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Citation for published version:
von Holst, S, Picelli, S, Edler, D, Lenander, C, Dalen, J, Hjern, F, Lundqvist, N, Lindforss, U, Pahlman, L, Smedh, K, Tornqvist, A, Holm, J, Janson, M, Andersson, M, Ekelund, S, Olsson, L, Ghazi, S, Papadogiannakis, N, Tenesa, A, Farrington, SM, Campbell, H, Dunlop, MG & Lindblom, A 2010, 'Association studies on 11 published colorectal cancer risk loci', *British Journal of Cancer*, vol. 103, no. 4, pp. 575-580. https://doi.org/10.1038/sj.bjc.6605774

Digital Object Identifier (DOI):
10.1038/sj.bjc.6605774

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
British Journal of Cancer

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Association studies on 11 published colorectal cancer risk loci

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BACKGROUND: Recently, several genome-wide association studies (GWAS) have independently found numerous loci at which common single-nucleotide polymorphisms (SNPs) modestly influence the risk of developing colorectal cancer. The aim of this study was to test 11 loci, reported to be associated with an increased or decreased risk of colorectal cancer: 8q23.3, 8q24.21, 10p14, 11q23.1, 14q22.2, 15q13.3, 16q22.1, 19q13.1 and 20p12.3. According to previous studies, each of these loci is associated with a modest number of risk alleles as reported previously. The loci 9p24 and 14q22.2 could not be confirmed. We show a higher number of risk alleles in affected individuals compared to controls. Four statistically significant genotype–phenotype associations were found; the G allele of rs9929218, 18q21.1 (rs4939827), 9p24 (rs719725), 10p14 (rs10795668), 11q23.1 (rs3802842), 14q22.2 (rs4444235), 15q13.3 (rs4779584), 16q22.1 (rs929218), 18q21.1 (rs4939827), 19q13.1 (rs10411210) and 20p12.3 (rs961253), in a Swedish-based cohort.

RESULTS: Of eleven loci, 5 showed statistically significant odds ratios similar to previously published findings: 8q23.3, 8q24.21, 10p14, 15q13.3 and 18q21.1. The remaining loci 11q23.1, 14q22.2, 19q13.1 and 20p12.3 showed weak trends but somewhat similar to what was previously published. The loci 9p24 and 14q22.2 could not be confirmed. We show a higher number of risk alleles in affected individuals compared to controls. Four statistically significant genotype–phenotype associations were found; the G allele of rs9929218 was associated to older age, the G allele of rs10795668 was associated with a younger age and sporadic cases, and the T allele of rs10411210 was associated with younger age.

CONCLUSIONS: Our study, using a Swedish population, supports most genetic variants published in GWAS. More studies are needed to validate the genotype–phenotype correlations.

Keywords: colorectal cancer; SNP (single-nucleotide polymorphism); association study; risk predisposition

Until some years ago, the candidate-gene approach was the only method available to the researchers for identifying potentially pathogenic variants. However, the fast technological development and the consequent acquisition of large amount of data in the past decade shifted the focus of research to genome-wide association studies (GWAS). Recent GWAS have identified multiple genetic loci associated with an increased or decreased risk of colorectal cancer (CRC) on 8q23.3, 8q24.21, 9p24, 10p14, 11q23.1, 14q22.2, 15q13.3, 16q22.1, 18q21.1, 19q13.1 and 20p12.3, explaining, at least to some extent, the genetics behind CRC as a complex disease (Broderick et al, 2007; Haiman et al, 2007; Tomlinson et al, 2007, 2008; Zanke et al, 2007; Houlston et al, 2008; Jaeger et al, 2008; Tenesa et al, 2008). Each of these loci is associated with a modest risk and, although fairly common they contribute very little to the overall burden of CRC. This case–control study focused on the known CRC single-nucleotide polymorphisms (SNPs) in a Swedish-based cohort and to compare our results with previous association studies in other populations. It also tested if there were more CRC patients than controls among individuals with higher number of risk alleles as reported previously (Tomlinson et al, 2010). Genotype–phenotype associations were analysed for age of onset, sex, family history of CRC and tumour location.

