

Case Report

Mucinous borderline ovarian tumour with concurrent germline WRN and somatic KRAS mutations: a case report

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Summary

We report the case of a 52-year-old woman who presented with a large pelvic mass, which was surgically removed and diagnosed as a mucinous borderline ovarian tumour (MBT) of intestinal type. Comprehensive genomic testing revealed two significant alterations: a pathogenic germline WRN stop-gain variant (NM_000553.4:c.1105C>T, p.Arg369Ter; exon 9/35) and a somatic KRAS mutation (c.35G>T, p.Gly12Val). The coexistence of these findings suggests that inherited impairment of DNA repair mechanisms, which, together with acquired activation of the RAS pathway, may have cooperated in driving tumour formation. Functionally, loss of WRN activity could have promoted genomic instability, allowing the emergence of oncogenic KRAS activation as a secondary event. The patient underwent a total hysterectomy with bilateral adnexectomy. Histopathological examination confirmed an intestinal-type MBT without stromal invasion. This case illustrates how integrating germline and somatic analyses can uncover the molecular interplay between inherited predisposition and tumour evolution, offering valuable information for personalised risk assessment, family counselling, and long-term clinical surveillance.

Key words: DNA repair deficiency, genetic counseling, germline variant, KRAS mutation, mucinous borderline ovarian tumour, oncogenic signalling, WRN gene



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Introduction

Borderline ovarian tumours (BOTs) represent an intermediate category between benign cystadenomas and invasive carcinomas, showing epithelial proliferation and nuclear atypia without stromal invasion (Seidman et al. 2004). Among them, mucinous borderline ovarian tumours (MBTs) of intestinal type form a well-defined subgroup that displays distinct morphological and molecular features (Ryland et al. 2015; National Academies of Sciences, Engineering, and Medicine 2016). These tumours often arise through a gradual transition from benign cystadenoma to borderline lesion and, in rare cases, to invasive mucinous carcinoma (Chui et al. 2025). KRAS mutations are the most frequent somatic driver in MBTs, found in up to 90% of cases,

supporting the concept of RAS pathway activation as an early event in mucinous tumourigenesis (Cancer Genome Atlas Research Network 2011). In contrast, the role of germline or DNA repair defects in this setting remains largely unexplored. The WRN gene encodes a RecQ helicase that maintains genomic stability by regulating DNA replication, repair, and telomere maintenance (Ding et al. 2015). Biallelic WRN loss causes Werner syndrome, but even monoallelic truncating variants have been associated with increased susceptibility to several malignancies, including ovarian cancer (Konstantinopoulos et al. 2020; Guan et al. 2025). This report presents a case of intestinal-type MBT carrying both a germline WRN truncating variant and a somatic KRAS mutation, illustrating how inherited and acquired molecular events may act together in the pathogenesis of borderline ovarian tumours.

Case report

A 52-year-old woman was admitted to the Oncogynecology Clinic following the detection of an abdominal mass. Her last menstrual period was reported on September 1, 2020, indicating post-menopausal status. Ultrasound imaging revealed a round, predominantly hypo- to non-echogenic mass in the pelvis measuring approximately 115 mm in diameter. During surgery, a mobile cystic tumour arising from the right ovary was identified, measuring about 15 cm in greatest dimension. The uterus appeared hypoplastic, and the left adnexa were macroscopically normal. The patient underwent a total hysterectomy with bilateral adnexectomy. Histopathological examination of the ovarian mass confirmed a mucinous borderline ovarian tumour of intestinal type, with papillary and glandular structures lined by intestinal-type epithelium and no stromal invasion (Fig. 1). The postoperative course was

