Everything you need to know about homologous recombination repair (HRR) and homologous recombination deficiency (HRD) testing

Introduction

The DNA damage response (DDR) pathways are critical to maintaining genome stability and integrity by detecting and correcting DNA damage. Activation of the precise pathway and mechanism of repair depends on the type of DNA damage. The inability to repair DNA damage is a critical factor in the development and progression of cancers.

Fundamental research in hereditary breast and ovarian cancers revealed the key roles of *BRCA1/2* in the genetic predisposition to cancer and their function in the homologous recombination repair (HRR) pathway. Subsequently, loss of *BRCA1/2* function has been well-studied as a cause of homologous recombination deficiency (HRD) that results in genomic instability. In addition to loss of *BRCA1/2* function, alterations in other genes involved in DNA repair pathways, either germline or somatic, can also be found in other cancer types, including prostate and pancreatic cancers.

DNA repair pathways are increasingly recognized as therapeutic targets, and further research on regulation of DDR pathways can contribute to better understanding of genome integrity, with implications for innovative treatment strategies for multiple tumor types.

BRCA, HRR, and HRD: roles and relevance in cancer

HRD is a phenotype characterized by the inability of a cell to effectively repair double-stranded DNA breaks using the HRR pathway [1].

The HRR pathway is an efficient and error-free pathway for accurate repair of double-stranded DNA breaks. The use of the template DNA strand enables high-fidelity repair of DNA damage to restore genome integrity.

BRCA1/2 proteins play critical roles in DNA repair by the HRR pathway and act as tumor suppressors. Cells with a compromised HRR pathway caused by alterations in *BRCA1/2* or other HRR genes can have a reduced capacity to accurately repair double-stranded DNA breaks. This results in an increased accumulation of genomic alterations due to reliance on other error-prone repair pathways, and in turn higher risk of cancer.

Exploiting HRD and genetic mutations in cancer

Poly(ADP-ribose) polymerases (PARPs) are involved in various cellular processes, including base excision repair of single-stranded breaks.

Blocking base excision repair with PARP inhibitors results in accumulation of DNA single-stranded breaks and replication fork collapse. This leads to DNA double-stranded breaks that can no longer be repaired in cells deficient in the HRR pathway [2].

Thus, inhibiting PARPs induces cell death in HR-deficient cancer cells by the mechanism of synthetic lethality (Figure 1).

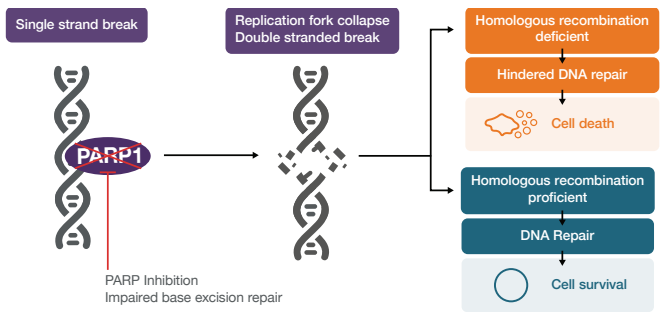

Figure 1. Synthetic lethality.

Identifying HRD

There are two principal approaches for identifying the homologous recombination status of tumors:

- Identify alterations in genes involved in the HRR pathway, or the potential “causes” of HRD
- Measure genomic scarring/instability, or “consequences” of HRD

Potential causes of HRD can be identified by sequencing genes involved in the HRR pathway (Figure 2). *BRCA1/2* play prominent roles in the HRR pathway, and impaired BRCA function is the most studied mechanism in tumor cells that results in HRD [1]. Beyond *BRCA1/2*, genetic or epigenetic alterations in other HRR genes have been associated with the HRD phenotype, and their clinical implications are an active area of research [1].

The consequences of HRD can be assessed by evidence of genomic scarring or instability. The inability to repair DNA in tumors that are HR-deficient results in the cells’ reliance on error-prone DNA repair through alternative pathways. This leads to an increased accumulation of genomic scars, irrespective of the underlying cause. Studies on breast and ovarian cancers have identified patterns or signatures associated with HRD. Quantifying genomic instability generally involves measuring somatic copy number variation across the tumor genome [1].

