelyanova A, Vang R, Kshirsagar M, et al. Immunohistochemical staining patterns of p53 can serve as a surrogate marker for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. Mod Pathol. 2011;24(9):1248–1253.

27. Wu RC, Wang TL, Shih IeM. The emerging roles of arid1a in tumor suppression. Cancer Biol Ther. 2014;15(6):655–664.

28. Inada R, Sekine S, Taniguchi H, et al. ARID1A expression in gastric adenocarcinoma: Clinicopathological significance and correlation with DNA mismatch repair status. World J Gastroenterol. 2013;19(7):2159–2166.

29. Abe H, Maeda D, Hino R, et al. ARID1A expression loss in gastric cancer: pathway-dependent roles with and without Epstein-Barr virus infection and microsatellite instability. Virchows Arch. 2012;461(4):367–377.

30. Zang ZJ, Cutcutache I, Poon SL, et al. Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. Nat Genet. 2012;44(5):570–574.

31. Wang K, Kan J, Yuen ST, et al. Exome sequencing identifies frequent mutation of arid1a in molecular subtypes of gastric cancer. Nat Genet. 2011; 43(12):1219–1223.

32. Luo B, Cheung HW, Subramanian A, et al. Highly parallel identification of essential genes in cancer cells. Proc Natl Acad Sci U S A. 2008;105(51):20380–20385.

33. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma [published correction appears in Nature. 2013;500(7461):2421]. Nature. 2013;497(7447):67–73.

34. Markowitz S, Wang J, Myeroff L, et al. Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. Science. 1995; 268(5215):1336–1338.

35. Streppel MM, Mata S, DelaBastide M, et al. Next-generation sequencing of endoscopic biopsies identifies arid1a as a tumor-suppressor gene in Barrett's esophagus. Oncogene. 2014;33(13):347–357.

36. Huang J, Zhao YL, Li Y, Fletcher JA, Xiao S. Genomic and functional evidence for an arid1a tumor suppressor role. Gene Chromosomes Cancer. 2007; 46(8):745–750.

37. Yamamoto S, Tsuda H, Takano M, Tamai S, Matsubara O. Loss of ARID1A protein expression occurs as an early event in ovarian clear-cell carcinoma development and frequently coexists with PIK3CA mutations. Mod Pathol. 2012; 25(4):613–624.

38. Ayyan A, Mao TL, Seckin T, et al. Loss of ARID1A expression is an early molecular event in tumor progression from ovarian endometriotic cyst to clear cell and endometrioid carcinoma. Int J Gynecol Cancer. 2012;22(8):1310–1315.