

Epigenetic mechanisms of PARP inhibitor resistance in ovarian cancer: A systematic review with bioinformatic analysis of clinically actionable genes

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ABSTRACT

PARP inhibitors (PARPi) improve ovarian cancer (OC) outcomes, but resistance remains a major challenge without reliable prognostic biomarkers. This study identified epigenetic hallmarks of PARPi resistance by integrating 27 studies (22 preclinical, 5 clinical) from the past 15 years, and validating candidate genes using web-based bioinformatics tools and public microarray/RNA-seq datasets from non-relapsed, primary OC tissues. We hypothesised that early aberrant expression of these epigenetically altered, PARPi resistance-related genes in tumours may be linked to disease progression (PFS) and could serve as early biomarkers to be associated with PARPi resistance during first-line treatment. We confirmed epigenetic involvement in PARPi resistance across 36 genes linked to epigenetic modifications. Of these, 10 genes ($n = 614\text{--}1435$)—including *RNASEH2B* (HR=1.41), *VHL* (HR=1.26), *ATM* (HR=1.22), *XRCC1* (HR=1.20), *NRP1* (HR=1.16), *KAT2B* (HR=1.16), *EZH2* (HR=1.15), *CREBBP* (HR=1.14), *FZD10* (HR=0.87), and *CARM1* (HR=0.86)—showed significant prognostic value for PFS (all: $p < 0.05$). This 10-gene signature remained collectively significant (HR 1.27, $p = 0.014$). RNA-seq validation showed differential expression of these genes, with highest fold-change overexpression in tumours for *FZD10* (4.20), *EZH2* (3.56), and *CARM1* (1.61), and lowest in *ATM* (0.22), *KAT2B* (0.33), and *NRP1* (0.44). GO and KEGG analyses revealed these genes are enriched in key resistance pathways, including impaired DNA repair, reduced replication stress, immune evasion, and stemness maintenance. This review with bioinformatic validation identified a 10-gene epigenetic signature associated with PARPi resistance and disease progression. These clinically actionable genes, aberrantly expressed before treatment, may serve as early biomarkers for risk stratification. Further validation in PARPi-sensitive and -resistant ovarian cancer cohorts is needed.

1. Introduction

Ovarian cancer (OC) remains one of the deadliest gynaecological malignancies, with 206,956 deaths globally in 2022 (IARC, 2023). Despite therapeutic advances, disease recurrence occurs in approximately 70 % of patients within two years of initial treatment (Summey and Uyar, 2022). Poly (ADP-ribose) polymerase inhibitors (PARPi) have emerged as a transformative therapy, particularly in *BRCA*-mutated or homologous recombination-deficient (HRD) OC. However, resistance to PARPi is a growing clinical challenge, often overlapping with platinum resistance due to shared DNA repair pathways. Notably, nearly 25 % of OC patients exhibit primary resistance to platinum (Miras et al., 2024), and over 40 % of those harbouring *BRCA1/2* mutations show minimal or no response to PARPi (Li et al., 2020). These statistics underscore the urgent need to elucidate mechanisms of resistance and guide stratified

therapeutic strategies.

Emerging evidence suggests that epigenetic dysregulation plays a pivotal role in modulating PARPi sensitivity (Kharat et al., 2020; Kirmizitas et al., 2024; Pinton et al., 2023). Several studies have revealed that alterations in DNA methylation (Aref-Eshghi et al., 2020; Kondrashova et al., 2018; Nesic et al., 2021; Sahnane et al., 2020), histone modification (Kukita et al., 2019; Watson et al., 2019), and non-coding RNA expression (Bustos et al., 2023; Choi et al., 2016; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020) may influence DNA repair pathways and apoptosis, contributing to therapeutic evasion. For example, *TET2* (a key regulator of 5-methylcytosine hydroxylation and replication fork stability) was shown to mediate resistance in *BRCA2*-deficient cells following PARPi-induced downregulation (Kharat et al., 2020). Moreover, *PARP1* itself has an epigenetic regulatory role by inhibiting DNA methyltransferase 1 (DNMT1) at CpG-rich sites. PARP1

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inhibition via PARPi restores DNMT1 activity, leading to hypermethylation and transcriptional silencing of DNA repair genes (Ummarino et al., 2021). Consequently, PARPi treatment can trigger widespread epigenomic reprogramming, altering expression of DNA repair and apoptotic genes to promote survival (Doege et al., 2012; He et al., 2024b; Lobo et al., 2021; Tolić et al., 2022). This reprogramming may involve hypermethylation of homologous recombination (HR) gene promoters or apoptosis regulators, thereby restoring HR proficiency or suppressing cell death and contributing to resistance. Moreover, PARP1 interacts with histone marks and *TET2* (Doege et al., 2012; Kharat et al., 2020; Tolić et al., 2022), and its inhibition further disrupts chromatin regulation and DNA methylation homeostasis (Tolić et al., 2022). Despite these findings, the full spectrum of epigenetic alterations driving PARPi resistance in OC remains poorly defined. A systematic, integrative approach is needed to identify the most clinically relevant epigenetic mechanisms and biomarkers.

While insights into individual mechanisms are expanding, no comprehensive synthesis currently exists to map the landscape of epigenetic alterations linked to PARPi resistance in OC. Prior reviews have predominantly focused on genetic drivers or isolated pathways, with limited integration of DNA methylation, histone modifications, and non-coding RNAs (ncRNA) in a unified framework. Moreover, there is limited validation of which epigenetic alterations are most clinically relevant or prognostically significant. This systematic review addresses these gaps by consolidating current evidence on epigenetic mechanisms of PARPi resistance in OC. We further integrate bioinformatic validation using transcriptomic and clinical outcome data from public repositories. By identifying genes and regulatory elements with mechanistic plausibility and clinical correlation, we aim to nominate candidate biomarkers associated with PARPi resistance. These findings may inform future strategies for patient stratification, therapeutic targeting, and personalised treatment optimisation in OC.

2. Method

2.1. Protocol, information sources, and search strategy

This study integrates a PRISMA-guided systematic review and bioinformatic analysis of epigenetic mechanisms driving PARPi resistance in OC, summarised in Fig. 1A (Page et al., 2021). A comprehensive literature search was performed on 1 March 2025 across PubMed, ProQuest, and Scopus using Medical Subject Headings (MeSH) and Boolean operators (Fig. 1B). Additional sources were identified via manual screening of Google Scholar. The search strategy was structured using the PICO framework: P (Population): PARPi-resistant OC; I (Intervention): epigenetic alterations (e.g., biomarkers, regulatory changes); C (Comparison): PARPi-sensitive samples or those lacking such alterations; O (Outcome): resistance mechanisms, prognostic implications, and predictive value of epigenetic markers. Detailed queries, keywords, and inclusion/exclusion criteria are provided in Tables S1 and S2. Only studies with clear clinical relevance and appropriate design were included.

2.2. Study selection, eligibility criteria, and data collection

Studies were selected based on predefined eligibility criteria. Inclusion criteria comprised original English-language publications from 2011 to 2025, reporting clinical data on gene expression associated with PARPi resistance, progression, or prognosis in OC. Eligible designs included randomised control trials, observational studies, and experimental *in vivo* and *in vitro* studies examining relevant epigenetic mechanisms. Exclusion criteria encompassed duplicates, reviews lacking mechanistic data, case reports, theses, letters, editorials, opinions, surveys, guidelines, conference abstracts, and commentaries. Titles and abstracts were independently screened by two reviewers, with discrepancies resolved by consensus. Studies without accessible full texts were

excluded from systematic analysis but referenced to support contextual discussion.

2.3. Risk of bias and quality assessment

The methodological quality of included studies was assessed using the Cochrane Risk of Bias (RoB) tool for interventional studies, encompassing nine domains: randomisation, allocation concealment, experimental conditions, blinding, data completeness, exposure characterisation, outcome assessment, selective reporting, and data sufficiency (Fig. 1C, Table S3) (Higgins et al., 2011). Responses were scored as low (2), unclear (1), or high risk (0), with total scores categorised as high (1–6), moderate (7–12), or low RoB (13–18). In parallel, the simplified version of Biomarker Toolkit Assessment—a 14-point checklist spanning four domains—was used to evaluate the translational strength of each study: (1) rationale, (2) analytical validity (e.g. design, biospecimen quality, and quality control), (3) clinical validity (e.g. sensitivity and specificity, method validation, population eligibility criteria, and statistical analysis), and (4) clinical utility (e.g. human factors, ethical approval, regulatory authorities, cost-effectiveness, and clinical care utility) (Fig. 1D, Table S4) (Savva et al., 2023). Studies were scored on the same scale and classified as low (1–9), intermediate (10–18), or high quality (19–28) based on the researchers' consensus. Discrepancies in scoring or eligibility were resolved through consensus.

2.4. Data extraction and synthesis of results

Data extraction was conducted using EndNote (v21.3) and Microsoft Excel (365 v2406), structured according to predefined variables aligned with the review objectives. Extracted variables included author(s), publication year, study location, design, sample size, gene targets, type of epigenetic modification, functional relevance to PARPi resistance, and quality assessments (RoB and biomarker toolkit). Study design classification followed standardised criteria (Table S5). Extracted outcomes captured key associations across four domains: (1) epigenetically regulated pathways in ovarian tumorigenesis and progression, (2) links to PARPi resistance mechanisms or risk factors, (3) prognostic value, and (4) biomarker potential for treatment response stratification. Summary tables were generated, with visual grouping based on epigenetic mechanism and publication year. Given the heterogeneity in experimental models and outcome reporting, quantitative synthesis (e.g., meta-analysis) was not feasible.

2.5. Bioinformatic validation and data visualisation

To assess the clinical relevance of genes implicated in PARPi resistance, we performed bioinformatic validation using web-based tools developed by (Györfy, 2024) (Fig. 1E), which integrate publicly available datasets from The Cancer Genome Atlas (TCGA) (Bell et al., 2011) and Gene Expression Omnibus (GEO) with the list of datasets used provided in Table S6 (Clough and Barrett, 2016). A total of 36 PARPi-resistant genes (and their aliases, listed in Table S7) were analysed for differential gene expression in tumour, normal, and metastatic tissues (TNMplot) (Bartha and Györfy, 2021), enrichment in cancer hallmark pathways by summarising commonalities in malignant transformation and progression across 6763 genes (Cancer Hallmark) (Baker et al., 2017; Menyhart et al., 2024), and associations with overall survival (OS) and progression-free survival (PFS) (KM Plotter) (Györfy, 2023; Lánckzy and Györfy, 2021), using default settings and a median cut-off (Table S8). All tools utilised embedded publicly available, reproducible transcriptomic datasets (gene chip/DNA microarray and RNA-seq), ensuring transparency and accessibility. Full details, including source links, software, and algorithms, are provided in Table S9. Data visualisation (e.g. PRISMA flow, quality charts, sample types, cell lines, epigenetic mechanisms, and publication trends) was