MATERIALS AND METHODS

Subjects

The case cohort was composed of 1786 consecutive CRC patients of Swedish origin recruited through the Swedish Low-Risk CRC Study Group from 14 different hospitals from central Sweden.
during 2004–2006. The mean age (at diagnosis) was 68.6 years (range 28–95 years), 53% were men and 47% were women and 22% had a family history of CRC among first- or second-degree relatives. The control cohort was composed of 1749 individuals as follows: 1319 blood donors from the general population between the age of 18 and 65 years and 430 unaffected spouses of CRC patients with the mean age of 66.3 (25–92) years, which were cancer-free and did not have a family history of any type of cancer.

**Loci and SNPs**

Exploiting linkage disequilibrium between SNPs, we selected one SNP from each locus among those published. Thus we genotyped rs6983267 on 8q24.21, rs719725 on 9p24, rs10795668 on 10p14, rs3802842 on 11q23.1, rs4444235 on 14q22.2, rs4779584 on 15q13.3, rs9929218 on 16q22.1, rs4939827 and rs3802842 were performed, using a technology developed by Nanogen, at deCode Genetics, Reykjavik, Iceland (http://www.decode.com).

**Quality control**

Sequencing was performed using Big-Dye terminator v3.1 cycle sequencing kit (Applied Biosystems), and fragments were separated on an ABI 3730 XL capillary sequencer. Chromatograms were analysed using Sequase v2.5 (Applied Biosystems). Primers and amplification conditions are available upon request.

**Genotype–phenotype analysis**

We studied sex, age of onset (early vs late, >60 years), family history of CRC (any case of CRC among first- or second-degree relatives), location, colon vs rectum and right vs left (proximal and distal to the splenic flexure).

**Statistical analysis**

Deviations of the genotype frequencies in cases and controls from those expected under Hardy–Weinberg equilibrium were calculated by \( \chi^2 \)-tests (one degree of freedom). Allelic frequencies of the SNPs in the case and control groups were compared using a \( \chi^2 \)-test (allele 1 (common) vs allele 2 (minor)), except for rs6983267 where the common allele is suggested to be the risk allele (Tomlinson et al, 2007). Where the most common allele G was suggested to be the risk allele (Tomlinson et al, 2007). To make comparisons, we chose to present risk and differences between cases and controls in the Swedish population is shown in Figure 1. There is a clear shift with a higher number of alleles in affected individuals compared to controls.

Genotype–phenotype analysis was performed for all 11 loci and for sex, age, family history and tumour location, and the \( P \)-values for all analyses are shown in Table 2. Four associations were found, three for age and one for family history (Table 3). Being homozygous for the risk allele G for rs6983267 was associated with older age (\( P = 0.0014 \)). In contrast, for rs10795668 the risk allele G was associated with younger age (\( P = 0.035 \)) and sporadic cases (\( P = 0.047 \)). The T allele of rs10411210 was associated with younger age (\( P = 0.045 \)) in homozygotes (Table 3).

**DISCUSSION**

We studied SNPs on 11 loci published to be associated with an increased or decreased risk for CRC and were able to show statistically significant results for 5 of them. The first SNP, rs6983267 on 8q24.21, was published by Tomlinson et al (2007), where the most common allele G was suggested to be the risk allele. Our study showed similar results as previous studies in other populations (Berndt et al, 2008; Tuapanen et al, 2008; Wokolorczyk et al, 2008; Curtin et al, 2009; Middeldorp et al, 2009). Likewise, the SNP rs16892766 on 8q23.3 was similar to both the GWAS study and one replicative study (Tomlinson et al, 2008; Wijnen et al, 2009). The protective effect associated with rs10795668 on 10p14 was confirmed for homozygous carriers in the Swedish material (Tomlinson et al, 2008). The SNP rs4779584 on 15q13.3, published by Jaeger et al (2008) as a risk association was confirmed and showed similar ORs as in previous publications (Broderick et al, 2007; Tomlinson et al, 2007, 2008; Jaeger et al, 2008). For SNP rs16892766 on 8q23.3, an increased risk of CRC was identified (\( P < 0.002 \)) for homozygous carriers in the recessive model with the highest OR equal to 1.34 (1.13–1.60) for the heterozygous. Likewise, the increased risk suggested for the variant rs6983267 on 8q24.21 was confirmed in all the analyses, with the highest OR equal to 1.37 (1.13–1.67) for the homozygous state. rs4779584 on 15q13.3 has been associated with an increased risk that could be confirmed for the heterozygous individuals, OR = 1.18 (1.02–1.36).