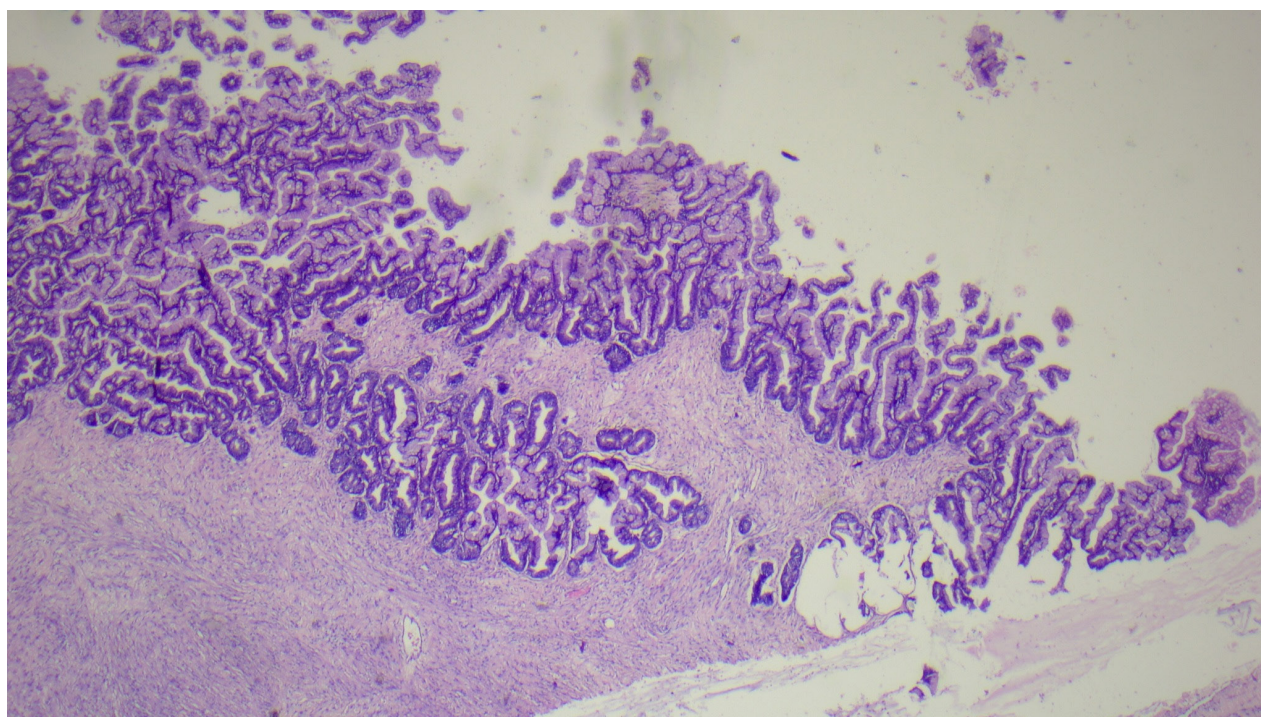


Figure 1. Histopathology (H&E, x2.5) showing mucinous borderline morphology without stromal invasion.

