# Bronchiolar Adenoma with *ERBB2* exon 20 insertion: report of four cases and review of the literature

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**Research**

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# Abstract

*Objectives:* Ciliated muconodular papillary tumor (CMPT) is a rare peripheral lung tumor and is considered to be a subtype of Bronchial Adenoma (BA). Although recent studies have suggested that BA belongs to a neoplastic disease, the complete histogenesis of BA is not fully understood and molecular data is limited.

*Methods:* We demonstrated clinicopathologic features of four cases of BA and performed immunohistochemical and next generation sequencing to characterize its molecular features. Besides, a review of previous literature was done to comprehensively conclude the molecular characteristic of this disease.

*Results:* We found *ERBB2, EGFR, BRAF* and *AKT1* mutations in BAs. It's the first time that *ERBB2* exon 20 insertion has been reported in BA.

*Conclusion:* BA is a rare pulmonary disease mainly affected elderly Asian patients. More and more abnormal molecular changes were observed, which confirmed the neoplastic nature of BA. However, it also raise the debate about BA's biological behavior.


# Introduction

Ciliated muconodular papillary tumor (CMPT) is newly recognized peripheral lung disorders, which was first described in 2002 by Ishikawa et al []. CMPT was once considered as a very rare tumor, mainly affected the East Asia patients. But in recent years, many cases have been reported with the increasing recognition of this entity [2–26]. Kamata reported 10 cases in 2015[6], and then both Chang (Western country cohort) [18] and Zheng [19] reported more than 20 cases in 2018. So far, nearly 100 cases have been reported in the English literatures and most of these patients are in East Asia countries. So this tumor may not be as rare as they are once believed.

CMPTs often affect middle-aged to elderly adults, and consist of ciliated columnar cells, mucous cells and basal cells. The entity is commonly surrounded by extracellular mucin pools in the peripheral lung. Some cases did not fit all diagnostic criteria, such as absent papillary architecture or lack of mucinous and/or ciliated cells, but shared the histological feature of bilayered bronchiolar-type proliferation and continuous layer of basal cells, which were termed as "non-classic" CMPTs by Zheng et al.[19]. Moreover, both Zheng et al.[19] and Chang et al.[18] have found these lesions also shared genomic abnormalities. Therefore, Chang et al.[18] proposed a concept of Bronchiolar Adenoma (BA) in 2018. In addition, they sub-categorized BA into 2 groups: proximal-type and distal-type, according to morphologic and immunohistochemistry (IHC) grounds. Hence, classic CMPT only represent a subset of proximal-type BA.

Until now, many evidence shown that BA is a neoplastic disease, but the histogenesis and biological behavior is still unknown and molecular data is limited. Recent studies have identified *BRAF, ALK, EGFR,*

*KRAS, HRAS* and *AKT1* mutations in BA [7,8,13–16,18,19,25,26]. Among them, the most commonly driver mutations are $BRAF^{V600E}$ mutations.

Here we report four cases of BA. All the cases were performed molecular analysis by next-generation sequencing (NGS) and identified *ERBB2, BRAF, AKT1* and *EGFR* gene mutations. To our knowledge, this is the first time that *ERBB2* mutation has been found.

# Materials And Methods

### Clinical samples

The four cases were diagnosed in West China Hospital of Sichuan University between 2017 and 2019. Clinical data were extracted from the hospital's electronic medical records. The samples were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). The clinical and pathological records were analyzed retrospectively, and histological analysis was performed on the surgically-resected specimens.

### Immunohistochemistry analysis

Immunohistochemical analysis was performed on paraffin-embedded sections using the following primary antibodies: CK7 (clone RN7, BIO), CK20 (clone EP23，BIO)，TTF-1 (clone 8G7G3/1, ZECA), p63 (clone UMAB4, BIO), MIB-1 (clone MIB-1, DAKO). All staining was performed on Leica Bond-Max or Roche Ventana. PBS was routinely used as a negative control.

