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ARTICLE

Pattern Recognition Receptor Polymorphisms as Predictors of Oxaliplatin Benefit in Colorectal Cancer


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Abstract

Background: Constitutional loss of function (LOF) single nucleotide polymorphisms (SNPs) in pattern recognition receptors FPR1, TLR3, and TLR4 have previously been reported to predict oxaliplatin benefit in colorectal cancer. Confirmation of this association could substantially improve patient stratification.

Methods: We performed a retrospective biomarker analysis of the Short Course in Oncology Therapy (SCOT) and COIN/COIN-B trials. Participant status for LOF variants in FPR1 (rs867228), TLR3 (rs3775291), and TLR4 (rs4986790/rs4986791) was determined by genotyping array or genotype imputation. Associations between LOF variants and disease-free survival (DFS) and overall survival (OS) were analyzed by Cox regression, adjusted for confounders, using additive, dominant, and recessive genetic models. All statistical tests were two-sided.

Results: Our validation study populations included 2929 and 1948 patients in the SCOT and COIN/COIN-B cohorts, respectively, of whom 2728 and 1672 patients had functional status of all three SNPs determined. We found no evidence of an association between any SNP and DFS in the SCOT cohort, or with OS in either cohort, irrespective of the type of model used. This included models for which an association was previously reported for rs867228 (recessive model, multivariable-adjusted hazard ratio [HR] for DFS in SCOT = 1.19, 95% confidence interval [CI] = 0.99 to 1.45, P = .07; HR for OS in COIN/COIN-B = 0.92, 95% CI = 0.63 to 1.34, P = .66), and rs4986790 (dominant model, multivariable-adjusted HR for DFS in SCOT = 0.86, 95% CI = 0.65 to 1.13, P = .27; HR for OS in COIN/COIN-B = 1.08, 95% CI = 0.90 to 1.31, P = .40).

Conclusion: In this prespecified analysis of two large clinical trials, we found no evidence that constitutional LOF SNPs in FPR1, TLR3, or TLR4 are associated with differential benefit from oxaliplatin. Our results suggest these SNPs are unlikely to be clinically useful biomarkers.

The antitumor immune response is an important determinant of clinical outcome in colorectal cancer (CRC). To date, attention has primarily focused on the role of the adaptive immune system, and particularly the T-cell response, the increasing intensity of which correlates with reduced recurrence in early-stage CRC (1,2). Although the influence of the innate immune system to clinical outcome is less well understood, several studies have suggested that this may also exert a meaningful antitumor effect through the recognition of endogenous ligands presented by dying cells (3–7). This effect has been reported to be especially relevant in the context of cell death induced by anthracyclines and oxaliplatin (3–5), an analog of cisplatin used...
commonly in the systemic therapy of CRC (8). Pattern recognition receptors present endogenous ligands to macrophages and as such are essential components of the innate immune response (9). Constitutional variants in several genes encoding these proteins have been shown to alter the innate immune response to systemic infection (10). Recently, polymorphisms that result in putative loss of function (LOF) alterations in pattern recognition receptor genes have also been reported to influence benefit from anti-angiocrine and oxaliplatin chemotherapy (4–7). These variants, which affect FPR1 [rs867228: c.1037A>C, p.Glu346Ala, where Ala is the LOF allele (11)], TLR3 [rs3775291: c.1234C>T, p.Leu412Phe, where Phe is the LOF allele (12)], and TLR4 [rs4986790: c.896A>G, p. Asp299Gly, where Gly is the LOF allele (4,7)] in strong linkage disequilibrium with rs4986791: c.1196C>T, p.Thr399Ile, are proposed to act by attenuating the immune response against the immunogenic cell death caused by these agents (4–7). These associations were reflected in statistically significant differences in both progression-free and overall survival (OS) between patients bearing LOF and functional alleles in these genes when treated with these agents (hazard ratios [HRs] for LOF allele of 1.37–2.13; summarized in Supplementary Table 1, available online) (4–7,13,14). If validated, these variants could be used as biomarkers to target these toxic therapies to those most likely to benefit from them, resulting in less harm to patients and cost savings for healthcare providers. Because anti-angiocrine and oxaliplatin are the mainstays of systemic treatment against two common cancers (breast and colorectal, respectively) (15,16) and because these LOF polymorphisms are relatively common (prevalence of 5% to 80% in populations of European descent), confirmation of this association could affect many thousands of patients each year in Europe and the United States alone. The purpose of this validation study was to confirm this association in the context of oxaliplatin treatment for CRC by analysis of two well-defined, prospectively treated cohorts from the Short Course in Oncology Therapy (SCOT) and COIN/COIN-B trials (17,18), encompassing both early-stage and advanced disease.