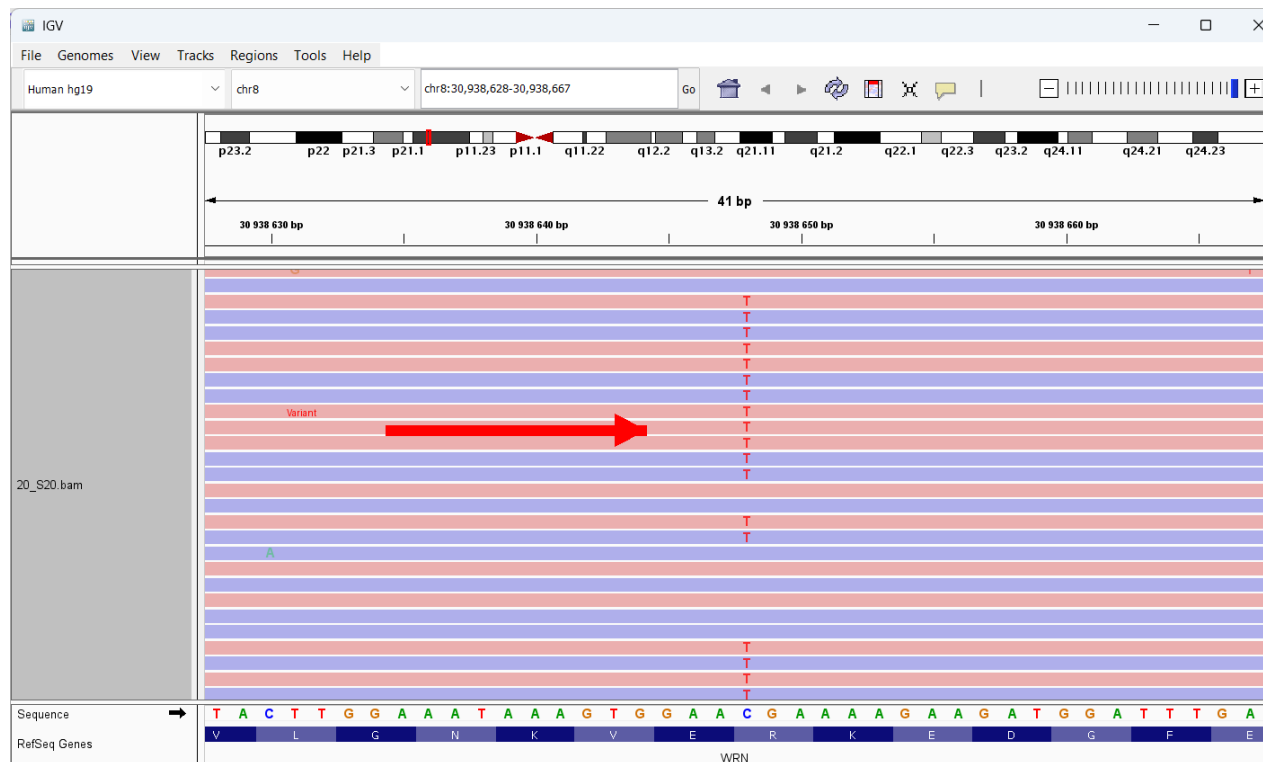


Figure 2. IGV visualization of WRN NM_000553.4:c.1105C>T variant.

uneventful, and the patient was referred for genetic counselling and molecular analysis to evaluate possible hereditary predisposition.

Genomic DNA extracted from peripheral blood and the tumour tissue underwent massive parallel sequencing (NGS) using hereditary and somatic cancer gene panels. Germline analysis revealed a WRN NM_000553.4:c.1105C>T (p.Arg369Ter) stop-gain variant in exon9/35, classified as pathogenic (Richards et al. 2015) (Fig. 2). Tumour sequencing detected a somatic KRAS c.35G>T (p.Gly12Val) mutation (Richards et al. 2015), which is a canonical activating alteration in mucinous tumours. These findings were interpreted as evidence of both inherited and acquired molecular contributions to the patient's borderline ovarian tumour.

Molecular findings

The WRN gene encodes a multifunctional protein with helicase and exonuclease activity, essential for maintaining genomic integrity (Ding et al. 2015). The identified p.Arg369Ter variant introduces a premature stop codon, leading to truncation of the helicase domain and functional loss. Such variants have been associated with genomic instability and increased cancer susceptibility in heterozygous carriers (Ding et al. 2015; Kargbo et al. 2025). Loss of WRN function results in replication stress and accumulation of double-strand DNA breaks, creating a permissive environment for oncogenic transformation.

The KRAS mutation detected in this tumour (c.35G>T, p.Gly12Val) is one of the most common oncogenic events in mucinous ovarian tumours (Cancer Genome Atlas Research Network 2011; Chui et al. 2025). It leads to constitutive activation of the RAS/MAPK pathway, promoting uncontrolled cell

proliferation and resistance to apoptosis. KRAS mutations are reported in 70–90% of MBTs and in a similar proportion of mucinous carcinomas, indicating that KRAS activation occurs early in tumour evolution (Cancer Genome Atlas Research Network 2011; Therachiyil et al. 2022). In the case we present, the KRAS G12V mutation likely served as the main somatic driver, while the germline WRN truncation provided a predisposing background through impaired DNA repair capacity.