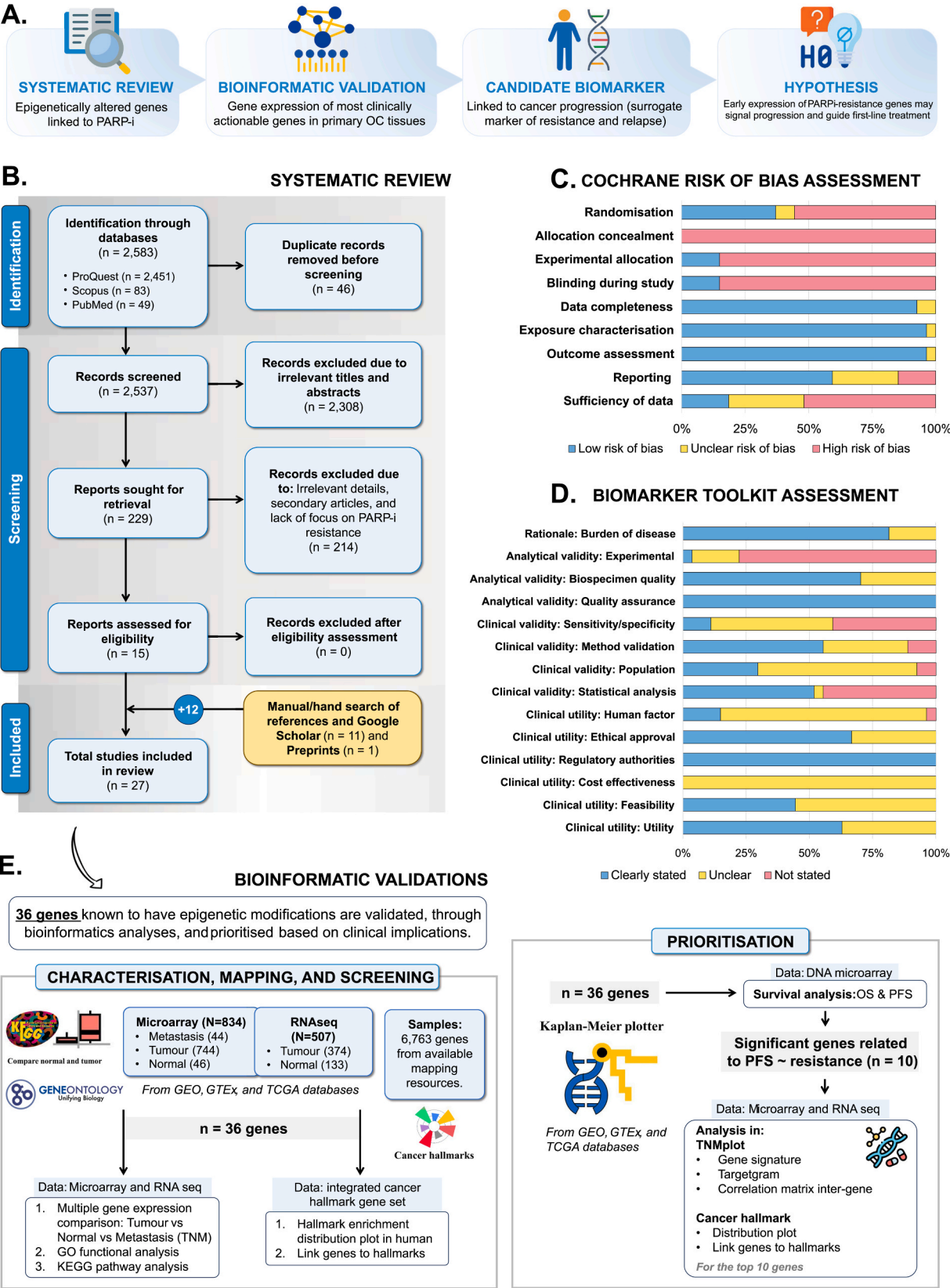


Fig. 1. Overview of study design and analytical workflow. (A) Schematic overview of the study, outlining the process from systematic literature review for gene identification to the prioritisation of clinically actionable biomarkers and hypothesis-driven bioinformatic validation. (B) PRISMA 2020-compliant flowchart illustrating the systematic review and article selection process. (C) Bioinformatic validation of identified genes using datasets from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA), enabling expression mapping, functional annotation, and prioritisation of ten candidate genes associated with progression-free survival as a surrogate marker of PARPi resistance and disease recurrence. (D) Risk of bias assessment for interventional studies conducted using the Cochrane tool. (E) Evaluation of biomarker readiness using an established translational biomarker assessment framework.

done using Excel and PowerPoint. Forest plots, KEGG pathway enrichment, and gene interaction networks were generated in R v4.4.0 and RStudio v2024.04.2 using meta-analysis (*meta*, *metafor*), visualisation (*ggplot2*, *dplyr*), and network mapping packages (*igraph*, *ggraph*, *tidygraph*). Additional outputs were obtained via online bioinformatics tools. KEGG pathways were considered significant at adjusted $p \leq 0.05$ (Benjamini–Hochberg) and $q \leq 0.02$, with default gene set thresholds (minGSSize = 10, maxGSSize = 500).

3. Results

3.1. Study selection and characteristics

A total of 2583 records were identified. After removing 46 duplicates and screening 2537 titles and abstracts, 229 full-text articles were assessed. Of these, 214 were excluded for irrelevance, secondary focus, or insufficient emphasis on PARPi resistance, leaving 15 studies. An additional 11 studies and 1 preprint were identified through manual

Table 1

Characteristics of studies, including authors, publication years, countries, sample sizes, genes studied, molecules investigated, gene roles, and study assessment results.

No	Author, year, and country	Study design	Genes that involve PARPi resistance	Type of epigenetics	Assessment	
					RoB ^a	Quality ^b
1.	Zhang et al., 2024; US	Experimental <i>in vitro</i> + E + T	Methylation of DNA repair genes, notably <i>PRMT1</i> , <i>PRMT4</i> , and <i>PRMT5</i>	DNA methylation	moderate	moderate
2.	Kirmizitas et al., 2024; Netherlands	Cohort + E + G	<i>SOX2</i> , <i>POU2AF1</i> , <i>PTK6</i> , <i>VHL</i> , <i>JAK3</i> , <i>EZH2</i> , and <i>RAD51C</i> methylation	DNA methylation	moderate	moderate
3.	Jamal et al., 2022; UK	Experimental <i>in vitro</i> + E	<i>BRCA1</i> , <i>BRCA2</i> , <i>RNASEH2</i> complex genes (<i>RNASEH2A</i> , <i>RNASEH2B</i> , <i>RNASEH2C</i>); and <i>DNPH1</i> complex genes (<i>XRCC1</i> , <i>POLB</i> , <i>LIG1</i>)	DNA methylation	high	moderate
4.	Nesic et al., 2021; Australia	Experimental <i>in vivo</i> + E	<i>RAD51C</i> methylation	DNA methylation	moderate	moderate
5.	Hurley et al., 2021; US	Part of clinical trial + experimental <i>in vivo</i> + E + T	<i>RAD51C</i> promoter methylation	DNA methylation	low	moderate
6.	Aref-Eshghi et al., 2020; Canada	Cohort + E + G	<i>BRCA1</i> and <i>BRCA2</i> , with <i>BRCA1</i> promoter methylation, is the most critical	DNA methylation	moderate	moderate
7.	Sahnane et al., 2020; Italy	Cohort + E	<i>BRCA1</i> and <i>BRCA2</i> : Mutations and epigenetic silencing	DNA methylation	moderate	high
8.	Kharat et al., 2020; US	Experimental <i>in vitro</i> + E + G	<i>TET2</i> , <i>BRCA2</i> , and others related to DNA damage response	DNA methylation: 5hmC	moderate	moderate
9.	Grimm et al., 2019a; Germany	Experimental <i>in vitro</i> + E	342 DNA repair genes, focusing on <i>BRCA1</i> , <i>ATM</i> , <i>ATR</i> , and <i>EP300</i> (<i>KAT3B</i>). <i>BRCA1</i> promoter methylation	DNA methylation	moderate	moderate
10.	Pulliam et al., 2018; US	Experimental <i>in vitro</i> + E	<i>BRCA1</i> methylation	DNA methylation	moderate	moderate
11.	Kondrashova et al., 2018; Australia	Experimental <i>in vivo</i> and <i>in vitro</i> + E + T	<i>BRCA1</i> methylation	DNA methylation	low	high
12.	Bi et al., 2013; China	Cohort + E	<i>PARP1</i> promoter methylation near the ETS motif	DNA methylation	moderate	moderate
13.	Drew et al., 2011; UK	Experimental <i>in vivo</i> and <i>in vitro</i> + E + G	<i>BRCA1</i> expression levels	DNA methylation	moderate	moderate
14.	Fukumoto et al., 2019; US	Experimental <i>in vivo</i> and <i>in vitro</i> + E	<i>FZD10</i> gene with elevated m6A modification.	N6-methyladenosine (m6A) methylation.	moderate	moderate
15.	He et al., 2024a; China	Experimental <i>in vitro</i> + E	<i>BRCA1</i> promoter methylation	DNA methylation and histone modification	high	moderate
16.	Kukita et al., 2019; Japan	Experimental <i>in vitro</i> + E	<i>SMYD2</i> overexpression and its methylation	DNA methylation and histone modification	moderate	moderate
17.	Bitler et al., 2023; US	Experimental <i>in vivo</i> and <i>in vitro</i> + E	Histone acetyltransferases (<i>HATs</i>), especially <i>PCAF</i> (<i>KAT2B</i>), <i>CBP/CREBBP</i> (<i>KAT3A</i>), <i>P300</i> (<i>KAT3B</i>), and <i>HBO1</i> (<i>KAT7</i>)	Histone modifications: H3K14ac and H3K9me2.	moderate	moderate
18.	Watson et al., 2019; US	Experimental <i>in vivo</i> and <i>in vitro</i> + E + T	<i>EHMT1</i> and <i>EHMT2</i> and their role in H3K9me2 methylation	Histone modification	moderate	moderate
19.	Wu et al., 2024; China	Experimental <i>in vivo</i> and <i>in vitro</i> + E + T	lncRNA <i>PART1</i> and the interaction with <i>PHB2</i>	Non-coding RNA (lncRNA)	moderate	moderate
20.	Bustos et al., 2023; US	Experimental <i>in vitro</i> + E + T	miRNA 181a and <i>TMEM173</i> in STING pathway.	Non-coding RNA (miRNA)	moderate	moderate
21.	Kong et al., 2022; China	Experimental <i>in vitro</i> + E + T	The key regulatory ceRNA axis includes 3 lncRNAs, 2 circRNAs, 7 miRNAs, and 12 mRNAs, with miR-320b as the crucial mediator.	Non-coding RNA (miRNA)	high	low
22.	Sun et al., 2021; China	Experimental <i>in vitro</i> + E + T + P	miRNA 506-3p and <i>EZH2</i>	Non-coding RNA (miRNA)	moderate	moderate
23.	Vescarelli et al., 2020; Italy	Experimental <i>in vitro</i> + E + T	miRNA 200c, <i>NRP1</i> , and <i>BRCA1</i>	Non-coding RNA (miRNA)	moderate	moderate
24.	Meghani et al., 2018; US	Experimental <i>in vitro</i> + E + T	miRNA 493-5p, <i>RNASEH2A</i> , <i>SSRP1</i> , and <i>FEN1</i>	Non-coding RNA (miRNA)	moderate	high
25.	Choi et al., 2016; US	Experimental <i>in vitro</i> + E + G + T	miRNA RNA-622 and <i>Ku80</i> complex	Non-coding RNA (miRNA)	moderate	moderate
26.	Sun et al., 2013; China	Experimental <i>in vivo</i> and <i>in vitro</i> + E + T	miRNA 9 and <i>BRCA1</i>	Non-coding RNA (miRNA)	low	high
27.	Wang et al., 2012; US	Experimental <i>in vivo</i> and <i>in vitro</i> + E + T	miRNA 96, <i>RAD51</i> , and <i>REV1</i>	Non-coding RNA (miRNA)	moderate	moderate

Abbreviation: E, epigenomic study; G, Genomic study; H3K14ac, Acetylation of histone H3 lysine 14; H3K9me2, Methylation of histone H3 lysine 9; lncRNA, Long non-coding RNA; miRNA, micro RNA; P, proteomic study; T, transcriptomic study; ^aCochrane Risk of Bias (RoB) assessment: 1–6 (high RoB), 7–12 (moderate RoB), 13–18 (low RoB); ^bStudy quality based on the perspective of the Biomarker Toolkit Assessment Tool: 1–9 (low), 10–18 (moderate), 19–28 (high).

search, yielding 27 eligible articles for in-depth evaluation (Table 1). Since the first report in 2011, interest in epigenetic mechanisms underlying PARPi resistance has increased steadily. However, the field remains largely preclinical, with only 5 studies conducted in clinical settings (Aref-Eshghi et al., 2020; Bi et al., 2013; Hurley et al., 2021; Kirmizitas et al., 2024; Sahnane et al., 2020), highlighting a critical translational gap (Figure S1A). Most publications originated from the United States (n = 11, 41 %) and China (n = 6, 22 %) (Figure S1B).