Oncomine Solutions for homologous recombination research

Oncomine™ Solutions are complete end-to-end NGS workflows for oncology research. Oncomine Solutions provide tools for research both causes and consequences of HRD (Table 1). The low sample input requirements help ensure smaller samples, and thus more samples can be tested. A high degree of automation along with a complete bioinformatics solution, including reporting, empower HRD assessment in your laboratory.

Featured solution: Oncomine Comprehensive Assay Plus

The Oncomine™ Comprehensive Assay Plus is a pan-cancer targeted NGS solution that provides comprehensive genomic profiling across more than 500 genes, including HRR genes and complex biomarkers, such as microsatellite instability, tumor mutational burden, and HRD through the Genomic Instability Metric (GIM). The GIM is a quantitative metric that summarizes unbalanced copy number changes using genomic segmentation. Multiple types of unbalanced copy number events are included to generate a metric that measures genomic instability as a consequence of HRD (Figure 3). The Oncomine Comprehensive Assay Plus enables research of HRR genes that may cause HRD, as well as reporting the consequences, i.e., genomic scarring, through the GIM.

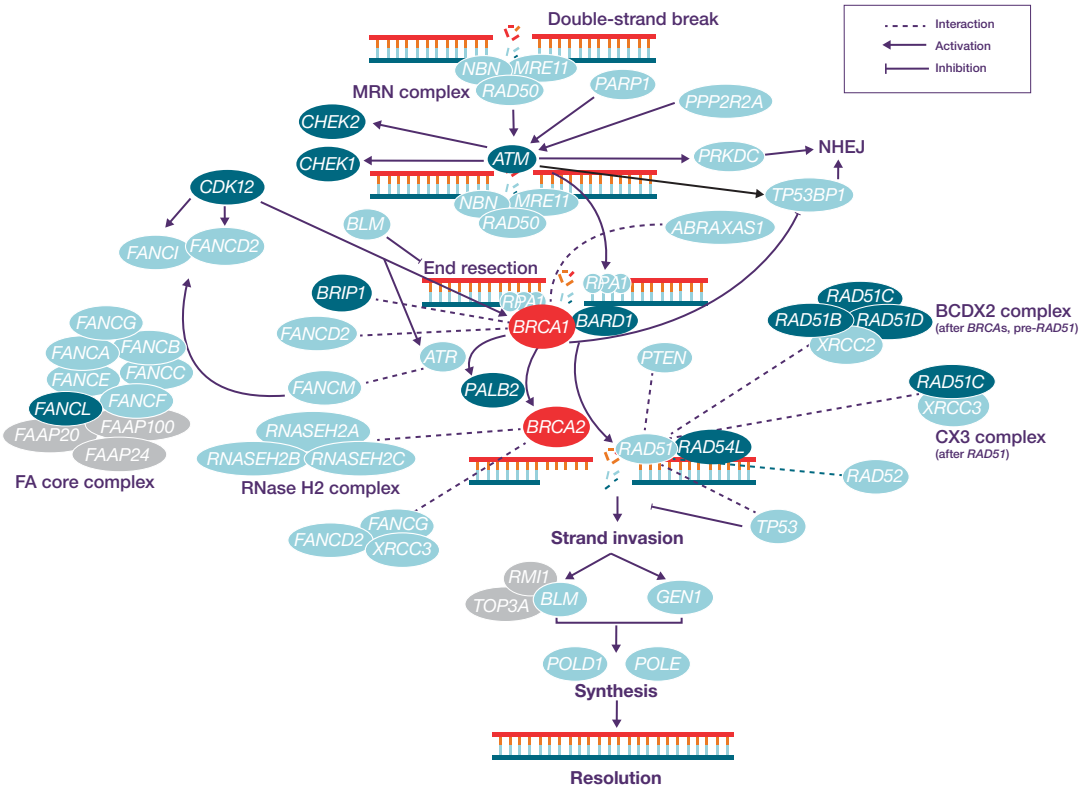

Figure 2. HRR pathway. Non-gray genes are covered in the Oncomine Comprehensive Assay Plus. Teal genes were included in clinical trials of prostate cancer clinical research samples.