The protected effects suggested for rs10795668 on 10p14 and rs4939827 on 18q21.1 were both confirmed for homozygous and heterozygous with an OR equal to 0.66 (0.52–0.83) and OR 0.82 (0.70–0.96), respectively. The ORs for rs3802842 on 11q23.1 showed a trend with an OR equal to 1.27 (NS) for homozygous. The rs9929218 on 16q22.1, rs10411210 on 19q13.1 and rs961253 on 20p12.3 showed weak trends in the same direction as published (NS), whereas the two SNPs rs719725 on 9p24 and rs4444235 on 14q22.2 were not confirmed. The distribution of risk alleles between cases and controls in the Swedish population is shown in Figure 1. There is a clear shift with a higher number of alleles in affected individuals compared to controls.
| Locus/SNP       | OR published | Genotypes | No cases (%) | No controls (%) | OR (95% CI)  | P-values |
|----------------|--------------|-----------|--------------|----------------|--------------|----------|
| 8q23.3         |              |           |              |                |              |          |
| rs16892766     | 1.27 (het)   | AA        | 1379 (79)    | 1404 (83)      | 1.24 (1.13–1.60) | 0.0009   |
|                | 1.43 (hom)   | AC        | 356 (20)     | 270 (16)       | 1.20 (0.63–2.30) | 0.586    |
| Tomlinson et al, 2008 | AC+CC     | Allelic   |              |                | 1.33 (1.13–1.58) | 0.0009   |
|                |             | Trend     |              |                | 1.29 (1.10–1.51) | 0.0016   |
| 8q24.21        | 1.27 (het)   | TT        | 397 (23)     | 332 (19)       | 1.20 (1.01–1.43) | 0.04     |
| rs6983267      | 1.47 (hom)   | TG        | 890 (51)     | 892 (51)       | 1.37 (1.13–1.67) | 0.001    |
| Tomlinson et al, 2007 | AG+GG     | Allelic   |              |                | 1.26 (1.07–1.48) | 0.006    |
|                |             | Trend     |              |                | 1.16 (1.06–1.28) | 0.0015   |
| 9p24           | 1.14 (com)   | AA        | 672 (39)     | 669 (39)       | 1.03 (0.89–1.19) | 0.733    |
| rs719725       |              | AC        | 821 (48)     | 797 (46)       | 0.91 (0.74–1.12) | 0.368    |
| Zanke et al, 2007 | CC        | Allelic   |              |                | 0.97 (0.88–1.07) | 0.554    |
|                |             | Trend     |              |                | 0.96         | 0.554    |
| 10p14          | 0.87 (het)   | GG        | 853 (48)     | 745 (44)       | 0.90 (0.78–1.04) | 0.151    |
| rs10795668     | 0.80 (hom)   | GA        | 779 (44)     | 754 (44)       | 0.997 (0.87–1.14) | 0.971    |
| Tomlinson et al, 2008 | GA+AA     | Allelic   |              |                | 0.85 (0.75–0.97) | 0.018    |
|                |             | Trend     |              |                | 0.85 (0.76–0.94) | 0.001    |
| 11q23.1        | 1.11 (com)   | AA        | 941 (53)     | 926 (55)       | 1.03 (0.90–1.19) | 0.659    |
| rs3802842      |              | AC        | 688 (39)     | 656 (39)       | 1.27 (0.96–1.66) | 0.076    |
| Tenesa et al, 2008 | CC        | Allelic   |              |                | 1.07 (0.93–1.22) | 0.347    |
|                |             | Trend     |              |                | 1.08 (0.97–1.21) | 0.143    |
| 14q22.2        | 1.13 (het)   | TT        | 573 (33)     | 533 (32)       | 1.02 (0.84–1.23) | 0.872    |
| rs444235       | 1.23 (hom)   | TC        | 829 (47)     | 838 (49)       | 0.95 (0.82–0.99) | 0.455    |
| Houlston et al, 2008 | TC+CC     | Allelic   |              |                | 0.997 (0.91–1.10) | 0.951    |
|                |             | Trend     |              |                | 1.00         | 0.952    |
| 15q13.3        | 1.23 (het)   | CC        | 1050 (61)    | 1104 (65)      | 1.11 (0.82–1.50) | 0.496    |
| rs4779584      | 1.70 (hom)   | CT        | 572 (35)     | 511 (30)       | 1.17 (1.02–1.34) | 0.029    |
| Jaeger et al, 2008 | TT        | Allelic   |              |                | 1.12 (1.00–1.26) | 0.051    |
|                |             | Trend     |              |                | 1.096        | 0.057    |
| 16q22.1        | 0.92 (het)   | GG        | 929 (53)     | 913 (54)       | 1.06 (0.92–1.22) | 0.404    |
| rs9929218      | 0.82 (hom)   | GA        | 700 (40)     | 648 (38)       | 0.81 (0.62–1.05) | 0.108    |
| Houlston et al, 2008 | GA+AA     | Allelic   |              |                | 1.02 (0.90–1.16) | 0.810    |
|                |             | Trend     |              |                | 1.12 (1.00–1.26) | 0.051    |
|                |             |           |              |                | 0.945        | 0.566    |
| 18q21.1        | 0.86 (het)   | TT        | 501 (28)     | 408 (24)       | 0.82 (0.70–0.96) | 0.013    |
| rs4939827      | 0.73 (hom)   | TC        | 886 (50)     | 884 (53)       | 0.83 (0.69–1.01) | 0.059    |
| Broderick et al, 2007 | TC+CC     | Allelic   |              |                | 0.82 (0.71–0.96) | 0.011    |
|                |             | Trend     |              |                | 0.91         | 0.048    |
| 19q13.1        | 0.87 (het)   | CC        | 1490 (84)    | 1421 (83)      | 0.93 (0.77–1.11) | 0.411    |
| rs10411210     | 0.72 (hom)   | CT        | 264 (15)     | 272 (16)       | 0.89 (0.62–1.22) | 0.753    |
| Houlston et al, 2008 | CT+TT     | Allelic   |              |                | 0.92 (0.77–1.11) | 0.389    |
|                |             | Trend     |              |                | 0.93 (0.78–1.10) | 0.385    |
|                |             |           |              |                | 0.930        | 0.387    |
Table 1 (Continued)