DNA Extraction, Genotyping, and Imputation

DNA was extracted from EDTA-venous bloods using standard methods. After exclusion of samples that failed DNA extraction (n = 28) and those for which trial IDs were missing or duplicates (n = 14), 3067 DNA samples from the SCOT cohort were genotyped using the Global Screening Array (Illumina, San Diego, CA). Genotyping quality control entailed removal of any sample or single nucleotide polymorphism (SNP) with more than 2% missing data, any sample with an outlying heterozygosity rate, any sample with discordant reported sex and genotype imputed sex, and any SNP violating Hardy-Weinberg equilibrium at P < 1 × 10−10 (n = 66 samples removed; n = 3285 SNPs removed). Identity by descent analysis was conducted in PLINK 1.9 (22) and population stratification was examined using EIGENSTRAT (23). Related individuals (n = 8) were removed (IBD > 0.185) along with those with non-European ancestry (n = 54, as assessed by merging SCOT with HapMap release 23a and removing outliers based on eigenvector 1). Genotypes for 2939 remaining individuals were phased using SHAPEIT (24) and imputed using IMPUTE2 (25) and the UK10K + 1000 genomes merged reference panel. Of the SNPs analyzed in this study, rs3775291, rs4986790, and rs4986791 were directly genotyped. The fourth, rs867228, was imputed with an info score of 0.95. For this imputed SNP, genotype probabilities were converted to genotypes using gtool (http://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html) with a minimum probability threshold of .9 set for specifying per sample genotypes.

Cases from the COIN and COIN-B studies were genotyped using Affymetrix Axiom Arrays according to the manufacturer’s recommendations (Affymetrix, Santa Clara, CA) at the King Faisal Specialist Hospital and Research Center, Saudi Arabia (under IRB approval 2110033). We excluded individuals from analysis if they failed one or more of the following thresholds: overall successfully genotyped SNPs less than 95% (n = 122), discordant sex information (n = 8), classed as out of bounds by Affymetrix (n = 30), duplication or cryptic relatedness (identity by descent > 0.185, n = 4), and evidence of non-white European ancestry by principal components analysis-based analysis in comparison with HapMap samples (n = 130). Imputation was performed using 1000 Genomes Project Pilot data as a reference.
**Statistical Analyses**

Comparison between groups was made using unpaired Student *t* test for continuous variables (e.g., age) and either *F* or Fisher exact test for categorical variables (e.g., mutation present vs absent, responder vs nonresponder). Biomarker analyses in this study were performed and are reported in accordance with the REMARK guidelines (27). All analyses were prespecified and are detailed in [Supplementary Table 2](#). Survival endpoints included disease-free survival (DFS, defined as time from study randomization to CRC recurrence or death from any cause in SCOT only) and OS (defined as time from randomization to death from any cause in both cohorts). Progression-free survival was not used as an endpoint in the COIN/COIN-B trials in view of the difficulty in defining its duration in the context of intermittent chemotherapy, which was tested in both studies. Survival curves for SNP genotypes were plotted using the Kaplan-Meier method and analyzed by the log-rank test. Survival endpoints were also analyzed by univariate and multivariable Cox proportional hazards models, under additive, recessive, and dominant genetic models (e.g., for rs867228, which has alleles A and C—or of which C is the LOF allele—the additive model implies CC [2] vs CA [1] vs AA [0], modelled as a continuous variable; the recessive model implies CC [1] vs both CA and AA [0]; and the dominant model implies both CC and CA [1] vs AA). Proportionality of hazards was confirmed by inspection of scaled Schoenfeld residuals. For the multivariable analyses, adjustment was made for baseline demographic variables (age, sex), clinico-pathological and molecular covariates of known prognostic value where available, and treatment type and schedule depending on the cohort. In the SCOT analyses, these comprised age, sex, disease site (colon vs rectum), primary tumor stage (pT1–2 vs pT3 vs pT4), nodal status (N0 vs N1 vs N2), treatment regimen (FOLFOX or CAPOX), and treatment duration (24 vs 12 weeks). In the COIN/COIN-B analyses, these comprised age, sex, disease site (colon vs rectum), World Health Organization (WHO) performance status (0 or 1 vs 2), primary tumor resection (unresected vs resected), tumor KRAS, NRAS, and BRAF mutation status (mutated vs wild type), patient white blood cell count (<10 000 cells per μL vs ≥10 000 cells per μL), cetuximab treatment (yes vs no), chemotherapy regimen (FOLFOX vs CAPOX), and chemotherapy schedule (intermittent vs continuous). In both cases, covariates were prespecified and no selection procedure (e.g., backwards elimination) was performed. Models included all cases for which data were available and excluded those with missing data. P-values for individual predictors in Cox models were calculated by the Wald test. Statistical analyses were performed in R version 3.4.4 (CRAN Corporation) and STATA version 13 (StataCorp, College Station, TX). All statistical tests were two-sided. Statistical significance was accepted at *P* less than .05. No correction for multiple testing was applied.