### Isolation of genomic DNA

Genomic DNA was extracted from paraffin-embedded tissue blocks by using the QIAamp DNA FFPE kit (Qiagen, German). The concentration and quality was determined using the ScanDrop 200 spectrophotometer (Analytik Jena, Germany), and the optical absorbance of wavelength 260nm and wavelength ratio of wavelength 260-280nm were calculated.

### Gene mutation analysis

All the cases underwent 56 genes (including *AKT1,ALK1, ARAF, ATM, BIM, BRAF, BRCA1, BRCA2, CCND1, CDK4, CDK6,CDKN2A, CTNNB1, CYP2C19, CYP2D6, CYP3A4, DDR2, DPYD, EGFR,ERBB2, ERBB3, ERBB4, FGF19, FGF3, FGF4, FGFR1, FGFR2, FGFR3,FLT3, HRAS, JAK1, JAK2, KDR, KIT, KRAS, MAP2K1, MET, MTOR,NRAS, NRG1, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PCTH1,PTEN, RAF1, RET, ROS1, SMO, STK11, TP53, TSC2, TSC1*, and *UGTIA1*) analysis on Illumina Genome Analyzer (San Diego, California) by NGS platform. The procedures are conducted as previously described [27]. Briefly, (1) library preparation; (2) Cluster generation; (3) Cluster amplification and sequencing.

# Results

## Clinical characteristics

Three of the four patients were female and one was male, the age range from 32 to 65 years. The male patient had a history of smoking, while all the female patients hadn't. All the four patients were found to have pulmonary nodules by physical examination. Computed tomography (CT) imaging shows solid or ground-glass nodules in the peripheral lung. The volume of all of our cases was less than 1 cm in diameter.

All of them received wedge resections either in West China Hospital of Sichuan University or other hospitals. The detailed clinicopathological features are shown in table 1. Some cases were misdiagnosed at first. Case 2 was originally diagnosed as atypical alveolar epithelial hyperplasia and suspected to adenocarcinoma in frozen section. Case 3 was misdiagnosed as mucinous adenocarcinoma. Two patients had combined diseases: case 1 had metastatic invasive ductal carcinoma of the breast and adenocarcinoma in situ (AIS) of the lung, whereas case 3 had a minimally invasive adenocarcinoma (MIA) of the lung.

## Pathological features

The gross examination of the four cases showed a well-demarcated gray-white solid masses. Microscopically, our cohort consisted with two proximal-type and two distal-type of BAs. The tumors were composed of various proportions of ciliated columnar cells, mucus cells and continuous basal cells with surrounding mucous lakes (Fig.1 A). The nuclear atypia was mild, mitosis and necrosis were not found. Muscular arteries are often seen in the center of the tumor, indicating that the tumor localized around the bronchioles.

One proximal-type case showed predominantly papillary architectural patterns (Fig.1 B) and the other showed predominantly adherence architectural patterns with occasionally papillary structure (Fig.1 C & D). The ciliated columnar cells were easily found in this subtype. The distal-type cases revealed adherence and glandular architecture, the papillary structure was not obvious, and lack of ciliated columnar cells.

Both the proximal and distal growth patterns revealed a skipping growth pattern (Fig.1 A) at the edge of the tumor, and the micropapillary tufts (Fig.1 B) were apparently detached into the alveolar cavities. In addition, we found fibrous tissue hyperplasia and lymphocytes, plasma cells infiltrating in focal areas (Fig.1 D).

## Immunohistochemistry

All tumor cells were positive for CK7 (Fig.1 E) but negative for CK20 (Fig.1 F), while basal cells were positive for P63 (Fig.1 G). Consistently, the Ki67 index was less than 5%, indicating relatively indolent biological behavior. For the proximal-type, a few ciliary cells and basal cells were weakly positive for TTF-1, whereas distal-type were strongly positive for it.

### Molecular analysis

All cases were performed NGS sequencing to profile the molecular abnormalities (Table 1). Precisely, case 1 harbored *ERBB2* exon 20 insertion in BA. Case 2 was detected *EGFR* mutations (deletion L747_S752). Case 3 was negative. Case 4 had $BRAF^{V600E}$ and *AKT1*-p. E17K mutations.