3.2. Assessment of study quality and reliability

Quality appraisal using the Cochrane RoB tool revealed 11 % (n = 3) of studies had high risk, 11 % (n = 3) low risk, and 78 % (n = 21) moderate risk (Figure S1C, Tables S3–S4). Rigorous criteria, most notably the lack of randomisation and blinding, partly account for these outcomes. Despite these limitations, included studies offer key mechanistic insights, primarily from preclinical research on PARPi resistance and epigenetic regulation. Using the Biomarker Toolkit Assessment, (4 %, n = 1) of studies were rated low-quality for clinical biomarker development, 81 % (n = 22) moderate, and 15 % (n = 4) high (Figure S1D). This underscores the urgent need for standardised, high-quality biomarker studies to advance clinical translation.

3.3. Design of the study and measurement of outcomes

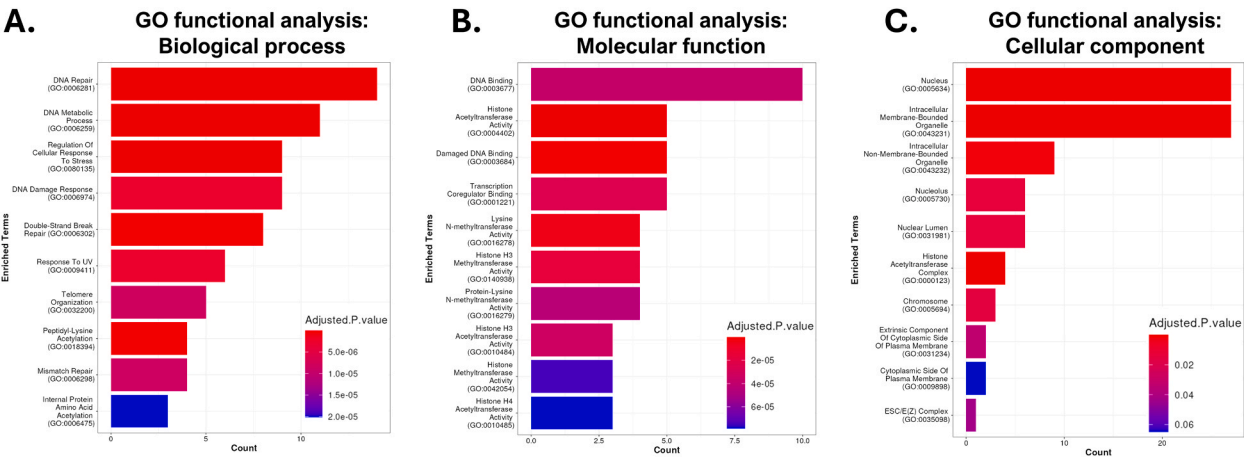
Seven types of research designs were identified across 27 studies, often used in combination (n = 81 designs). All investigations utilised epigenomic techniques (n = 27, 100 %), with the majority incorporating *in vitro* (n = 21, 78 %) (Bitler et al., 2023; Bustos et al., 2023; Choi et al., 2016; Fukumoto et al., 2019; Grimm et al., 2019a; He et al., 2024a; Jamal et al., 2022; Kharat et al., 2020; Kondrashova et al., 2018; Kong et al., 2022; Kukita et al., 2019; Meghani et al., 2018; Nesic et al., 2021; Pulliam et al., 2018; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Wang et al., 2012; Watson et al., 2019; Wu et al., 2024; Zhang et al., 2024) and transcriptomics (n = 13, 48 %) analyses (Bustos et al., 2023; Choi et al., 2016; Hurley et al., 2021; Kondrashova et al., 2018; Kong et al., 2022; Meghani et al., 2018; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Wang et al., 2012; Watson et al., 2019; Wu et al., 2024; Zhang et al., 2024) (Figure S1E). Only 19 % (n = 5) involved clinical cohorts or trials (Aref-Eshghi et al., 2020; Bi et al., 2013; Hurley et al., 2021; Kirmizitas et al., 2024; Sahnane et al., 2020), reflecting a translational gap in the current literature. Methylation emerged as the most studied epigenetic mechanism (59 %, n = 16) (Aref-Eshghi et al., 2020; Bi et al., 2013; Drew et al., 2011; Fukumoto et al., 2019; Grimm et al., 2019a; He et al., 2024a; Hurley et al., 2021; Jamal et al., 2022; Kharat et al., 2020; Kirmizitas et al., 2024; Kondrashova et al., 2018; Kukita et al., 2019; Nesic et al., 2021; Pulliam et al., 2018; Sahnane et al., 2020; Zhang et al., 2024), followed by non-coding RNAs (33 %, n = 9) (Bustos et al., 2023; Choi et al., 2016; Kong et al., 2022; Meghani et al., 2018; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Wang et al., 2012; Wu et al., 2024) and histone modifications (13 %, n = 4) (Bitler et al., 2023; He et al., 2024a; Kukita et al., 2019; Watson et al., 2019). Most investigations employed cancer cell lines (Bi et al., 2013; Bitler et al., 2023; Bustos et al., 2023; Choi et al., 2016; Drew et al., 2011; Fukumoto et al., 2019; Grimm et al., 2019a; He et al., 2024a; Jamal et al., 2022; Kharat et al., 2020; Kondrashova et al., 2018; Kong et al., 2022; Kukita et al., 2019; Meghani et al., 2018; Pulliam et al., 2018; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Wang et al., 2012; Watson et al., 2019; Wu et al., 2024; Zhang et al., 2024), tumour tissues (Aref-Eshghi et al., 2020; Bi et al., 2013; Bitler et al., 2023; He et al., 2024a; Hurley et al., 2021; Kukita et al., 2019; Meghani et al., 2018; Sahnane et al., 2020; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Watson et al., 2019; Wu et al., 2024), and murine xenograft (Bitler et al., 2023; Drew et al., 2011; Fukumoto et al., 2019; Hurley et al., 2021; Nesic et al., 2021; Pulliam et al., 2018; Sun et al., 2013; Wang et al., 2012; Watson et al., 2019; Wu et al., 2024;

Zhang et al., 2024). Sample sizes ranged from two cell lines (Fukumoto et al., 2019) to 196 patients from a cohort study (Hurley et al., 2021), with as few as ten tumour samples (Bi et al., 2013), six normal ovarian tissues (Kukita et al., 2019). While blood-based analyses ranged from 10 OC samples (Bi et al., 2013) to 31 serially collected cell free DNA (cfDNA) samples from patients with recurrent HGSOE (Kirmizitas et al., 2024) (Figure S1F). The most frequently utilised cell lines included SKOV3 (n = 9) (Grimm et al., 2019a; He et al., 2024a; Jamal et al., 2022; Kondrashova et al., 2018; Kong et al., 2022; Sun et al., 2013; Sun et al., 2021; Vescarelli et al., 2020; Wu et al., 2024), PEO1 (n = 7) (Bitler et al., 2023; Fukumoto et al., 2019; Grimm et al., 2019a; Kondrashova et al., 2018; Pulliam et al., 2018; Wang et al., 2012; Watson et al., 2019), and OVCAR8 (n = 5) (Fukumoto et al., 2019; Grimm et al., 2019a; Kondrashova et al., 2018; Wu et al., 2024; Zhang et al., 2024) (Figure S1G, Table S10).

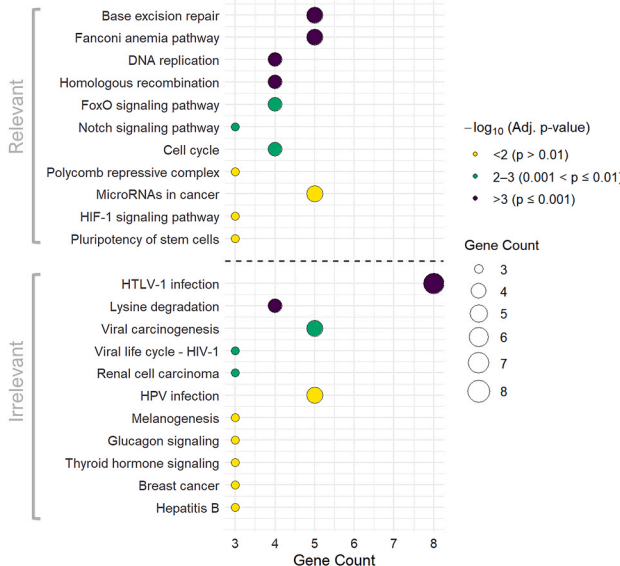
Despite heterogeneity in the composition of the epigenetic hallmarks investigated and limitations in outcome measures (Figure S1H), the findings remain clinically informative and several key mechanisms underlying PARPi resistance were consistently observed (Table S11 and S12). Notably, inhibition of *PRMTs* restored PARPi sensitivity in HR-proficient tumours (Zhang et al., 2024), while increased differential methylation regions (DMRs) and aneuploid cfDNA correlated with resistance (Kirmizitas et al., 2024). In total, 36 genes were linked to epigenetic alterations influencing PARPi response. These include DNA methylation changes in *CARM1*, *PRMT1*, *PRMT5* (Zhang et al., 2024), *EZH2*, *JAK3*, *SOX2*, *POU2AF1*, *PTK6*, *VHL* (Kirmizitas et al., 2024), *RAD51C* (Hurley et al., 2021; Kirmizitas et al., 2024; Nesic et al., 2021), *POLB*, *LIG1*, *RNASEH2A*, *RNASEH2B*, *XRCC1* (Jamal et al., 2022), *BRCA1*, *BRCA2* (Aref-Eshghi et al., 2020; Drew et al., 2011; Grimm et al., 2019a; He et al., 2024a; Jamal et al., 2022; Kharat et al., 2020; Kondrashova et al., 2018; Pulliam et al., 2018; Sahnane et al., 2020), *TET2* (Kharat et al., 2020), *ATR* (Grimm et al., 2019a), *EP300* (Grimm et al., 2019a), *PARP1* (Bi et al., 2013), and *FZD10* (Fukumoto et al., 2019). Histone-modifying enzymes (e.g., *EHMT1* and *EHMT2* (Watson et al., 2019), *SMYD2* (Kukita et al., 2019), *CREBBP*, *EP300*, *KAT2B*, and *KAT7* (Bitler et al., 2023),) and chromatin remodelling genes also featured prominently. Additionally, ncRNAs—including microRNA (miRNAs, e.g., miR-181a (Bustos et al., 2023), miR-506-3p (Sun et al., 2021), miR-200c (Vescarelli et al., 2020), miR-493-5p (Meghani et al., 2018), miR-622 (Choi et al., 2016), miR-9 (Sun et al., 2013), and miR-96 (Wang et al., 2012)) and long ncRNAs (lncRNAs) which were linked to *PART1* and *PHB2* (Wu et al., 2024)—modulated DNA repair and apoptosis pathways. Specific miRNAs were also associated with epigenetic regulators like *EZH2* (Sun et al., 2021), *BRCA1* (Sun et al., 2013; Vescarelli et al., 2020), *NRP1* (Vescarelli et al., 2020), *FEN1*, *RNASEH2A*, *SSRP1* (Meghani et al., 2018), *Ku80* (Choi et al., 2016), *RAD51*, and *REV1* (Wang et al., 2012), meanwhile enhanced lncRNAs such as *PART1* stabilised mRNAs of resistance-associated targets (Wu et al., 2024). Of all genes reported, *BRCA1*, *BRCA2*, and *RAD51C* were the most frequently implicated genes, with loss of methylation in promoter region consistently linked to acquired resistance (Hurley et al., 2021; Jamal et al., 2022; Nesic et al., 2021). Emerging evidence also shows that N6-methyladenosine (m6A) (Fukumoto et al., 2019) plays an increasing role in RNA epigenetics, modulating drug response through altered transcript stability.