Discussion

This case highlights the complex interplay between genetic predisposition and somatic mutation in the development of borderline ovarian tumours. Although mucinous borderline tumours are generally considered sporadic and carry an excellent prognosis, the identification of a germline WRN variant suggests that inherited factors may also contribute in selected patients. The dual presence of WRN deficiency and KRAS activation fits a ‘two-hit’ model, in which impaired DNA repair facilitates the acquisition of oncogenic mutations that drive neoplastic growth.

The WRN helicase belongs to the RecQ family, often referred to as the “guardian of the genome” for its central role in maintaining chromosomal stability (Ding et al. 2015; Richards et al. 2015). Experimental data have shown that WRN-deficient cells accumulate replication errors and show heightened sensitivity to genotoxic stress (Ding et al. 2015; Baltgalvis et al. 2024). Interestingly, cancers with WRN deficiency exhibit synthetic lethality when treated with ATR inhibitors, suggesting potential therapeutic implications (Wang et al. 2023; Baltgalvis et al. 2024). Although such targeted therapy is not currently indicated for borderline tumours, molecular characterisation can reveal future therapeutic opportunities, particularly in cases showing recurrence or progression.

From a clinical perspective, most MBTs are unilateral, large, and confined to the ovary at diagnosis (Seidman et al. 2004; Ryland et al. 2015). Surgical resection remains the mainstay of treatment, and prognosis is generally favourable. However, recurrence and malignant transformation occur in up to 10% of cases (Cancer Genome Atlas Research Network 2011). Identifying molecular markers associated with progression could improve postoperative surveillance and patient counselling. In this context, the coexistence of a DNA-repair defect and a KRAS mutation may represent a biologically distinct subset deserving closer follow-up. Moreover, the detection of a germline WRN pathogenic variant warrants consideration of genetic testing for family members and tailored surveillance strategies for the proband (Ding et al. 2015; Konstantinopoulos et al. 2020).

This case also emphasises the value of comprehensive NGS testing that combines germline and somatic analysis. Traditional testing strategies often focus on BRCA1/2 and mismatch repair genes, but expanding the panel to include WRN and other RecQ helicases may uncover previously unrecognised predisposition patterns (Ding et al. 2015). Future studies should explore whether WRN variants influence tumour behaviour or treatment response in mucinous ovarian neoplasms. Large-scale sequencing efforts and functional assays are needed to clarify the clinical relevance of these findings.

Conclusion

In summary, we report a rare case of an intestinal-type mucinous borderline ovarian tumour carrying a germline WRN stop-gain variant and a somatic KRAS G12V mutation. This combination suggests that defects in DNA repair may cooperate with oncogenic signalling pathways to promote tumour initiation in the ovarian epithelium. The case underscores the importance of integrated molecular diagnostics in borderline ovarian tumours, not only for understanding tumour biology but also for informing genetic counselling and long-term surveillance strategies.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors’ representatives: Approved by the Ethics Committee of Medical University - Pleven (approval No. 574- KEHH^A, date 04.07.2023). Written informed consent for publication of her data was obtained from the patients.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

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Author contributions

ZK designed the study, supervised sequencing and interpretation, and drafted the manuscript. SP performed a histopathology review and contributed to the interpretation. CT recruited patients and provided clinical data. All authors read and approved the final version.