| Locus/SNP     | OR published | Genotypes | No cases (%) | No controls (%) | OR (95% CI) | P-values |
|---------------|--------------|-----------|--------------|----------------|-------------|----------|
| 20p12.3       |              | CC        | 694 (39)     | 693 (40)       | 1           |          |
| rs961253      | 1.14 (het)   | CA        | 806 (46)     | 791 (46)       | 1.02 (0.88 – 1.18) | 0.813 |
|               | 1.24 (hom)   | AA        | 265 (15)     | 237 (14)       | 1.12 (0.91 – 1.37) | 0.290 |
| Houlston et al., 2008 |              | CA+AA     |              |                | 1.04 (0.91 – 1.19) | 0.568 |
|               |              | Allelic   |              |                | 1.05 (0.95 – 1.16) | 0.344 |
|               |              | Trend     |              |                | 1.05         | 0.349   |

Abbreviations: allelic = allele frequency difference; trend = Armitage’s trend test; com = common odds ratio; hom = homozygous; het = heterozygous; all = allelic. Minor allele frequencies Swedish cohort cases/controls: 8q23.3 (0.11/0.09), 8q24.21 (0.49/0.45), 9p24 (0.37/0.38), 10p14 (0.30/0.34), 11q23.1 (0.27/0.26), 14q22.2 (0.44/0.44), 15q13.3 (0.22/0.20), 16q22.1 (0.27/0.27), 18q21.1 (0.47/0.49), 19q13.1 (0.08/0.09), 20p12.3 (0.38/0.37). The bold values indicate P < 0.005.

Figure 1 Polygenic model of 11 CRC-related SNPs. Distribution of risk alleles among cases and controls: black, cases; grey, controls.
more studies aiming to define additional SNPs and hopefully also some more high-penetrant predisposing genes are welcomed.

ACKNOWLEDGEMENTS

We thank the patients for collaboration and Berith Wejderot for excellent administrative service. This study was funded by The Swedish Cancer Society, the Swedish Research Council, Stockholm County Council and the Stockholm Cancer Society. The work carried out in Edinburgh was funded by grants from Cancer Research UK (C348/A8896); a Centre Grant from CORE as part of the Digestive Cancer Campaign (http://www.corecharity.org.uk); Scottish Government Chief Scientist Office (K/OPR/2/2/D333); Medical Research Council (G0000657-53203).

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