3.4. Bioinformatics analyses of all identified genes

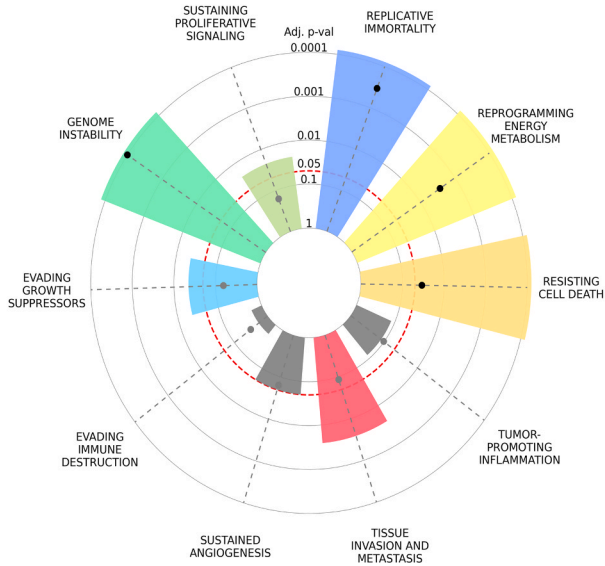
To elucidate the biological relevance of all identified 36 genes, we conducted hallmark and pathway enrichment analyses. These analyses indicated that genes are functionally and spatially linked to DNA repair pathways and localised primarily within the nucleus and intracellular organelles (Fig. 2A–C). The majority of enriched KEGG pathways hypothetically relevant to OC and PARPi resistance revealed significant involvement of base excision repair (BER) (adjusted $p = 1.3 \times 10^{-5}$) and DNA replication (adjusted $p = 8.5 \times 10^{-6}$), with *CREBBP*, *EP300*, and



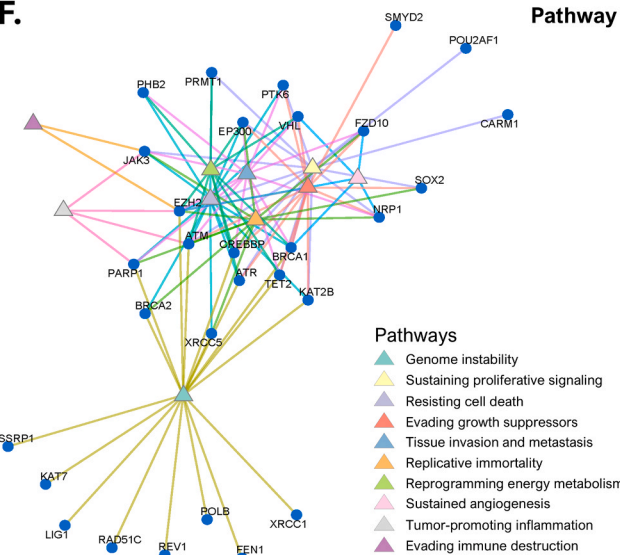
D. KEGG pathways enrichment: Hypothetically relevant and irrelevant to ovarian carcinogenesis and PARPi resistance



E. Cancer hallmarks related to disease mechanisms



F.



Pathway gene interaction map

Pathways	Genes involved
Genome instability (n=18/747)	ATM, ATR, BRCA1, BRCA2, CREBBP, EZH2, FEN1, KAT2B, KAT7, LIG1, PARP1, POLB, RAD51C, REV1, SSRP1, TET2, XRCC1, XRCC5
Sustaining proliferative signaling (n=16/3574)	ATM, ATR, BRCA1, CARM1, CREBBP, EP300, EZH2, FZD10, JAK3, KAT2B, NRP1, POU2AF1, PRMT1, PTK6, SOX2, TET2
Resisting cell death (n=15/1941)	ATM, ATR, BRCA1, BRCA2, CREBBP, EP300, EZH2, JAK3, KAT2B, PARP1, PHB2, PRMT1, PTK6, VHL, XRCC5
Evading growth suppressors (n=14/3288)	ATM, ATR, BRCA1, CREBBP, EP300, EZH2, FZD10, KAT2B, NRP1, PTK6, SMYD2, SOX2, TET2, VHL
Tissue invasion and metastasis (n=13/2318)	ATM, BRCA1, CREBBP, EP300, EZH2, FZD10, JAK3, NRP1, PARP1, PHB2, PTK6, TET2, VHL
Replicative immortality (n=10/547)	ATM, BRCA2, CREBBP, EP300, EZH2, FZD10, JAK3, NRP1, PARP1, SOX2, XRCC5
Reprogramming energy metabolism (n=10/740)	ATM, ATR, BRCA1, CREBBP, EP300, EZH2, PHB2, PRMT1, TET2, VHL
Sustained angiogenesis (n=5/796)	BRCA1, EZH2, FZD10, NRP1, VHL
Tumor-promoting inflammation (n=4/769)	ATM, EZH2, JAK3, PARP1
Evading immune destruction (n=2/749)	EZH2, JAK3

(caption on next page)

Fig. 2. Integrated analysis of cancer hallmarks of epigenetically regulated PARPi resistance genes using TCGA and GSE DNA microarray datasets to reveal their potential mechanisms. (A–C) Gene Ontology (GO) analysis indicated functional enrichment in DNA repair mechanisms (biological process); sequence-specific double-stranded DNA binding (molecular function; and nuclear or organelle-associated localisation (cellular component). (D) KEGG pathway enrichment identified pathways relevant to ovarian carcinogenesis and drug resistance, including dysregulated DNA replication (adj. $p = 9.3 \times 10^{-6}$), base excision repair (adj. $p = 1.3 \times 10^{-5}$), and compensatory pathways including homologous recombination and NHEJ. Upregulation of *FoxO*, *Notch*, *HIF-1*, pluripotency, and cell cycle pathways suggest multilayered regulatory architecture in transcriptional reprogramming. In contrast, less directly relevant pathways—such as HTLV-1 infection, lysine degradation, viral carcinogenesis, and hormone signalling—were also enriched, likely reflecting shared DNA repair genes (*FEN1*, *LIG1*, *RNASEH2A*, and *RNASEH2B*), tissue specificity, or broader oncogenic processes. (E) Enrichment analysis revealed strong associations with cancer hallmarks, including genomic instability ($p \leq 0.0001$), replicative immortality ($p \leq 0.001$), metabolic reprogramming ($p \leq 0.01$), and evasion of cell death ($p \leq 0.05$). (F) Network topology analysis identified central nodes such as *ATM*, *A TR*, *EZH2*, *BRCA1*, and *CREBBP*, highlighting their pivotal regulatory roles. *EZH2* emerged as a key chromatin modifier across ten pathways. Distinct functional genes, such as *SMYD2* and *PHB2*, were linked to specialised oncogenic processes. Synergistic interactions (e.g., *ATM*–*BRCA1* in genomic instability; *EZH2*–*NRP1* in angiogenesis) reveal integrated resistance circuits and nominate *KAT2B*/*CREBBP* as candidate biomarkers or targets.

ATM complex emerging as key players (Fig. 2D, Table S13). Compensatory repair pathways such as HR (adjusted $p = 1.2 \times 10^{-4}$) and non-homologous end joining (adjusted $p = 8.1 \times 10^{-3}$) were also upregulated. In parallel, activation of *FoxO*, *Notch*, and *HIF-1* signalling pathways suggested roles in survival, proliferation, and hypoxia adaptation. Further enrichment highlighted the involvement of Fanconi anaemia

pathway, pluripotency and cell cycle regulation, alongside cancer-associated microRNAs, suggesting complex regulatory networks governing resistance phenotypes. Although hypothetically not specific to OC (or at least not yet established as such), another pathway such as HTLV-1 infection (adjusted $p = 1.3 \times 10^{-5}$) was enriched through overlapping DNA repair genes (*FEN1*, *LIG1*, *RNASEH2*), underscoring

DNA microarray (gene expression) and its association with PFS in primary OC cases

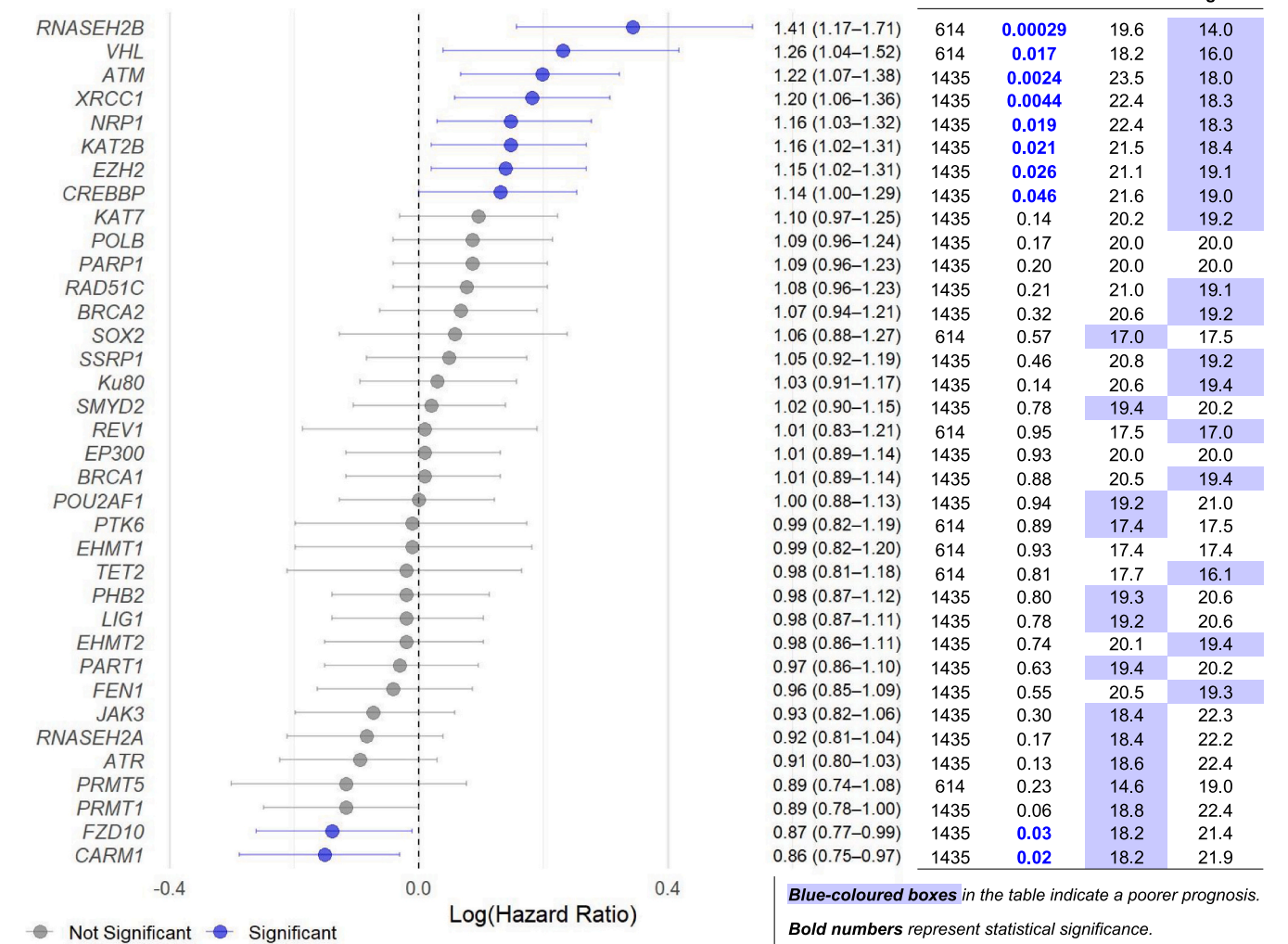


Fig. 3. Progression-free survival analysis of epigenetically regulated genes associated with PARPi resistance. Forest plot showing univariate progression-free survival analysis of 36 candidate genes identified through epigenetic hallmark profiling of PARPi resistance in ovarian cancer, using pre-relapse mRNA microarray data. Twelve genes were significantly associated with progression-free survival ($n = 614$ – 1435), indicating their potential utility as early biomarkers of therapeutic resistance.