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Data availability

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

References

- Baltgalvis KA, Lamb KN, Symons KT, Wu CC, Hoffman MA, Snead AN, Song X, Glaza T, Kikuchi S, Green JC, Rogness DC, Lam B, Rodriguez-Aguirre ME, Woody DR, Eissler CL, Rodiles S, Negron SM, Bernard SM, Tran E, Pollock J, Tabatabaei A, Contreras V, Williams HN, Pastuszka MK, Sigler JJ, Pettazzoni P, Rudolph MG, Classen M, Brugger D, Claiborne C, Plancher JM, Cuartas I, Seoane J, Burgess LE, Abraham RT, Weinstein DS, Simon GM, Patricelli MP, Kinsella TM (2024) Chemoproteomic discovery of a covalent allosteric inhibitor of WRN helicase. *Nature* 629: 435–442. <https://doi.org/10.1038/s41586-024-07318-y>
- Cancer Genome Atlas Research Network (2011) Integrated genomic analyses of ovarian carcinoma. *Nature* 474: 609–615. <https://doi.org/10.1038/nature10166>
- Chui MH, Song Q, Zhu J, Jiao Y, Wang B, Wang Y, Wang TL, Vang R, Shih IM (2025) Early genetic divergence of high-grade carcinomas originating from low-grade serous ovarian neoplasms. *Modern Pathology* 38: 100629. <https://doi.org/10.1016/j.modpat.2024.100629>
- Ding L, Liu Y (2015) Borrowing nuclear DNA helicases to protect mitochondrial DNA. *International journal of molecular sciences* 16: 10870–10887. <https://doi.org/10.3390/ijms160510870>
- Guan X, Liao S, Zhang F, Zhu Q, Qiu H, Qin L, Zhang X (2025) Identifying the germline variation spectrum and predisposition genes in Chinese ovarian cancer using whole exome sequencing. *BMC Cancer* 25: 924. <https://doi.org/10.1186/s12885-025-14302-w>
- Kargbo RB (2025) Targeting Werner syndrome helicase with small molecules in mismatch repair-deficient cancers. *ACS Medicinal Chemistry Letters* 16: 945–947. <https://doi.org/10.1021/acsmchemlett.5c00262>
- Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong DK, Burger RA, Grisham RN, Goodfellow PJ, Kohn EC, Levine DA, Liu JF, Lu KH, Sparacio D, Annunziata CM (2020) Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. *Journal of clinical oncology* 38: 1222–1245. <https://doi.org/10.1200/JCO.19.02960>
- National Academies of Sciences, Engineering, and Medicine (2016) Ovarian cancers: Evolving paradigms in research and care. The National Academies Press. <https://doi.org/10.17226/21841>
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehms HL (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine* 17: 405–424. <https://doi.org/10.1038/gim.2015.30>
- Ryland GL, Hunter SM, Doyle MA, Caramia F, Li J, Rowley SM, Christie M, Allan PE, Stephens AN, Bowtell DD, Australian Ovarian Cancer Study Group, Campbell IG, Goringe

- KL (2015) Mutational landscape of mucinous ovarian carcinoma and its neoplastic precursors. *Genome Medicine* 7: 87. <https://doi.org/10.1186/s13073-015-0210-y>
- Seidman JD, Soslow RA, Vang R, Berman JJ, Stoler MH, Sherman ME, Oliva E, Kajdacsy-Balla A, Berman DM, Copeland LJ (2004) Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Human Pathology* 35: 918–933. <https://doi.org/10.1016/j.humpath.2004.03.004>
- Therachiyil L, Anand A, Azmi A, Bhat A, Korashy HM, Uddin S (2022) Role of RAS signaling in ovarian cancer. *F1000Research* 11: 1253. <https://doi.org/10.12688/f1000research.126337.1>
- Wang M, Ran X, Leung W, Kawale A, Saxena S, Ouyang J, Patel PS, Dong Y, Yin T, Shu J, Manguso RT, Lan L, Wang XF, Lawrence MS, Zou L (2023) ATR inhibition induces synthetic lethality in mismatch repair-deficient cells and augments immunotherapy. *Genes & Development* 37: 929–943. <https://doi.org/10.1101/gad.351084.123>