METHYLDETECT
DNA METHYLATION ASSAYS

Technical Guide: BRCA1 Gene & DNA Methylation

Introduction & Molecular Biology

The breast cancer type 1 susceptibility gene (*BRCA1*), located on chromosome 17q21, encodes a 1,863-amino-acid nuclear protein that serves as a key tumor suppressor and guardian of genomic stability. Structurally, the protein contains an N-terminal cysteine-rich RING domain, a central zinc-binding domain, and tandem C-terminal BRCT phosphopeptide-binding domains.

BRCA1 forms an obligatory heterodimer with BARD1 via its RING domain, functioning as an E3 ubiquitin ligase. The functional specificity of BRCA1 is dictated by signal-dependent recruitment into distinct multi-protein complexes to mediate:

- **Double-Strand Break (DSB) Repair:** Promotes high-fidelity homologous recombination repair (HRR).
- **Replication Fork Protection:** Protects and restarts stalled or damaged replication forks.
- **Cellular Checkpoints:** Regulates cell-cycle checkpoints, centrosome duplication, transcriptional modulation, and chromatin remodeling.

BRCA1 Deficiency in Carcinogenesis

Loss of functional BRCA1 impairs HRR, driving tumorigenesis through unrepaired DSBs, genomic instability, increased somatic mutation rates, and large-scale structural chromosomal rearrangements.

- **Epidemiology & Cancer Risk:** Pathogenic variants occur in ~0.11% of the population. Germline variants in *BRCA1* or *BRCA2* account for 5–10% of all breast cancers and up to 21% of ovarian cancers.
- **Lifetime Penetrance:** *BRCA1* mutation carriers exhibit a lifetime risk of 40–90% for breast cancer (with high risk of contralateral disease) and 40–65% for ovarian cancer.
- **Tumor Phenotypes:** *BRCA1* deficiency strongly correlates with early-onset, high-grade serous ovarian cancer (HGSOC) and triple-negative breast cancer (TNBC; ER-, PR-, HER2-).

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BRCA1 Promoter Hypermethylation & Epimutations
Epigenetic silencing of the *BRCA1* promoter causes Homologous Recombination Deficiency (HRD) via transcriptional downregulation, mimicking the phenotype of germline pathogenic variants:

- **Constitutional Epimutations:** Epigenetic alterations arising early in utero lead to monoallelic constitutional epimutations and somatic mosaicism across tissues.

- **Prevalence in Primary Tumors:** *BRCA1* promoter hypermethylation is detected in up to 44% of sporadic cancers, ~30% of TNBCs, and 10–20% of HGSOCs.

- **Systemic Detection in Blood:** Pioneering studies by **Wojdacz, Hansen et al.** demonstrated that *BRCA1*hypermethylation is detectable in peripheral blood cell DNA. It is observed in 4–10% of cancer-free adult females and newborns, as well as 14.2% of Arab breast cancer cohorts, functioning as a non-invasive, constitutional predisposing biomarker specifically associated with an increased risk of triple-negative breast cancer (TNBC).

Therapeutic Exploitation: Platinum Salts & PARP Inhibition
Because *BRCA1*-methylated tumors are homologous recombination deficient (HRD), they display profound therapeutic vulnerabilities:

- **Platinum Chemotherapy:** HRD tumors cannot execute error-free resolution of DNA inter- and intrastrand cross-links induced by platinum salts (cisplatin/carboplatin), leading to apoptosis.

- **PARP Inhibitors (Synthetic Lethality):** PARP1 signals single-strand break repair. PARP inhibitors (PARPis; e.g., olaparib, talazoparib) trap PARP1 on DNA. In HRD cells lacking functional BRCA1, replication forks collapse into unrepairable DSBs, causing synthetic lethality. PARPis significantly improve progression-free survival in both primary and recurrent disease.

EpiMelt MS-HRM Assay Applications
Evaluating *BRCA1* promoter methylation provides essential prognostic and predictive value for stratifying patients for PARPi and platinum therapies.

MethylDetect offers ready-to-use **EpiMelt MS-HRM Assays** featuring proportional primer design for unbiased, highly sensitive detection (0.1% limit of detection) compatible with standard qPCR equipment.

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For technical support or to order assay kits, contact **info@methyldetect.com** or visit **www.methyldetect.com**.

Key Literature & References

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