# Detection of *PAK* Family Gene Fusions in Serous Carcinoma of Ovary, Fallopian Tube, and Peritoneum

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## Introduction

- Increased expression of p21-activated kinase 4 (Pak4) has been associated with reduced chemosensitivity, advanced stage, and inferior survival outcomes in serous carcinomas of the gynecological tract.
- As efforts are underway to therapeutically target this protein and its regulatory genes from the *PAK* family, our study seeks to further characterize *PAK1*/*PAK2*/*PAK3* gene fusions that have been infrequently observed in ovarian, fallopian tube, and primary peritoneal cancers.

## Materials and Methods

- Paraffin-embedded tumor samples submitted to Caris Life Sciences (Phoenix, AZ) underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing, utilizing the Agilent SureSelect Human All Exon V7 bait panel (Santa Clara, CA) and Illumina NovaSeq technology (San Diego, CA).
- *PAK* family gene fusion events were included for analysis if they demonstrated ≥ 3 junction reads.
- Real-world event-free survival (EFS) information was obtained from insurance claims data and calculated from the time of biopsy to last contact.

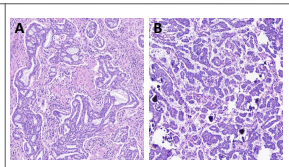



**Figure 1.** Representative images of cribriform (A) and micropapillary (B) morphologies in cases harboring *CD63*::*PAK1* and *DLG1*::*PAK2* fusions, respectively.

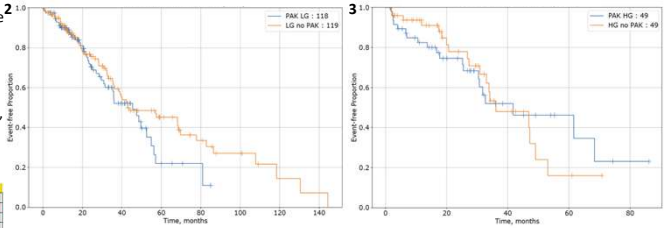
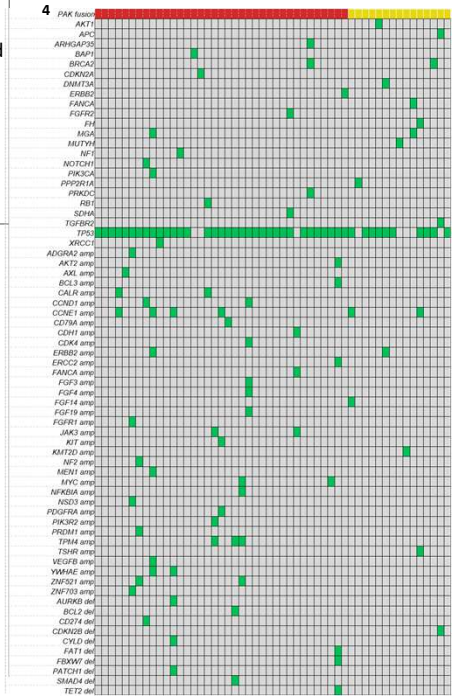



**Figure 2 & 3.** EFS of low-grade/borderline serous tumors with *PAK* fusions (PAK LG) versus cases without fusions of similar grade (LG no PAK) [2] and OS of high-grade serous tumors with *PAK* fusions (PAK HG) versus cases without fusions [3]



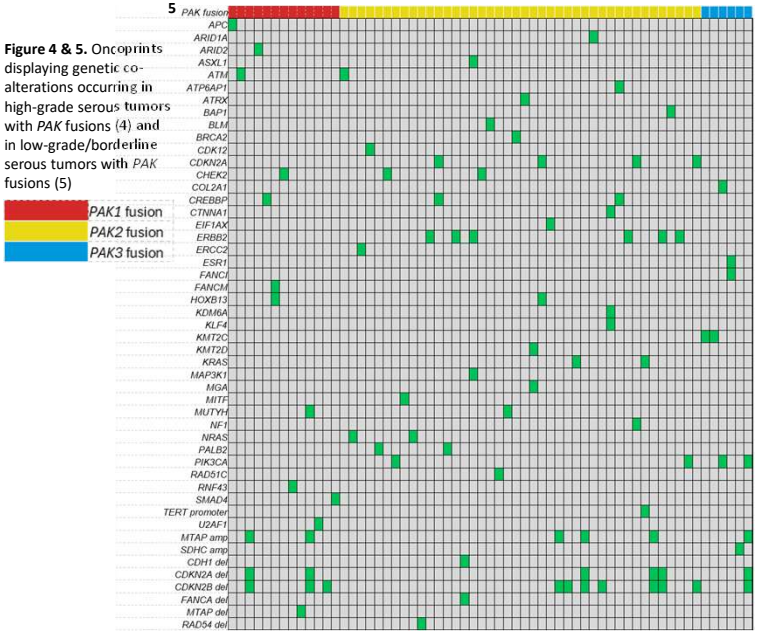




**Figure 4 & 5.** Oncoprints displaying genetic co-alterations occurring in high-grade serous tumors with *PAK* fusions (4) and in low-grade/borderline serous tumors with *PAK* fusions (5)

## Results

- Ovarian, fallopian tube, and primary peritoneal carcinomas demonstrated an incidence of 0.61% for pathogenic and likely pathogenic *PAK1* (41%)/*PAK2* (54%)/*PAK3* (5%) fusions, which were identified in 237 patient tumors.
- Pathology review demonstrated no distinct morphologic features; both wildtype and *PAK* fusion-positive cases had similar frequencies of papillary and micropapillary morphologies, calcifications, and necrosis. Occasional cases demonstrated nuclear grooves.
- The detected fusion partners included *DLG1* (n=89), *GAB2* (n=47), *CTNND1* (n=12), *RNF13* (n=10), and 47 other less frequent partners.
- All breakpoints occurred within *PAK1*/*PAK2*/*PAK3* such that an intact kinase domain was preserved. The tested samples had been previously diagnosed as high-grade serous carcinoma (64/237, 27%) or borderline serous tumor/low-grade serous carcinoma (173/237, 73%).
- Only three high-grade cancers were classified as TMB-high with ≥ 10 mut/MB, and three low- and two high-grade specimens demonstrated homologous recombination deficiency.
- *PAK1*/*PAK2*/*PAK3* fusions were mutually exclusive with pathogenic or likely pathogenic variants in the MAPK signaling pathway ($p < 0.001$).

## Conclusions

- *PAK1*/*PAK2*/*PAK3* fusion events are found in borderline/low-grade and high-grade serous tumors of the ovary, fallopian tube, and peritoneum and feature a diversity of gene partners.
- Despite their rarity, they may in the future have important treatment implications with the emergence of new targeted therapies.

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