

CRT Licensing Opportunity



Polymorphisms that Predict Colorectal Cancer Risk

- Genetic susceptibility underlies up to 30% of colorectal cancers
- A panel of SNPs linked with CRC incidence has been discovered
- SNP screening may accurately predict an individual's CRC risk
- Opportunity to develop SNP panels for population screening

DIAGNOSTICS | Discovery

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Introduction

Genome wide association studies have identified a panel of single nucleotide polymorphisms that are each associated with an increased risk of colorectal cancer. Development of risk-profiling tests based on these SNPs, and their application in improved population screening programmes may result in early detection of cancer in those most at risk.

Background

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer mortality worldwide. Inherited susceptibility is thought to underlie up to 30% of CRC cases. However, the known high penetrance mutations that have been identified (including APC, SMAD4 and DNA repair genes) can account for less than 5% of cases. Large-scale genotyping studies are now being undertaken in order to identify polymorphic markers that are more commonly found in cancer patients. The detection of these and other variants will allow for screening for individuals at increased risk of developing CRC and would allow more effective monitoring and early disease detection, potentially having a significant effect on overall survival rates.

The Technology

Cancer Research UK has funded a number of genome wide association studies (GWAS) in laboratories at the London Research Institute, The Institute of Cancer Research, and the University of Edinburgh to identify low penetrance genetic changes that may be indicative of an increased risk of

colorectal cancer.

The groups carried out multi-phase analysis of more than 500,000 human single nucleotide polymorphisms (SNPs) across thousands of cancer patients and normal controls. This has led to recent publications describing the identification of the first common genetic variants for CRC predisposition, at chromosome 8q24, the HMPs/CRCAC locus on 15q13, the SMAD7 gene on 18q21 as well as loci at 8q23.3, 10p14 and 11q23 and four new loci identified in a large-scale meta-analysis study. Presence of one or more of these SNPs in an individual confers a significantly increased lifetime risk of developing CRC (Figure 1).

Number of risk alleles	OR (95% CI) ¹
0	1.00 (ref)
1	1.33 (0.51-3.44)
2	1.36 (0.55-3.37)
3	1.48 (0.60-3.63)
4	1.50 (0.61-3.69)
5	1.52 (0.62-3.75)
6	1.68 (0.68-4.18)
7	2.63 (1.02-6.82)
8+	3.21 (0.91-11.41)
Total	1.07 (1.03-1.11) per allele $P_{trend}=7.0 \times 10^{-4}$

Figure 1. Odds ratios corresponding to increasing numbers of 5 different risk alleles, including those at 8q24, 15q13 and 18q21, based on Phase 2 data from more than 5600 patient and control samples

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In addition to those published, a further panel of such SNPs has been identified that each confers on an individual a small yet significant increased risk of developing CRC. These SNPs are supported by compelling data across multiple patient populations.

Measuring these SNP markers or those in linkage disequilibrium may be used to deduce the CRC risk for an individual compared to the general population, and for individuals with sufficiently elevated risk to allow tailoring of intensity, frequency or invasiveness of cancer screening strategies. Furthermore, additional analysis has shown that interaction of more than one of these common risk alleles can substantially increase an individual's risk, suggesting the use of SNP panels may have clinical utility.

Zanke, B.W. *et al.* Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nature Genetics*. 2007. **39**(8): 989-994.

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Commercial Opportunity

Validation of a preferred panel of SNP markers would allow the creation of screening tools for prediction of colorectal cancer risk that may significantly improve population-wide screening programmes.

Intellectual Property

CRT has a portfolio of patent applications relating to more than 20 SNP loci including these above and further unpublished loci. The patents are available for non-exclusive licensing, together with associated data.

References

Houlston, R.S. *et al.* Meta-analysis of genome-wide association data identifies four new susceptibility loci for colorectal cancer. *Nat. Genet.* 2008 Nov 16. [Epub ahead of print]

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Tomlinson, I.P. *et al.* A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. *Nature Genetics*. 2008. **40**(5):623-630

Jaeger, E. *et al.* Common genetic variants at the CRAC1 (HMPS) locus on chromosome 15q13.3 influence colorectal cancer risk. *Nature Genetics*. 2008. **40**(1): 26-28.

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