Table 1. Oncomine Solutions for homologous recombination research.

		Oncomine *BRCA* Research Assay GX	Oncomine HRR Pathway Predesigned Panel	Oncomine Comprehensive Assay Plus
Panel details	**Specimen types**	FFPE tissue, whole blood	FFPE tissue	FFPE tissue
	Nucleid acid types	DNA	DNA	DNA, RNA
	Alteration types	Substitutions, insertions, deletions, and large genomic rearrangements including exon-level and gene-level deletions or duplications	Substitutions, insertions, deletions, and large genomic rearrangements including exon-level and gene-level deletions or duplications	Substitutions, insertions, deletions, copy number variants, fusions, and large genomic rearrangements including exon-level and gene-level deletions or duplications
	Complex biomarkers	–	–	gene-level LOH, MSI, TMB, HRD
	Homologous recombination assessment	HRR: 2 genes	HRR: 26 genes	HRR: 46 genes HRD: GIM
	Total number of genes	2	28	>500
	DNA or RNA input amount	10 ng	10 ng	20 ng
Instrument		Ion Torrent™ Genexus system	Ion GeneStudio™ S5 System	Ion GeneStudio™ S5 System
Turnaround time*		1 day	4 days	4 days

* Timing varies by number of samples and sample type.

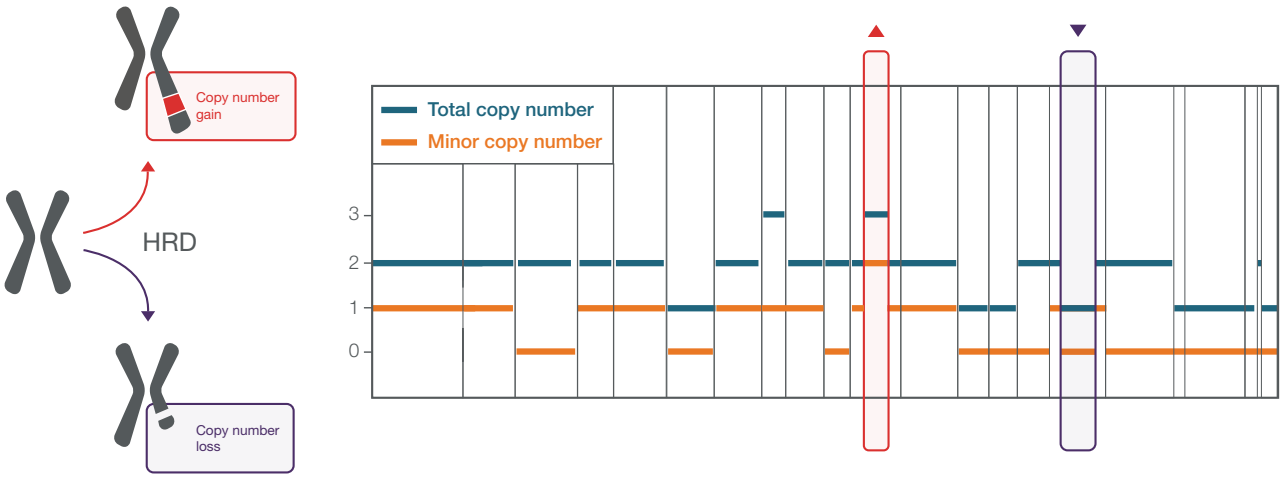

Figure 3. Genomic instability metric. The GIM is a quantitative approach to identifying genomic instability associated with HRD. GIM summarizes unbalanced copy number changes using genomic segmentation with multiple types of unbalanced copy number events included. Examples of copy number gain and loss are shown in red and purple, respectively.

References

1. Stewart MD, et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. *The Oncologist* (2022) 27(3):167–174.
2. Miller RE, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Annals of Oncology* (2020) 31(12):1606–1622.
3. Iglehart JD, and Silver DP. Synthetic lethality—a new direction in cancer-drug development. *New England Journal of Medicine* (2009) 361(2):189–191.

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