Germline *APC* I1307K and *MITF* E318K variants in a patient with high-grade serous ovarian carcinoma: A case report

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Case presentation:
We report a detailed clinical history of a 76-year-old woman with high grade serous ovarian carcinoma (HGSOC) whose pathological and molecular findings revealed germline variants *APC* I1307K and *MITF* E318K. At age 74, the patient presented to clinic with dysuria and vaginal bleeding and upon further evaluation, discovered an endometrial stripe with trace fluid (4 × 14mm) and a cystic and solid right adnexal mass inseparable from the right ovary (11.6 × 9.2 × 8.1cm). The patient reported menopause at starting at age 50 and denied use of hormone replacement therapy. Past medical history consisted of a tubulovillous adenoma detected during a colonoscopy at age 62 with following colonoscopies showing no abnormalities and no history of abnormal Papanicolaou smears or mammograms. History of cancer in the family consisted of only her son, who had a pilocytic astrocytoma at age 12 with reoccurrence at age 15. The patient underwent cytoreductive surgery and the mass was confirmed to be HGSOC. The patient completed six cycles of carboplatin and paclitaxel with maintenance PARP inhibitor therapy. Later liver biopsy confirmed metastatic ovarian carcinoma. Somatic testing was positive for *TP53*, *FGFR2*, *MITF*, *APC*, and *FAT1* gene deletion. *TP53* is known to be somatic in high-grade serous ovarian carcinoma and was confirmed to be somatic in this case with germline testing. Only *MITF* and *APC* variants were positive in germline testing. The *APC* variant showed a VAF of only 16% on tumor testing, far below the expected 50%. However, because this *APC* variant is a well-established founder variant, we proceeded with germline testing, which ultimately confirmed its presence. The patient was offered continued treatment options including retreatment with platinum-based chemotherapy and potential enrollment in a clinical trial but the final treatment plan will be determined following further discussion.

Discussion:
APC I1307K and *MITF* E318K are both founder variants linked to distinct carcinomas: *APC* I1307K variant associated with colorectal carcinoma while *MITF* E318K variant associated with melanoma and renal cell carcinoma. Although *APC* and *MITF* do not interact directly, they both influence shared pathways, with *APC* playing a pivotal role in forming the destruction complex in the WNT/β-catenin pathway while *MITF* is regulated by different component of the destruction complex, GSK3β, to synergistically produce controlled proliferation in a normal cell. Although neither of these variants are linked to ovarian cancer risk, we hypothesize that a co-occurrence of *APC* I1307K and *MITF* E318K may reflect a polygenic modifier effect**.** Co-occurrence of *APC* I1307K and *MITF* E318K variants may potentiate tumor activity at the level of GSK3β where each of their pathways meet. This interaction has not been characterized and may explain the result in atypical cancers for these mutations including ovarian cancer, although this must be interpreted with caution as the features of this particular case of HGOSC, including metastasis, may have been unrelated to these variants. There is limited data but some clinical evidence

may suggest an association between *MITF* E318K and gynecologic malignancies. Oliveira et al. reported that among six *MITF* E318K carriers, one individual was diagnosed with ovarian/fallopian tube cancer alongside other gynecologic carcinomas including breast and cervical cancer, and two first-degree relatives of *MITF* E318K carriers had ovarian cancer [1]. Overall, this case highlights the importance of investigating atypical variant combinations and performing comprehensive germline profiling.

1. Oliveira, L. J. C., Gongora, A. B. L., Lima, F. A. S., Canedo, F. S. N. A., Quirino, C. V., Pisani, J. P., ... & Rossi, B. M. (2021). Expanding the phenotype of E318K (c. 952G> A) MITF germline mutation carriers: case series and review of the literature. *Hereditary Cancer in Clinical Practice*, *19*(1), 32.