

## IN THE SPOTLIGHT

## BluepRINT for Moderate-to-Low Penetrance Cancer Susceptibility Genes Needed: Breast Cancer and Beyond

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**Summary:** *RINT1* is a novel moderately penetrant cancer susceptibility gene seen in breast cancer as well as possibly in Lynch syndrome-related cancers. *Cancer Discov*; 4(7); 762-3. ©2014 AACR.

See related article by Park et al., p. 804 (2).

The phrase “*scientia potentia est*” is a Latin aphorism often translated as “knowledge is power.” Certainly in medicine, we have seen numerous examples of how genomic discoveries have transformed clinical care, especially in cancer care. Genomics allows us to better understand why certain patients developed cancer or how their cancer should be best treated, and clinicians and patients alike have benefited from an era of gene-enabled management. Currently, more than 200 hereditary cancer susceptibility syndromes have been described. Although many of these are rare syndromes, they are thought to account for at least 5% to 10% of all cancer, amounting to a substantial burden of morbidity and mortality in the human population. Although highly penetrant genes are the ones most likely to be clinically relevant, they explain only a small portion of the heritability of cancer. As cancer is relatively common in the general population, it is possible to have a chance clustering of the same or related cancers within a family. These familial clusterings are most likely due to moderate-to low-penetrance alleles with risks that may not clearly exceed an action threshold. Genome-wide association studies have identified large numbers of genetic variants that are, individually, associated with very limited increases in risk, and the clinical utility of identifying these variants remains completely unclear (1).

This is why clinical cancer geneticists will both celebrate and bemoan the study by Park and colleagues (2) in this issue of the journal. The current estimate of the proportion of heritable risk explained by rare mutations in the high-risk breast cancer susceptibility genes is 20% (*BRCA1/2*, *TP53*, *PTEN*, etc.). A further approximately 5% is likely to be explained by mutations in genes in the homologous recombination repair, detection, and signaling pathways (*MRE11*, *RAD50*, *ATM*, etc.). The authors conducted whole-exome sequencing of women affected with

breast cancer at an early age from highly selected multiple-case breast cancer families followed by gene-specific mutation screening using large international breast cancer research consortium data. The authors identified three germline mutations in RAD50 interactor 1 (*RINT1*) that are not present in the general population [c.343C>T (p.Q115X), c.1132\_1134del (p.M378del), and c.1207G>T (p.D403Y)]. On the basis of this finding, a population-based case-control mutation-scanning study was conducted and identified a 3-fold overrepresentation of rare, likely pathogenic, *RINT1* variants in early-onset breast cancer cases compared with population-matched controls. *RINT1* mutation scanning of probands from 798 multiple-case breast cancer families identified four additional carriers of rare genetic variants within *RINT1*.

*RINT1*, as its name suggests, was identified from a yeast-2-hybrid experiment to find proteins interacting with RAD50 (3). It has since been shown to play complex roles in the G<sub>2</sub>-M checkpoint, telomere elongation, maintenance of centrosome integrity, and vesicle trafficking between the endoplasmic reticulum and Golgi apparatus (3-6). On the basis of our current understanding of *RINT1* activity, it is unclear how *RINT1* contributes to tumor initiation or progression.

Interestingly, the observation that the incidence of first primary cancers in women belonging to *RINT1* mutation-segregating families estimated that carriers were at increased risk of Lynch syndrome-spectrum cancers [standardized incidence ratio (SIR), 3.35; 95% confidence interval (CI), 1.7-6.0; *P* = 0.005], particularly for relatives diagnosed with cancer under the age of 60 years (SIR, 10.9; 95% CI, 4.7-21; *P* = 0.0003). It remains to be seen how common germline *RINT1* mutations are in Lynch syndrome patients who test negative for the known mismatch repair (MMR) genes; this will require, as the authors suggest, large studies enrolling patients with Lynch syndrome-spectrum cancers.

Mechanistically, however, this clinical observation is exciting. Lynch syndrome is a heritable condition leading predominantly to the development of colorectal cancer and endometrial cancer. The crucial cause is malfunction of DNA MMR that is characterized by high levels of microsatellite instability (MSI). It is suggested that MMR deficiency *per se* is not sufficient to increase the risk of cancer; recent data suggest that an additional molecular mechanism other than MMR inactivation, probably inappropriate recombinational DNA repair, contributes to the extensive MSI seen in some patients. MMR maintains genomic stability through recognition and repair of postreplicative errors that occur at a frequency of one

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for every 10 million replicated nucleotides. This rate of genome alteration is thought to be too low to account for the level of genomic instability conducive for Lynch syndrome-related cancer development in MMR-deficient patients. It is believed that MMR defects first have to create mutations in genes that are critical for maintaining genomic stability and proper DNA-damage signaling.

Maintenance of genomic integrity during the DNA replication process is provided by a group of BRCA1-associated proteins of the BRCA1-associated genome surveillance complex (7). The components of this complex are MMR proteins and also a heterotrimer, MRE11-RAD50-NBS1, which is essential for DNA double-strand break repair performing homologous recombination or non-homologous end joining. There are several lines of evidence supporting a direct association of MRE11 with the MMR machinery. The most direct evidence came from studies revealing physical interaction between MRE11 and MLH1 through *in vitro* and *in vivo* approaches (8, 9). The *MRE11* and *MLH1* genes also share similar expression profiles in human normal and tumor samples representing 11 tissue types (kidney, breast, prostate, uterus, ovary, cervix, colon, lung, stomach, rectum, and small intestine), attesting to a high likelihood for them to act in common cellular processes (8). Both MLH1 and the MRE11 complex are known to play critical roles in mediating cellular DNA-damage response. Further studies are warranted to determine the precise molecular mechanism of action and to elucidate the dynamic interplay between the MRE11 complex and the MMR pathway in DNA-damage surveillance and cancer development and how RINT1 fits into the overall schema. In a recent study exploring the functional genomics of glioblastoma multiforme (GBM), a Lynch syndrome-spectrum cancer, the authors identified six candidate GBM oncogenes, and *RINT1* was validated as a novel GBM oncogene based on its ability to confer tumorigenicity to primary nontransformed murine astrocytes *in vivo* (10). It would be interesting to determine whether the Lynch syndrome-spectrum cancers seen in patients with germline *RINT1* mutations show signs of MSI and the immunohistochemical expression of MMR, MRE11, and RAD50 in these tumors.

Over the past 50 years, we have come to appreciate that inherited genetic susceptibility to cancers is a collage of predisposition alleles with different levels of risk and prevalence in the population. The ultimate goal in oncology is to markedly decrease death from cancer. Improved detection of patients harboring deleterious mutations has allowed for tailored gene-enabled management both in terms of novel targeted therapy as well as a targeted surveillance approach

for affected individuals with known mutations in highly penetrant genes. *RINT1* will be inducted to the growing list of genes in which rare sequence variants are associated with moderate levels of breast cancer risk. However, the optimal management of low-to-moderately penetrant genes conferring modestly increased relative risks remains incompletely defined and will continue to pose problems for clinical cancer geneticists unless a blueprint for how best to proceed can be established.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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