However, NGS was not only performed on the sample of BA, but also on the tissues of metastatic breast cancer and AIS of the lung for case 1. As a result, multiple gene mutations had been detected in the breast cancer metastatic focus including *KRAS-G12U* (48.82%), *PIK3CA-H1047R* (45.53%), *TP53*-ex5-V173L (42.76%), *ATM*-ex18-C907F (27.64%) and increase of *KRAS* copy number (CN=3.51). In contrast, there was no *ERBB2* mutation was found, which means that the *ERBB2* exon 20 insertion was unique for BA. Unfortunately, tissue of adenocarcinoma in situ was unable to extract DNA because of limited sample.

## Discussion

BA is a newly entity defined by Chang et al.[18], which is a more extensive terminology than CMPT. It has not been well recognized by pathologists and could not be classified according to 2015 WHO classification system [28]. So far, 26 English literatures about this family of neoplasms are searched, plus our cases, there are 99 cases have been reported. The clinicopathologic features of these cases were summarized in Table 2.

BA often affect middle-aged to elderly adults from East Asia (77/99, 77.8%), with the median age of 64 years old (range from 19 to 84 years old). Expect one patient is 19 years' old [10], the remaining are range from 31 to 84 years old. The incidence rate of male and female was similar, close to 1:1.3. It occurs almost exclusively in peripheral lung. Chest computed tomography (CT) shows peripheral solid, part-solid nodules or ground-glass opaque (GGO) with an irregular border, part of the patients show a central cavity on the CT images [3,6,9,10,16,17,19,21,23,24]. The median diameter was 0.9cm (range 0.2 to 4.5cm), mostly between 0.2 to 2cm. Only two cases were 3.5cm and 4.5cm in diameter [11].

Grossly, the tumor is a pale mucinous nodule with irregular border and sometimes a central cavity in resected specimens. Histologically, BA displays a diverse morphological pattern such as adherence, glandular, papillary, micropapillary architecture, with abundant mucin around the tumor and the mucinous pool spreading into adjacent alveolar spaces. The tumor mainly composed of mucous cells and basal cells, whereas ciliated columnar cells could present or absent. A few cells showed apical cytoplasmic snouts like club (Clara) cells [18]. The tumor cells lacked nuclear atypia, mitosis, and necrosis. Chang et al. reported 25 lesions from 21 patients [18], most lesions were flat and only 7 lesions contained focal papillary architecture. They categorized the lesions into 2 groups: proximal-type and distal-type based on the morphologic and IHC similarity with the bronchiolar structures. The classical CMPT belongs to the proximal-type BA and the TTF1 staining is negative or weakly positive. But for distal-type BAs, TTF1 and Napsin A showed diffuse positivity.

Some cases revealed discontinuous (skipping) growth pattern which is resembling Tumor Spread Through Air Spaces (STAS) and micropapillary tufts detached into the alveolar cavity which is similar to the micropapillary adenocarcinoma. Chang et al. hypothesized that these cells being interconnected with each other in 3-dimensional spaces [18], because these skip lesions do not extend away for more than a few alveoli. Anyway, the basal cells were always present. However, these microscopic features of BA may be an extremely diagnostic challenge for pathologists, especially for intraoperative frozen sections.

Immunohistochemically, the three types of cells are strongly expressed CK7, always express CEA, HNF4α, MUC1, MUC5B and MUC5AC [3,5,9,11,12,15], consistent with the primary lung adenocarcinoma. The ciliated columnar cells are focally positive for MUC5AC, while the mucous cells lacked staining for MUC5AC. Some of the cases are positive membrane staining for β-catenin [9]. The tumor cells always negative for CK20, CDX-2, P53, MUC2 and MUC6 and have a low ki-67 index, usually less than 10% (often less than 1%) [2,3,5,9-12,15,17]. The basal cells are positive for p63 and CK5/6.

