RAD51D Mutation

- HR eye & MMR eye: one-day assessment of DNA repair-defective tumors eligible for targeted therapy
- Genomic Signature for Initial Brain Metastasis Velocity (iBMV) in Non-Small-Cell Lung Cancer Patients: The Elusive Biomarker to Predict the Development of Brain Metastases?

RAD51D is a gene involved in the repair of double-stranded DNA breaks via the homologous recombination (HR) pathway.

Overview

- **Gene function**: RAD51D encodes a RAD51 paralog that participates in homologous recombination, a critical mechanism for error-free DNA repair.
- **Chromosomal location**: 17q12
- **Protein complex**: Forms a complex with RAD51B, RAD51C, and XRCC2.

Clinical Relevance

Cancer Susceptibility

- **Germline mutations** in RAD51D increase the risk of:
  - **Ovarian cancer** (significant risk)
  - **Breast cancer** (moderate risk)
  - Possibly **prostate and pancreatic cancer** (emerging evidence)

Therapeutic Implications

- RAD51D-mutated tumors show **homologous recombination deficiency (HRD)**.
- Sensitivity to **PARP inhibitors** (e.g., olaparib, rucaparib) via **synthetic lethality**.
- Implicated in treatment decisions for:
  - High-grade serous ovarian carcinoma
  - Triple-negative breast cancer (TNBC)
  - Prostate and pancreatic cancer (under study)

Diagnostic Use

- Detected via:
  - **Germline testing** in hereditary cancer panels
  - **Somatic mutation profiling** in tumor DNA
- Often assessed alongside BRCA1/2, RAD51C, and PALB2.

Mutation Types

- **Loss-of-function mutations** (nonsense, frameshift, splicing) may lead to complete HRD.
- **Monoallelic germline mutations** confer cancer susceptibility.
- **Biallelic inactivation** (somatic + germline or two somatic hits) required for therapeutic sensitivity.

Summary Table

Aspect	RAD51D Mutation Summary
Gene function	Homologous recombination DNA repair
Inheritance	Autosomal dominant (cancer risk)
Cancer association	Ovarian > Breast > Others (under study)
Therapy implication	PARP inhibitors (HRD-targeted)
Diagnostic testing	Germline and tumor profiling

Homologous recombination (HR) and mismatch repair (MMR) act as guardians of the human genome, and defects in HR or MMR are causative in at least a quarter of all malignant tumors. Although these DNA repair-deficient tumors are eligible for effective targeted therapies, fully reliable diagnostic strategies based on functional assay have yet to be established, potentially limiting safe and proper application of the molecular targeted drugs.

Saito et al. showed that transient transfection of artificial DNA substrates enables ultrarapid detection of HR and MMR. This finding led them to develop a diagnostic strategy that can determine the cellular HR/MMR status within one day without the need for control cells or tissues. Notably, the accuracy of this method allowed the discovery of a pathogenic RAD51D mutation, which was missed by existing companion diagnostic tests. The methods, termed HR eye and MMR eye, are applicable to frozen tumor tissues and roughly predict the response to therapy. Overall, the findings presented here could pave the way for accurately assessing malignant tumors with functional defects in HR or MMR, a step forward in accelerating precision medicine [1)].

The role of Homologous Recombination (HR) and Mismatch Repair (MMR) pathways in maintaining genomic stability is well established, and defects in either are known drivers of tumorigenesis. As such, their disruption is not only a hallmark of malignancy but also a therapeutic opportunity, particularly with PARP inhibitors and immune checkpoint inhibitors, respectively. However, functional and timely identification of HR/MMR deficiency remains a bottleneck for effective clinical implementation of these therapies.

Study Contributions Saito et al. address a long-standing need for rapid, functional diagnostics of HR and MMR deficiency by introducing a novel transfection-based assay—HR eye and MMR eye—capable of delivering results within 24 hours. Their approach uses transient transfection of artificial DNA substrates in tumor cells, bypassing the need for germline controls or matched tissues. This is a notable innovation, as current methods (e.g., IHC, genomic sequencing, or MSI testing) are limited by sample quality, turnaround time, or interpretability in the context of complex variants.

Key findings include:

Detection of HR/MMR deficiency using a functional, rather than purely genetic, approach.

Identification of a pathogenic RAD51D mutation missed by conventional diagnostics.

Applicability to frozen tumor tissue, improving versatility and relevance in clinical settings.

Strengths Functional Relevance: Unlike genomic panels that may detect variants of uncertain significance (VUS), this method interrogates the actual repair capacity of tumor cells.

Speed and Simplicity: A one-day protocol significantly shortens diagnostic timelines, crucial in aggressive malignancies.

Sensitivity: The detection of a missed RAD51D mutation highlights the method's potential to improve diagnostic yield over current companion diagnostics.

Translational Potential: By offering predictive value for treatment response, this assay aligns with precision oncology goals.

Limitations and Concerns Validation Scope: The study would benefit from larger validation cohorts across multiple cancer types and clinical settings. Performance metrics (sensitivity, specificity, PPV, NPV) are not extensively reported.

Predictive vs. Prognostic: While the assay correlates with therapy response, prospective clinical trials are needed to confirm predictive value.

Tumor Heterogeneity: Functional assays may be affected by intra-tumoral heterogeneity or sample viability, especially in necrotic or poorly preserved specimens.

Infrastructure and Expertise: Although simple in concept, the method may require technical expertise and infrastructure not universally available in routine pathology labs.

Regulatory Considerations: Being a new diagnostic class, regulatory validation (e.g., CLIA, CE marking) may be a barrier to rapid adoption.

Clinical and Research Implications This work could shift the paradigm of HR/MMR testing from static genotyping to dynamic functional assessment, enabling:

Better selection of patients for PARP inhibitors and immune therapy.

Enhanced stratification in clinical trials for DNA repair-targeted therapies.

Reduction in false negatives due to non-coding mutations or epigenetic silencing, often missed in standard testing.

Conclusion Saito et al. present a pioneering functional diagnostic platform that overcomes key limitations of current HR/MMR detection methods. While promising, widespread adoption will require further clinical validation, standardization, and integration into therapeutic decision-making pipelines. If validated, HR eye and MMR eye could represent a major advancement toward real-time, functional precision oncology.

1)

Saito S, Kato S, Arai U, En A, Tsunezumi J, Mizushima T, Tateishi K, Adachi N. HR eye & MMR eye: one-day assessment of DNA repair-defective tumors eligible for targeted therapy. Nat Commun. 2025 May 12;16(1):4239. doi: 10.1038/s41467-025-59462-2. PMID: 40355434.