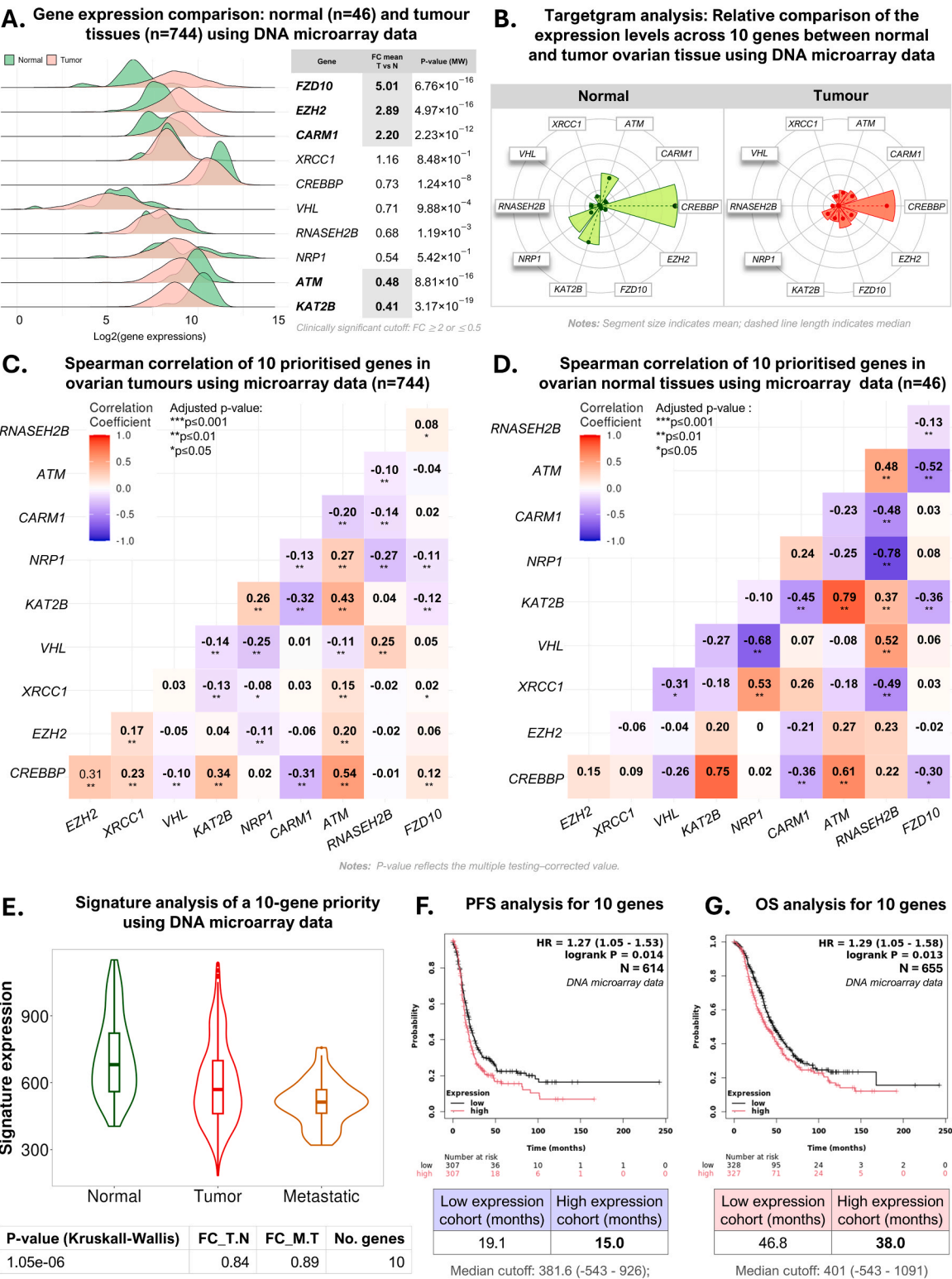


Fig. 4. Characterisation of a 10-gene epigenetic signature associated with PARPi resistance. (A) Violin plot showing differential expression between tumour and normal tissues across ovarian cancer cohorts. Of 10 prioritised genes, 6 were differentially expressed, with *FZD10* showing the highest overexpression (fold change [FC]=5.01) and *KAT2B* the lowest (FC=0.41). (B) Targetgram analysis of the top 10 prioritised genes revealed tissue-specific expression patterns: tumours exhibited elevated levels of *CREBBP*, *FZD10*, *EZH2*, and *CARM1*; normal tissues showed higher expression of *ATM*, *KAT2B*, and *NRP1*; and metastatic samples were enriched for *CREBBP*, *NRP1*, *CARM1*, and *ATM*. Segment size reflects mean expression; dashed lines represent medians. (C) Correlation analysis in ovarian cancer tissues revealed moderate co-expression among genes, with the strongest positive correlation between *CREBBP* and *ATM* ($p=0.54$), and the strongest negative between *KAT2B* and *CARM1* ($p=-0.32$). In normal ovarian tissues, the highest positive correlation was observed for *KAT2B* and *ATM* ($p=0.79$), and the strongest negative for *NRP1* and *RNASEH2B* ($p=-0.78$). (D) Gene signature scoring showed reduced expression in tumours versus normal tissues (DNA microarray FC=0.84) and marginal reduction in metastatic tissues (FC=0.89). (E) Higher expression of the 10-gene signature was associated with significantly shorter progression-free survival ($n = 614$; HR 1.27; 95 %CI: 1.05–1.53; $p = 0.014$). (F) Elevated signature expression predicted worse overall survival ($n = 655$; HR 1.29; 95 %CI: 1.05–1.58; $p = 0.013$).

conserved mechanisms of genomic maintenance. Other enriched pathways (i.e., lysine degradation, viral carcinogenesis, and hormone-related signalling) may reflect tissue-specific biology, broader oncogenic processes, or gene involvement in alternative disease mechanisms, but might not be directly implicated in PARPi resistance in OC. Fig. 2E shows that the hallmarks of these 36 genes are significantly associated with core oncogenic processes, including genomic instability ($p \leq 0.0001$), replicative immortality ($p \leq 0.001$), metabolic reprogramming ($p \leq 0.01$), and cell death resistance ($p \leq 0.05$) (Table S14).

Each enriched pathway was anchored by key genes with critical roles in oncogenic processes (Fig. 2F). Central hubs such as *ATM*, *ATR*, *BRCA1*, *CREBBP*, and *EZH2* emerged across multiple pathways, regulating genome stability, cell proliferation, apoptosis, and chromatin dynamics. *EZH2*, involved in ten distinct pathways, exemplifies the broad influence of epigenetic silencing and chromatin remodelling in treatment resistance. In contrast, genes like *SMYD2* (growth suppression evasion) and *PHB2* (cell death resistance, metabolic reprogramming) demonstrate more specialised, pathway-specific functions. Gene-pathway interactions, including *ATM*–*BRCA1* in genomic instability and *EZH2*–*NRP1* in angiogenesis, illustrate synergistic mechanisms. Broadly expressed regulators such as *CREBBP* and *KAT2B* appear across multiple hallmarks, reinforcing their relevance as potential biomarkers or therapeutic targets.

3.5. Prioritisation of genes as biomarkers

To pinpoint the most clinically actionable genes linked to PARPi resistance, we integrated findings from this systematic review with transcriptomic analyses of non-relapsed, primary OC tissues. We hypothesised that if these genes are dysregulated prior to relapse and are linked to disease progression, they may serve as biomarkers useful for early identification or risk stratification of PARPi resistance during first-line treatment.

Using publicly available datasets and web-based bioinformatics platforms, we assessed the prognostic value of candidate genes for PFS (Figs. 3 and S3) and OS (Figure S2 and S4), the former being the most relevant surrogate for therapeutic resistance and cancer relapse, as disease progression or recurrence in OC is primarily driven by chemoresistance and resistance to PARPi (Flynn and Ledermann, 2022; Shahnam et al., 2024; Timothée et al., 2024). Guided by the hypothesis that early gene expression may anticipate eventual resistance, we applied median expression thresholds to ensure reproducibility and cross-cohort consistency. Of 36 genes, four were significantly associated with OS, while ten were linked to PFS ($n = 614$ – 1435), underscoring their potential as early biomarkers of resistance. Ten genes (i.e., *RNASEH2B*, *VHL*, *ATM*, *XRCC1*, *NRP1*, *KAT2B*, *EZH2*, *CREBBP*, *FZD10*, and *CARM1*) were prioritised for downstream analysis (based on significant highest HR to lowest HR in PFS).

Among the ten prioritised genes, DNA microarray analysis revealed that five exhibited significant differential expression between tumour and normal tissues (considering p -value and cut-off fold change/FC ≤ 0.5 or ≥ 2 ; Fig. 4A). *FZD10* was the most upregulated (5.01-FC), while *KAT2B* was among the most downregulated (0.41-FC). We extended this analysis to 36 genes using both DNA microarray and RNA-seq, with results shown in Figure S5A–B. Furthermore, pan-cancer RNA-seq analysis across tumour types in which PARPis are clinically used (i.e., breast, ovarian, pancreatic, and prostate cancers) revealed consistent tumour-specific differential expression of the ten priority genes compared to normal tissue, with a few non-statistically significant exceptions (e.g., *XRCC1* in ovary, *CREBBP* in breast, *CARM1* in breast and pancreas, and *NRP1* and *XRCC1* in prostate; Figure S6).

Of these 10 genes, targetgram analysis revealed distinct tissue-specific expression patterns in DNA microarray (Fig. 4B) and RNA-seq (Figure S7A) data showed elevated *FZD10*, *EZH2*, and *CARM1* in tumours, whereas normal tissues showed higher levels of *ATM*, *KAT2B*, and *NRP1*, suggesting potential shifts in regulatory networks associated

with resistance. Using microarray data, correlation analysis in OC tissues highlighted modest co-expression among the top 10 genes, with strongest positive correlations observed between *CREBBP*–*ATM* ($\rho = 0.54$) and the strongest negative between *KAT2B*–*CARM1* ($\rho = -0.32$) (Fig. 4C). Similar trends were found in normal tissue, particularly *XRCC1*–*NRP1* ($\rho = 0.79$) and *NRP1*–*RNASEH2B* ($\rho = -0.78$) (Fig. 4D). RNA-seq correlation matrices showed similar pairwise associations, though with weaker correlation strength compared to tissue DNA microarray analysis—likely due to platform-specific technical differences and smaller sample sizes (Figures S7C–D).

Together, we created gene signature scores derived from the top 10 genes. We found that their expression were lower in cancer versus normal tissues (DNA microarray FC=0.84; RNA-seq FC=0.74) (Figs 4E and S7B). Importantly, higher expression of the 10-gene signature is associated with significantly worse PFS ($n = 614$, HR 1.27, 95 %CI: 1.05–1.53, $p = 0.014$) and OS ($n = 655$, HR 1.29, 95 %CI: 1.05–1.58, $p = 0.013$) (Fig. 4F and G). These results underscore the potential of a shared PARPi-resistance transcriptional landscape across multiple tumour types and support the relevance of these genes as biomarkers associated with resistance or therapeutic targets. Further, topological analysis among top 10 genes (Figure S7E) identified *ATM*, *CREBBP*, and *EZH2*, as central network hubs, implicated in key cancer hallmarks such as genomic instability, sustained proliferation, and evasion of growth suppressors—highlighting their broad regulatory influence on epigenetic control and DNA repair. The most enriched pathways—genomic instability (OR 19.19) and replicative immortality (OR 18.4)—indicate the centrality of *ATM*, *CREBBP*, and *EZH2* in maintaining tumour viability under therapeutic pressure. Additional pathways, including tissue invasion and metastasis, implicated *FZD10* and *NRP1* in extracellular matrix remodelling and WNT signalling, while *KAT2B* and *VHL* contributed to cell death resistance via hypoxia adaptation and histone acetylation. On the other hand, *FZD10*, *NRP1*, and *VHL* exhibit pathway-specific functions—angiogenesis, immune evasion, and hypoxic response—demonstrating integrative roles in cancer hallmarks. Tumour-promoting inflammation (OR 5.45) and immune evasion (OR 3.0) were comparatively less enriched. Together, these findings demonstrate *ATM* and *EZH2* as central regulatory hubs with extensive roles in epigenetic regulation and DNA repair, positioning them as key therapeutic targets in genomic instability and tumour progression.