Previous reported gene mutations of BA were summarized in Table 3. Until now, several molecular alterations have been identified in BAs, including *BRAF, EGFR, KRAS, ALK* rearrangement, *AKT1,* and *HRAS* (Table 3). Consistent with them, we performed molecular analysis on the 4 cases and found *EGFR, BRAF* and *AKT1* mutations. Importantly, *ERBB2* mutation was first described in our present cohort. As showed in Figure 2, the most common mutation was $BRAF^{V600E}$ (38%), followed by *EGFR* (15%), *KRAS* (12%), *ALK* rearrangement (4%), *AKT1* (4%), *HRAS* (1%), $BRAF^{G606R}$(1%) and *ERBB2* (1%).

Again, it's the first time that *ERBB2* exon 20 insertion has been reported in BA. Human epidermal growth factor receptor 2 (*HER2 /ERBB2*) is a receptor tyrosine kinase of the *ERBB* family, which plays a significant role in cancer development and progression, especially in breast, ovarian and gastric cancers. Overexpression of HER2 protein associated with poor prognosis. Recent research shows that *HER2* mutations is a distinct subset of lung adenocarcinomas. *ERBB2* mutations are exclusive to *EGFR/KRAS/ALK* mutations, representing 6% of *EGFR/KRAS/ALK* negative specimens of non-small cell lung cancers (NSCLC). In NSCLCs, the most common mutations of *ERBB2* are in-frame insertions in exon 20, and were more frequent among non-smokers [29]. It is obvious that there is some overlap on genetic changes between BA and NSCLC. But of all the patients, there are no recurrence or metastasis after 2-120 months of follow-up. However, this type of disease often leads to misdiagnosis, because they may morphologically mimic mucinous adenocarcinoma.

Of all the 99 patients, twenty-three were diagnosed with adenocarcinoma originally (23.0%) [6,17-19,5,21,23,24], two were suspected of malignant tumors (2.0%) [6]. Furthermore, some cases were just pathologically descriptive diagnosis. So it's important for pathologist to distinguish BA from malignant tumors, especially in intraoperative diagnosis. The well-differentiated mucinous adenocarcinoma could have ciliated columnar cells especially when adenocarcinoma infiltrates into bronchioles, but never present basal cells. Evidence support to malignancy should be carefully ruled out, and immunohistochemistry highlighted basal cells with p63 and/or CK5/6 is helpful. Otherwise, solitary

peripheral ciliated glandular papilloma, mixed squamous cell and glandular papilloma and mucoepidermoid carcinoma needs to be considered as differential diagnosis.

In conclusion, we reported four cases of BAs and detected the mutation of *ERBB2* exon 20 insertion for the first time. BA is likely a rare peripheral tumor, and exhibit characteristics similar to adenocarcinoma, including morphological and genetic changes. At present, BA shows benign biological feature might due to the limited number of cases. The pathogenesis and biological behavior of BA need to be further clarified, requiring more cases and longer follow-up.

## Availability Of Data And Materials

The data used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Abbreviations

BA
Bronchial Adenoma
CMPT
Ciliated muconodular papillary tumor
CT
Computed tomography
CN
copy number
GGO
ground-glass opaque
H&E
hematoxylin and eosin
IHC
immunohistochemistry
NGS
next-generation sequencing
NSCLC
non-small cell lung cancers
STAS
Spread Through Air Spaces

## Declarations

### Acknowledgements

Not applicable.

### Ethics approval and consent to participate

This study obtained the approval of the ethics committee of West China Hospital of Sichuan University. Written informed consent was obtained from each patient.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

Q.W. and L.L. contributed equally to this work

Q.W. and L.L. wrote this manuscript, L.L. collected and reviewed all the cases; Q.W. did data analysis and review; K. Z. did the IHC; Y.T. did the NGS; L.J. revised the manuscript. All authors read and approved the final manuscript.