4. Discussion

PARPi, used as maintenance therapy, have reshaped the therapeutic landscape of OC, particularly in HGSOc. By exploiting synthetic lethality, PARPi target HRDs and disrupt the BER pathway, leading to accumulation of DNA damage and tumour cell death (Li and Zou, 2024). PARPi have demonstrated PFS benefits in both newly diagnosed and recurrent HGSOc, regardless of *BRCA* mutation status though responses are markedly stronger in *BRCA1/2*-mutated tumours (Domchek et al., 2016; Matulonis et al., 2016; Moore et al., 2018). Despite initial success, resistance to PARPi remains common, and current biomarkers (e.g., *BRCA* mutation status and HRD scores) are insufficient to predict long-term response. Despite regulatory approval, *BRCA* mutation status is an imperfect biomarker: only ~50 % of *BRCA*-mutant tumours respond to PARPi, with resistance frequently emerging via *BRCA1/2* reversion mutations (Konstantinopoulos et al., 2019; Mohyuddin et al., 2020; Oza et al., 2017). Meanwhile, the majority of patients are *BRCA*-proficient and excluded from treatment (Zhao et al., 2024). HRD scores, although predictive, are not universally reliable (Hodgson et al., 2018; Stronach et al., 2018; Zhao et al., 2024). They are limited by their inability to capture dynamic tumour evolution (Goodall et al., 2017; Patch et al., 2015; Zhao et al., 2024), incomplete representation of functional HR status (Lin et al., 2019; Miller et al., 2020; Zhao et al., 2024), and susceptibility to confounding genomic features (Hodgson et al., 2018; Lheureux et al., 2017; Pennington et al., 2014; Zhao et al., 2024). These limitations collectively contribute to patient

misclassification and suboptimal clinical decision-making, implying the urgent need for complementary or superior biomarkers of PARPi response and resistance.

One of the most well-studied areas in precision oncology is epigenetics; epigenetic modifications regulate gene expression and influence treatment outcomes. A recent strategy enhances PARPi sensitivity by epigenetically disrupting DNA damage response (DDR) genes in HR-proficient tumours, inducing HR deficiency to improve efficacy (Pilié et al., 2019). Epigenetic strategies show promise in sensitising HR-proficient cancers to PARPi by repressing DDR genes, a well-tolerated approach that enhances precision and minimises side effects. As most HGSOC patients are now eligible for PARPi, efforts focus on identifying responders and overcoming resistance. This study is the first to consolidate epigenetic biomarkers linked to PARPi resistance, which is likely driven by changes in DNA accessibility. We identified key epigenetically altered genes in PARPi resistance and evaluated their prognostic value and roles in tumour development, progression, metastasis, and chemoresistance.

4.1. Epigenetic modifications related to PARPi resistance: current evidence

4.1.1. DNA methylation as a modulator of PARPi resistance

DNA methylation has emerged as a key regulator of PARPi sensitivity and resistance in OC, primarily by modulating HR proficiency, replication fork stability, and tumour plasticity (Cuozzo et al., 2007). DNA methylation is dynamically regulated by DNA methyltransferases, which establish methylation, and TET enzymes, which maintain its fidelity by converting 5-methylcytosine to 5-hydroxymethylcytosine (5hmC) to facilitate active demethylation. A genome-wide siRNA screen identified loss of TET activity as a driver of PARPi and cisplatin resistance in *BRCA2*-deficient models, mediated through replication fork protection and reduced 5hmC (Kharat et al., 2020). Hypoxia-induced TET suppression further reinforces resistance phenotypes, suggesting that restoration of TET function or 5hmC levels may resensitise tumours to PARPi (Thienpont et al., 2016).

While *BRCA1/2* biallelic loss is a well-established predictor of PARPi response, many responsive tumours harbour monoallelic mutations, deletions, or promoter hypermethylation (Aref-Eshghi et al., 2020). Grimm et al. employed a comprehensive repair gene capture library across OC cell lines, identifying *BRCA1/2* mutations, including a reversion event in PEO1, as resistance drivers, while promoter hypermethylation of *BRCA1* and *MGMT* in OVCAR8 correlated with olaparib sensitivity. Mutations in *ATM*, *ATR*, and *EP300* were enriched in sensitive models, implicating these pathways in PARPi responsiveness (Grimm et al., 2019b).

Pyrosequencing and digital PCR analyses have revealed that *BRCA1* (but not *BRCA2*) promoter methylation is associated with increased PARPi sensitivity and is mutually exclusive from *BRCA* mutations (Kondrashova et al., 2018; Sahnane et al., 2020). *BRCA1* promoter hypermethylation, detected in 10–15 % of OC, correlates with platinum sensitivity and favourable outcomes (Aref-Eshghi et al., 2020). The ARIEL2 trial further demonstrated that homozygous *BRCA1* methylation predicts low *BRCA1* expression, loss of heterozygosity, and rucaparib sensitivity, while heterozygous methylation often arises post-chemotherapy and correlates with resistance (Kondrashova et al., 2018; Swisher et al., 2017). Loss of *BRCA1* methylation during treatment may mirror the impact of reversion mutations, leading to acquired resistance (Sahnane et al., 2020). These findings show the potential of methylation status as a dynamic biomarker. Importantly, Swisher et al., 2021 reported a 50 % response rate to rucaparib in *BRCA1*-hypermethylated tumours, functionally recapitulating *BRCA1*-mutant phenotypes. These epigenetic alterations appear early in tumorigenesis, span histological subtypes, and are rarely found in normal tissue, thereby making them attractive therapeutic biomarkers.

While germline or somatic *BRCA1/2* mutations and HRD are

established predictors of PARPi sensitivity, a subset of responders lacks these canonical biomarkers. In such cases, hypermethylation of other HR genes (e.g., *ATM*, *CHEK2*, *BARD1*, and *BRIP1*) may induce a “BRCAness” phenotype in *BRCA* wild-type tumours, thereby expanding the population that could benefit from PARPi therapy. Nevertheless, intratumoural heterogeneity and epigenetic reprogramming continue to challenge robust patient classification and durable therapeutic responses (Aref-Eshghi et al., 2020). ARIEL2 Part 1 has also reinforced the predictive potential of *RAD51C/D* mutations and *BRCA1* methylation in rucaparib sensitivity (Swisher et al., 2017). Parallel findings from trials such as NOVA (Del Campo et al., 2019) and ARIEL3 (Coleman et al., 2017) have highlighted the predictive value of epigenetic alterations, particularly *BRCA1* and *RAD51C* promoter hypermethylation, as well as defects in other HR repair (HRR) genes, such as *XRCC3* (Drew et al., 2011). Building on functional screening (Jamal et al., 2022) assessed olaparib sensitivity across candidate genes previously implicated in patient stratification. *RAD51C* loss, in particular, mimicked *BRCA* deficiency and conferred marked sensitivity, whereas *RAD51B* and *ATM* conferred partial responses. These findings suggest combinatorial strategies (e.g., co-targeting with *ATR* or *DNA-PK* inhibitors) may potentiate efficacy in HR-proficient contexts (Jamal et al., 2022).

Methylation plasticity, however, poses a challenge to biomarker reliability. Nesic et al. identified *RAD51C* promoter methylation as a marker of initial PARPi sensitivity; however, even “partial demethylation” during therapy reactivated *RAD51C* expression, restoring HR and driving resistance. The accuracy of methylation-based detection is further limited by tumour purity, copy number variations, and epiallelic heterogeneity—only fully unmethylated alleles strongly associate with gene re-expression (Patch et al., 2015). Moreover, intratumoural heterogeneity may present as “partial demethylation,” where a subpopulation of cells becomes fully demethylated and resistant, while others remain methylated and potentially PARPi-sensitive, complicating both detection and therapeutic response (Mazor et al., 2016). In one pre-treated HGSOC case, homozygous *meRAD51C* shifted to a heterozygous state (defined by the emergence of both methylated and unmethylated alleles) following chemotherapy (Kondrashova et al., 2018). Another study confirmed that demethylation-induced reactivation of *RAD51C* drives cross-resistance to PARPi, accompanied by transcriptomic shifts involving cGAS/STING signalling and interferon regulatory factor (IRF) pathway activation—mechanisms not directly tied to methylation status or platinum sensitivity (Hurley et al., 2021). Complementing *BRCA1/2* and *RAD51C* methylation, *XRCC3* inactivation has emerged as a recurrent, *BRCA*-independent mechanism of PARPi sensitivity, acting through the *RAD51C*-containing CX3 complex (a distinct HR submodule critical for DNA repair fidelity) (Jamal et al., 2022).

Despite strong mechanistic and clinical evidence, real-time methylation profiling is not currently integrated into standard biomarker panels for PARPi eligibility, representing a major translational gap (Drew et al., 2011). Recent advances in epigenetic editing offer proof-of-concept that promoter hypermethylation (e.g., at *BRCA1*) and histone deacetylation (e.g., H3K27ac removal) can be synthetically introduced to suppress HRR and enhance PARPi efficacy (He et al., 2024b). Concurrently, methylation-dependent interference with transcription factor binding adds a critical regulatory layer to PARPi response. For example, promoter hypermethylation can inhibit the binding of E26 transformation-specific (ETS) family transcription factors—recognisers of the 5'-(C/A)GGA(A/T)-3' motif—at sites such as the *PARP1* promoter, where these motifs are enriched (Legrand et al., 2023; Wei et al., 2023). In *BRCA*-mutant OC, *PARP1* promoter hypomethylation permits ETS binding, driving overexpression and contributing to tumour progression (Bi et al., 2013). Moreover, *PARP1* itself can upregulate *DNMT1*, reinforcing aberrant methylation patterns. As a chromatin-bound protein, *DNMT1* reshapes the epigenome and may act as both a mediator and biomarker of epigenetic resistance pathways (Bi et al., 2013). Given the reversible nature of epigenetic modifications, therapeutic targeting of methylation has gained traction. Pulliam et al.

(2018) reported that combining the DNMT inhibitor (guadecitabine) with talazoparib reduced tumour burden and improved survival in *BRCA*-proficient models. Similarly, *TET2* knockdown enhanced PARPi sensitivity, underscoring the role of active demethylation. Mechanistic studies revealed that DNMT inhibition elevates reactive oxygen species and protein kinase A (PKA), enhancing *PARP* trapping independent of *BRCA2* status. These effects were not reversed by *BRCA2* overexpression, supporting a *BRCA*-independent sensitisation mechanism. This supports the promise of epigenetic–PARPi combination therapies, particularly in otherwise unresponsive tumours (Pulliam et al., 2018).

RNA modifications are emerging as critical regulators of PARPi resistance. Fukumoto et al. demonstrated that elevated N6-methyladenosine (m⁶A) methylation at the 3′ untranslated region of *FZD10* mRNA stabilises its expression, promoting resistance. Suppression of the m⁶A demethylases *FTO* and *ALKBH5* intensified this effect. Functionally, *FZD10* knockdown impaired HR in resistant cells, whereas its upregulation enhanced HR in parental lines—implicating Wnt/ β -catenin signalling in HR regulation independently of *BRCA2* reversion. These findings reveal a novel epitranscriptomic axis driving resistance and suggest that targeting Wnt signalling may overcome resistance in specific settings. Beyond discrete gene-level alterations, global epigenetic reprogramming appears to underlie adaptive resistance (Fukumoto et al., 2019). Kirmizitas et al. identified a higher burden of differentially methylated regions (DMRs) in resistant versus sensitive patients across both pre- and post-treatment samples, indicating widespread epigenetic plasticity. Genome-wide cfDNA and MeD-seq analyses from patients receiving PARPi maintenance revealed pre-treatment hypermethylation signatures in resistant cases. These were further categorised into “predictive,” “dynamic,” and “response” epigenetic hallmarks, mapping resistance and progression to distinct stages. Notably, tumour driver genes (*SOX2*, *EZH2*, *PTK6*) and HRD-related genes (*RAD51C*) were recurrently altered, reinforcing the link between methylation shifts and therapy failure (Kirmizitas et al., 2024).

Converging evidence, as outlined above, highlights methylation-driven epigenetic reprogramming—encompassing DNA and RNA methylation, chromatin accessibility, and transcriptional regulation—as a central mechanism of PARPi resistance, underscoring the therapeutic potential of epigenetic co-targeting to enable durable and precise resensitisation strategies in PARPi-resistant OC.