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# Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

# Figures

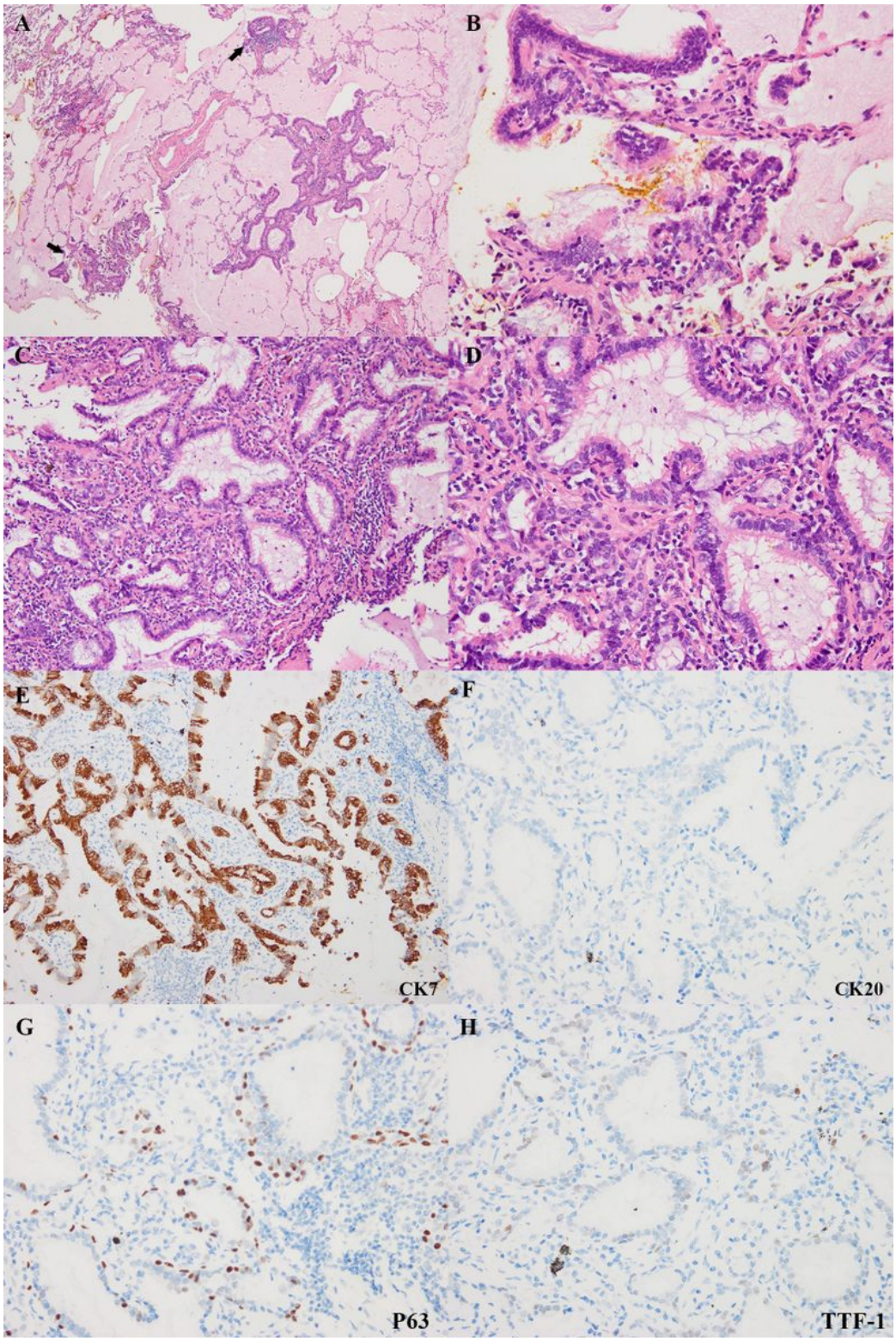


**Figure 1**

Morphology and IHC of BAs (A) proximal-type BA: shows the skipping growth pattern (arrow) and massive mucous lake (×4)；(B) proximal-type BA with prominent papillary architectural pattern and micropapillary tufts in the alveolar cavity (×10)；(C) proximal-type BA with mainly adherence architectural and occasionally papillary structure(×20), (D) proximal-type BA consist of ciliated columnar cells, mucus cells and basal cells with lymphoplasmacytic infiltrating in interstitial(×40), (E) ciliated columnar cells and mucus cells are positive for CK7 (×40)；but negative for CK20 (F,×40), (G) P63 outlines the basal cells (×40)；(H) ciliated columnar cells, mucus cells and basal cells shows weak and focal TTF-1 positivity (×40) .