4.1.2. Histone modification and chromatin dynamics in PARPi resistance

Histone modifications are increasingly recognised as pivotal regulators of PARPi resistance in OC, acting through chromatin remodelling and transcriptional reprogramming. Accumulating evidence implicates both histone methylation and acetylation in shaping tumour cell survival and DNA repair capacity under therapeutic pressure. demonstrated that PARPi-resistant cells exhibit elevated levels of H3K9me2 due to upregulation of the methyltransferases *EHMT1/2*. Targeted knockdown of *EHMT1/2* not only reduced H3K9me2 but also impaired DNA repair and resensitised cells to PARPi. Furthermore, these enzymes were shown to interface with key pro-survival pathways (*mTOR*, *AKT*, *MYC*), reinforcing their role in resistance (Watson et al., 2019). Histone acetylation also contributes to therapy escape. Bitler et al. (2023) reported increased H3K14 acetylation in resistant OC cells, associated with heightened histone acetyltransferase (HAT) activity and a transcriptionally permissive chromatin state (He et al., 2024a). Inhibition of specific HATs, such as *BRPF3*, restored PARPi sensitivity, while *PCAF* depletion paradoxically conferred resistance, suggesting distinct, context-dependent roles of individual HATs. Conversely, pharmacological inhibition of *HBO1* (via WM-3835) showed limited efficacy, highlighting the complexity of HAT function (Bitler et al., 2023).

The histone methyltransferase *SMYD2* has also emerged as a key player in resistance, particularly in HGSOC. Kukita et al. (2019) observed marked *SMYD2* overexpression in HGSOC tissues relative to normal ovarian epithelium. Its inhibition disrupted chromatin structure, induced PARP cleavage, enhanced p53-mediated apoptosis, and

impaired cell proliferation, thereby supporting its potential as a therapeutic target, either alone or in combination with PARPis. These findings suggest the critical role of histone methylation (e.g., H3K9me2) and acetylation (e.g., H3K14ac) in modulating PARPi response. Altered expression of chromatin modifiers reshapes DNA accessibility and repair fidelity, contributing to both intrinsic and acquired resistance. Despite growing preclinical evidence, the clinical relevance of histone-based resistance mechanisms remains underexplored.

4.1.3. Non-coding RNAs as epigenetic modulators of PARPi resistance

Non-coding RNAs, including microRNAs (miRNAs), lncRNAs, and circular RNAs (circRNAs), have emerged as potential regulators of PARPi response in OC, influencing DNA repair fidelity, apoptosis, immune evasion, and chromatin remodelling. Through their multifaceted roles, ncRNAs either potentiate resistance or enhance drug sensitivity, representing an underexplored frontier in overcoming therapeutic failure. Among lncRNAs, *PART1* has been shown to modulate PARPi sensitivity via its transcript variant *PART1-TV3*, which stabilises *PHB2*, a mitophagy receptor integral to apoptotic maintenance (Wu et al., 2024). Loss of *PART1* induces resistance by activating senescence-associated signalling (MAPK, FoxO, p53, AGE-RAGE), increasing IL-6 secretion, and promoting an inflammatory, drug-tolerant phenotype (Wu et al., 2024). Restoration of *PHB2* reverses this effect, underscoring the *PART1*–*PHB2* axis as a therapeutic vulnerability.

Multiple miRNAs also orchestrate PARPi resistance by targeting DNA repair genes, pro-apoptotic factors, and replication stress mediators. For instance, miR-181a, elevated in olaparib- and cisplatin-resistant OC, suppresses STING-dependent inflammatory responses and propagates resistance via extracellular vesicle (EV)-mediated intercellular transfer (Bustos et al., 2023). miR-493-5p, upregulated in *BRCA2*-mutant tumours, promotes resistance by stabilising replication forks and down-regulating key genome stability regulators (e.g., *MRE11*, *CHD4*, *EXO1*, *RNASEH2A*, *FEN1*, *SSRP1*) without restoring HR (Meghani et al., 2018). Conversely, certain miRNAs sensitise tumours to PARPis. miR-506-3p suppresses the *EZH2*/Wnt/ β -catenin axis and downstream targets such as *CDH2*, *SNAI2*, and *CDK4*, curbing epithelial–mesenchymal transition, proliferation, and metastasis (Sun et al., 2021). miR-96 disrupts HR by targeting *RAD51* and *REV1* (Wang et al., 2012), while miR-9 enhances PARPi and platinum sensitivity (HR 0.63) via dual suppression of *BRCA1* and *PARG*, correlating with favourable prognosis (Sun et al., 2013). miR-622 promotes resistance by inhibiting *Ku80* and redirecting DNA repair from non-homologous end joining (NHEJ) to HR restoration in *BRCA1*-deficient cells, effectively bypassing synthetic lethality (Choi et al., 2016). miR-200c, by targeting *NRPI1*, reverses olaparib resistance via suppression of autophagy and restoration of apoptosis (Vescarelli et al., 2020). Despite these mechanistic insights, clinical translation remains limited, with few ncRNAs validated as biomarkers associated with resistance or therapeutic targets.

Growing evidence also reveals the role of circular RNAs (circRNAs) and competing endogenous RNA (ceRNA) networks in mediating PARPi response. Kong et al. identified a lncRNA *SNHG14*–miR-320b–circRNA network regulating *ATP8A1* (lipid homeostasis) and *WNK3* (cell survival), genes implicated in lipid homeostasis and cell survival, respectively. Downregulation of *WNK3* in resistant cells further implicates this axis in therapeutic escape (Kong et al., 2022). Collectively, these findings position ncRNAs as central players in the epigenetic regulation of PARPi resistance. While some ncRNAs facilitate resistance via replication fork protection, DNA repair reprogramming, or immune suppression, others restore drug sensitivity by disrupting survival pathways. However, the lack of translational progress in ncRNA research highlights a critical bottleneck in addressing PARPi resistance.

4.1.4. Other resistance mechanisms involving epigenetic regulators

Beyond methylation itself, other epigenetic regulators are increasingly implicated. Arginine methyltransferases (*PRMTs*), including *PRMT1*, *CARM1*, and *PRMT5*, have been shown to maintain DDR gene

expression via chromatin regulation and alternative splicing (Zhang et al., 2024). *PRMT* inhibition sensitises HR-proficient OC cells to PARPis by reducing *ERCC1* expression and enhancing DNA damage, particularly when *PRMT1* and *PRMT5* are co-inhibited. The observed *PRMT* "addiction" in certain tumour contexts suggests that *PRMT* inhibition could induce synthetic lethality by destabilising *DDR* gene transcription and mimicking *BRCA*-deficient states. Given the limited clinical activity of *PRMT* inhibitors as monotherapies, their rational combination with PARPis presents a promising avenue to overcome resistance in HR-proficient tumours (Jarrold and Davies, 2019).

4.2. Prioritised epigenetic regulators of PARPi resistance: prognostic and therapeutic implications

Despite growing recognition of epigenetic mechanisms in shaping PARPi response, the clinical translation of these findings remains limited. We systematically evaluated the expression and prognostic relevance of ten candidate genes with established or putative roles in PARPi resistance in primary OC tissue: *ATM*, *EZH2*, *FZD10*, *EP300*, *CREBBP*, *NRP1*, *CARM1*, *RNASEH2B*, *VHL*, and *XRCC1*. These genes, selected based on associations with PFS, formed a composite expression score linked to poor prognosis, suggesting their collective potential as

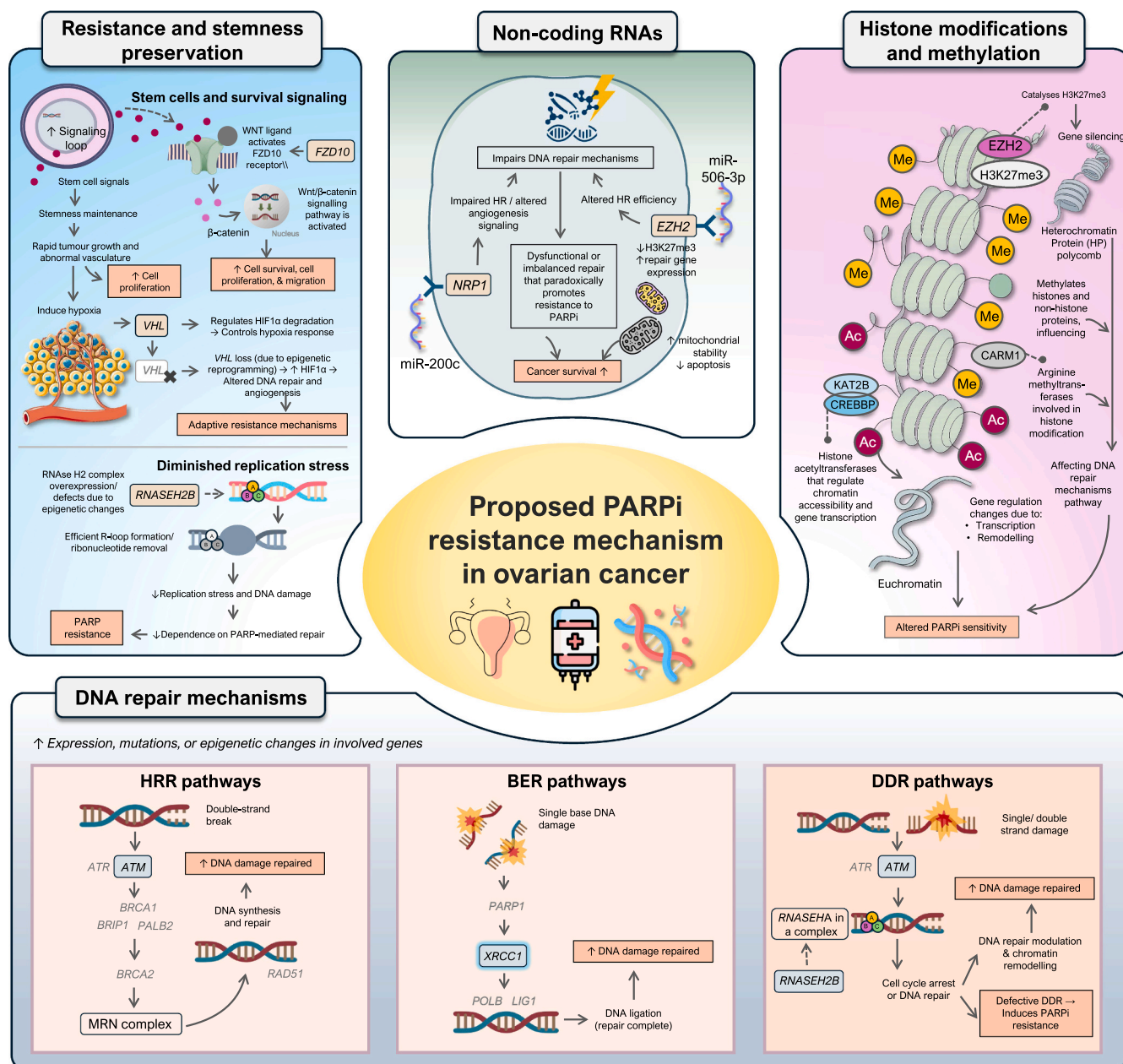


Fig. 5. Proposed epigenetic mechanisms contributing to PARP inhibitor (PARPi) resistance in ovarian cancer involving the ten prioritised genes. Resistance to PARPis in ovarian cancer is driven by complex epigenetic reprogramming. Aberrant promoter methylation impairs homologous recombination repair (HRR) and promotes stemness. Upregulation of histone methyltransferases (including *EZH2* and the protein arginine methyltransferase *CARM1*) along with dysregulation of histone acetyltransferases such as *KAT2B* and *CREBBP*, represses DNA repair gene expression. Post-transcriptional regulation by non-coding RNAs—including microRNAs such as miR-200c (targeting *NR1*) and miR-506-3p (targeting *EZH2*)—modulates DNA repair, apoptosis, survival, and angiogenesis signalling. These alterations converge on key repair pathways, including HRR, base excision repair (BER), and the DNA damage response (DDR). The expression of *ATM*, *XRCC1*, and *RNASEH2B* is further modulated by oncogenic signalling via Wnt (*FZD10*), hypoxia-inducible factor 1 (HIF-1), and angiogenic (*VHL*) pathways. Functional enrichment analysis links these genes to core cancer hallmarks, supporting their potential as targets for combined epigenetic and DNA repair-based therapies.

biomarkers of therapeutic resistance (Table S16), suggesting potential for predictive modelling in future research.