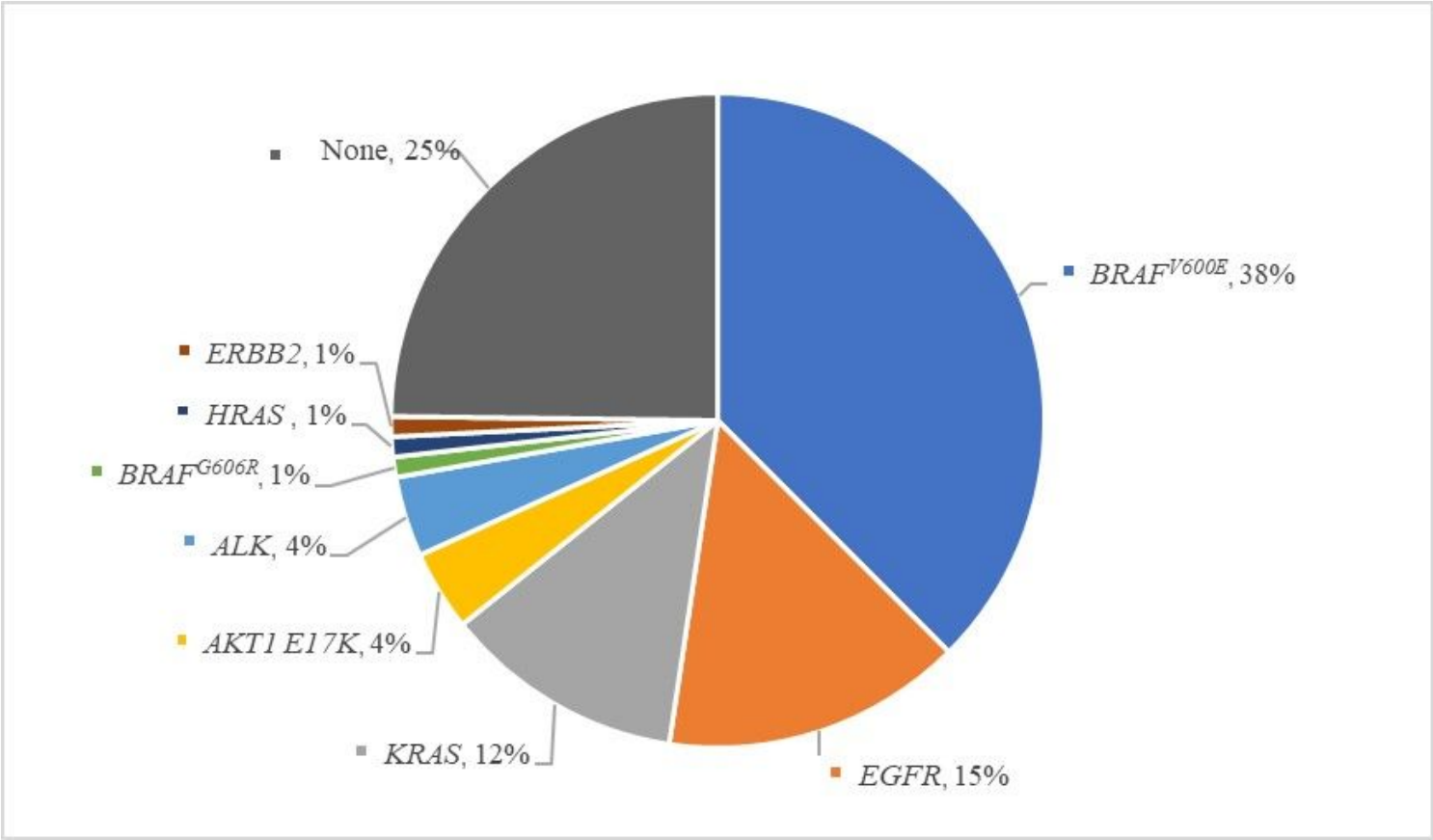


**Figure 2**

Molecular finding in BAs result from previous report and our present cohort.

# Supplementary Files

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- table2.docx
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