ATM, a central mediator of the DNA damage response, has been associated with increased OC risk (OR 2.85, 95 %CI: 1.30–6.32), though its role in treatment resistance and prognostic outcomes remains insufficiently defined (Lu et al., 2019). *EZH2*, a histone methyltransferase and key Polycomb complex component, has been implicated in poor OS ($p < 0.05$) (Rao et al., 2010), platinum resistance (2-fold overexpression in resistant tumours lacking tumour-infiltrating lymphocytes; $p = 0.01$), and unfavourable TCGA subtypes ($p = 6.7 \times 10^{-5}$) (Reid et al., 2021). *EZH2* methylation has also predicted chemotherapy response (OR 0.110; 95 %CI: 0.013–0.906; $p = 0.040$), while phosphorylated *EZH2* correlated with improved PFS (HR 0.388; 95 %CI: 0.164–0.917; $p = 0.031$) (Sun et al., 2020). *FZD10*, a Wnt signalling receptor, has shown inconsistent prognostic associations, with elevated expression linked to poorer OS (HR 1.34, $p = 0.037$), while promoter hypermethylation predicted improved PFS (HR 0.43, $p = 0.001$) and OS (HR 0.47, $p = 0.003$) (Tomar et al., 2017).

KAT2B, a histone acetyltransferase often dysregulated in cancer, was downregulated in epithelial OC and correlated with high tumour grade ($p = 0.038$), advanced FIGO stage ($p = 0.036$), and recurrence ($p = 0.027$) (Yao et al., 2025). Notably, cytoplasmic *KAT2B* localisation was associated with smaller tumour size ($p = 0.026$) and longer OS (HR 0.38, $p < 0.0001$), and remained an independent prognostic factor in multivariate analysis (HR 0.41, $p = 0.0007$) (Fermento et al., 2014). *CREBBP* overexpression predicted adverse outcomes (PFS: HR 1.25, $p = 0.00079$; OS: HR 1.19, $p = 0.014$); functional studies demonstrated its silencing increased cisplatin sensitivity via unfolded protein response inhibition and apoptosis induction (Hu et al., 2021). *NRP1*, significantly upregulated in OC (474 vs. 232 copies/ μ l, $p = 0.008$), was associated with metastasis and reduced 5-year OS (14.3 % vs. 49.1 %; $p < 0.001$) (Jiang et al., 2015). Elevated serum *NRP1* levels predicted poor PFS (HR 0.541, $p = 0.037$) and OS (HR 0.459, $p = 0.032$), independent of HGF/MET signalling (Klotz et al., 2022), which is a key pathway in epithelial–mesenchymal interactions, regulating cell proliferation, survival, and motility (Sonnenberg et al., 1993).

CARM1, amplified in ~10 % of HGSOs, correlated with poor OS (Karakashev et al., 2018), while low expression conferred improved PFS (HR 0.80, $p = 0.00056$) (Qiu et al., 2022). Although underexplored in OC, *RNASEH2B* was linked to shorter PFS (HR 1.53, $p = 9.7 \times 10^{-6}$) and reduced OS (28 vs. 33 months; $p = 0.01$) in TCGA (Polaczek et al., 2020). *VHL*, a negative regulator of HIF-1 α , suppresses OC cell proliferation and invasion, induces apoptosis and G1 arrest (Liu et al., 2014), and modulates downstream effectors by upregulating *BAX* and downregulating *MMP2*, *MMP9*, *E-cadherin*, *Akt*, and *Bcl-2* (Li et al., 2021). Its expression negatively correlated with HIF-1 α in both endometrioid ($r = -0.657$, $p = 0.039$) and serous ($r = -0.66$, $p = 0.027$) subtypes of OC (Lee et al., 2007). Finally, *XRCC1*, essential for BER (Krokan and Bjørås, 2013), was associated with poor PFS ($p = 0.048$), OS ($p = 0.020$) (Ali et al., 2020), platinum resistance ($p = 0.003$) (Abdel-Fatah et al., 2013), and aggressive disease features (e.g. FIGO stage $p = 0.001$, serous histology $p < 0.0001$, suboptimal debulking ($p = 0.002$)). Its Arg399Gln variant conferred adverse prognosis in late-stage OC (HR 1.79, $p = 0.003$), but improved OS in early-stage cohorts (HR 0.47, $p = 0.004$) (Zhang et al., 2018). A meta-analysis ($n = 1159$) linked the rs25487 T allele to increased OC risk (OR 1.46, $p = 0.00005$) (Zavarykina et al., 2024).

These findings demonstrate the evidence of epigenetic regulators' expression in OC prognosis, though clinical translation for patients receiving PARPi remains limited.

4.3. Mechanisms linking 10-gene signature to epigenetic PARPi resistance

Based on the reviewed literature, we synthesised the mechanisms of PARPi resistance in OC, with a focus on epigenetic hallmarks in a 10-gene signature as a candidate biomarker (Fig. 5); a full list of 36 genes

is shown in Figure S8). KEGG enrichment analyses (Table S13) and cancer hallmark (Table S15) revealed these genes are enriched in key resistance pathways, including impaired DNA repair, reduced replication stress, immune evasion, and stemness maintenance. PARPi resistance in OC arises from complex epigenetic reprogramming and other signalling pathways. Histone methyltransferase *EZH2* (via H3K27me3) is upregulated in resistant cells, repressing DNA repair genes (Sun et al., 2021). Arginine methyltransferases (*CARM1*) also modulate chromatin and repair proteins (Zhang et al., 2024). Resistance is reinforced through dysregulated histone acetylation via *KAT2B* and *CREBBP*, altering transcriptional accessibility (Watson et al., 2019). Another epigenetic modification, non-coding RNAs exert post-transcriptional control: miRNAs target key repair regulators—miR-506-3p (*EZH2*) (Sun et al., 2021) and miR-200c (*NRP1*) (Vescarelli et al., 2020)—enhancing resistance or survival. These changes converge on key repair axes: HRR (*ATR*) (Grimm et al., 2019a), BER (*XRCC1*) (Bi et al., 2013; Jamal et al., 2022), and DDR (*RNASEH2B*) (Jamal et al., 2022). Additional signalling through *FZD10* (Wnt) (Fukumoto et al., 2019), *VHL* (hypoxia) (Kirmizitas et al., 2024), and *NRP1* (angiogenesis/epigenetics) (Vescarelli et al., 2020) integrates cellular stress and survival cues, promoting resistance. Collectively, these interconnected epigenetic alterations drive a robust PARPi-resistant phenotype, identifying potential targets for combinatorial epigenetic and DNA repair-based therapies.

Our systematic analysis of genes implicated in PARPi resistance reveals expression patterns aligned with key oncogenic hallmarks, including genomic instability (Caracciolo et al., 2021; Oike et al., 2013), replicative immortality (Yaswen et al., 2015), metabolic reprogramming (Michels et al., 2014; Wang et al., 2022), and evasion of cell death (Noordermeer and van Attikum, 2019). Gene Ontology and pathway enrichment analyses further reveal DNA repair, DNA binding, and nuclear processes as central nodes of dysregulation (Fojo and Bates, 2013; Kanev et al., 2024; Pettitt and Lord, 2019). While classical mechanisms such as HR and BER remain central to PARPi response (Kanev et al., 2024), emerging evidence points to additional layers of complexity involving replication stress pathways, cell cycle checkpoints, and chromatin modulators (Khamidullina et al., 2024). Notably, signalling networks such as Fanconi (Del Valle et al., 2020; Taylor et al., 2020), *Notch* (Kawahara et al., 2017; Muñoz-Galván et al., 2019; Rebekah and Denise, 2022), *HIF-1* (Martí et al., 2021; Mehibel et al., 2021), and pluripotency pathways (Alizadeh et al., 2025; Xia et al., 2014), which are frequently enriched in resistant tumours, suggest epigenetically mediated shifts toward stem-like phenotypes and therapy-persistent states (Liu et al., 2017; Peng et al., 2024). The involvement of epigenetic regulators, including the Polycomb repressive complex (Campbell et al., 2013; Yang et al., 2021), underscores the role of chromatin state transitions in facilitating escape from synthetic lethality (Oike et al., 2013). However, the contribution of specific epigenetic mechanisms to PARPi resistance remains unclear, emphasising the need to prioritise the most clinically actionable drivers and guide their implementation in a clinical framework.

4.4. Proposed clinical implementation for the biomarker

Despite the increasing use of PARPi as frontline maintenance therapy for OC (regardless of *BRCA* mutation or HRD status), early identification of patients predisposed to resistance remains a critical clinical gap (Lorusso et al., 2020). Our proposed 10-gene signature potentially offers a clinically relevant tool to stratify patients based on their intrinsic susceptibility to PARPi resistance at diagnosis. While this universal approach maximises broad access to PARPi treatment at diagnosis (Tew et al., 2022), it inadvertently exposes a substantial subset to treatment-related toxicities (e.g., fatigue, myelosuppression, and rare but severe risks such as myelodysplastic syndromes) without clinical benefit (Szalontai et al., 2025). In such patients, quality of life and cost-effectiveness are significantly compromised. Additionally, PARPi therapies come with high financial costs, posing substantial challenges

for healthcare systems, particularly in low- and middle-income countries where cost-effectiveness and resource allocation are paramount.

Our 10-gene signature provides a clinically actionable framework to inform precision maintenance strategies: optimising PARPi duration, intensifying surveillance, or guiding early introduction of rational combination therapies. Many of these genes converge on epigenetic regulation (e.g. *CARM1*, *CREBBP*, *EZH2*, *KAT2B*), DNA damage response (*ATM*, *XRCC1*, *RNASEH2B*), and tumour-stroma interactions (*FZD10*, *NRP1*, *VHL*), all of which are targetable with existing or emerging small-molecule inhibitors. Preclinical data support combinatorial strategies such as *EZH2* inhibition restoring PARPi sensitivity in resistant models (Bitler et al., 2015). These findings suggest that patients stratified as high-risk for PARPi resistance may benefit from upfront adjuvant strategies or early therapeutic switching to rational drug combinations. Such an approach not only optimises clinical efficacy but mitigates harm, improves cost-effectiveness, and provides a roadmap for biomarker-driven clinical trials targeting resistance mechanisms in OC maintenance therapy.

5. Conclusion

This systematic review, integrated with transcriptomic analysis of publicly available microarray and RNA-seq datasets, confirmed the expression of 36 genes implicated in epigenetically mediated PARPi resistance across 27 studies. From these, we prioritised 10 clinically relevant genes and validated their prognostic significance as a signature for OS and PFS using non-relapsed OC tissue datasets. Our findings support the hypothesis that early transcriptional dysregulation of these genes, involving both upregulation and downregulation, may serve as indicators of PARPi resistance, detectable prior to the emergence of relapse-associated epigenetic alterations. *RNASEH2B* emerged as a key candidate, showing the highest hazard ratio for PFS, likely reflecting its role in replication stress response and DDR dysfunction. Of the prioritised genes (e.g., *ATM*, *XRCC1*), most of them converge on DDR pathways, suggesting resistance is primarily driven by enhanced repair capacity and genomic maintenance. These results offer a foundation for early risk stratification and personalised therapy in newly diagnosed OC. We propose future studies to further validate these biomarkers in PARPi-sensitive and -resistant OC cohorts.

CRedit authorship contribution statement

Conceptualisation: MH, JMF, Data curation: MH Formal Analysis: MH, JMF Funding Acquisition: JMF Investigation: MH Methodology: MH, JMF Project Administration: MH, JMF Resources: MH, JMF Software: MH Supervision: JMF Validation: JMF Visualisation: MH Writing – draft preparation: MH, JMF Writing – review & editing MH, JMF JMF served as the principal investigator for this study, secured funding, and made the decision to publish. As the guarantor, JMF assumed full responsibility for the work. MH and JMF conceptualised the research, contributed to the analysis, conducted the investigation, designed the methodology, managed project administration, provided resources, did literature review, drafted the paper, and reviewed and edited the manuscript to the manuscript. MH curated the data, did investigation, utilised software, and created visualisations of the study findings. JMF validated all evidence analyses and thoroughly supervised the study process. All mentioned authors critically revised the manuscript for important intellectual content and approved the final version for publication.

Ethics statement

Not applicable

Financial disclosure statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.critrevonc.2025.105012](https://doi.org/10.1016/j.critrevonc.2025.105012).

Data availability

All relevant data and materials supporting the findings of this study are available upon request from the corresponding author.

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