**Ethical Approval**

Informed consent for the collection and analysis of samples was provided by study participants at the time of study recruitment under trial-specific ethical approval. Molecular analysis of samples from the SCOT cohort was performed under North West – Liverpool Central Research Committee approval (17/NW/0252). Molecular analysis of COIN/COIN-B samples was performed under REC approval (04/MRE06/60).

**Results**

**Patient Characteristics and SNP Genotyping**

The CONSORT diagram demonstrating the flow of patients eligible for this biomarker study is shown in Figure 1. Demographic
and clinicopathological characteristics of the 2929 SCOT cases with samples informative for this analysis were broadly similar to those of the SCOT trial population as a whole, although they differed statistically significantly, albeit modestly, from the nonbiomarker population in age, disease site, disease stage, and nodal status (Supplementary Table 2, available online). Characteristics of 2244 patients in the COIN/COIN-B biomarker subgroup were similar to the combined COIN/COIN-B trial population (not shown). Details of baseline demographic, clinicopathological, and molecular variables, and SNP genotypes in cases from both biomarker cohorts are provided in Table 1. Of 2929 patients in the SCOT cohort, 2728 (93.1%), 2924 (99.9%), and 2929 (100%) underwent successful genotyping or imputation and were informative for analysis of rs867228, rs3775291, and rs4986790/ rs4986791 respectively. The slightly lower number of cases informative for rs867228 reflects the exclusion of those in which the genotype could not be imputed with high confidence. The corresponding numbers in the COIN/COIN-B cohort of 1948 patients were 1672 (85.6%), 1948 (100%), and 1948 (100%) respectively. The allelic frequencies of all SNPs in both cohorts were concordant with the reported population frequency in ExAC (Supplementary Table 4, available online). As expected, rs4986790 and rs4986791 were in strong linkage disequilibrium in both the SCOT (D' = 0.99 and r^2 = 0.93) and COIN/COIN-B (D' = 0.99 and r^2 = 0.89) cohorts. Because analyses of these two SNPs individually yielded essentially identical results (Supplementary Figure 1, available online), we largely limited subsequent investigations to rs4986790.

The effect sizes (hazard ratios) of each SNP detectable in multivariable analyses using recessive and dominant genetic models, based on a power (1-β) of 0.8 and a two-sided α of 0.05, are shown for both cohorts in Supplementary Table 4 (available online). For comparison with previous reports, our power to detect an association of identical effect size using the same (recessive) model was 0.65 and 0.31 for DFS and OS, respectively, in the SCOT cohort and 1.0 for OS in the COIN/COIN-B cohort. Our power to detect an association of the same effect size as that previously reported for rs4986790 using the same (dominant) model was 0.65 and 0.31 for DFS and OS, respectively, in the SCOT cohort and 0.96 for OS in the COIN/COIN-B cohort.

### Pattern Recognition SNPs and Clinical Outcome in the SCOT Cohort

Biomarker analyses were performed with data used for the primary analysis of the SCOT trial, at which point the 2929 patients...
Table 2. Univariate and multivariable analyses of DFS and OS in SCOT cohort by LOF SNP*  

<table>
<thead>
<tr>
<th>Polymorphism/genetic model</th>
<th>No.</th>
<th>DFS events</th>
<th>OS events</th>
<th>HR (95% CI)</th>
<th>P†</th>
<th>HR (95% CI)</th>
<th>P†</th>
<th>HR (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs687228 (FPR1 c.1037A&gt;G)</td>
<td>2728</td>
<td>487</td>
<td>167</td>
<td>1.13 (0.96 to 1.32)</td>
<td>.15</td>
<td>1.09 (0.83 to 1.44)</td>
<td>.55</td>
<td>1.16 (0.98 to 1.37)</td>
<td>.08</td>
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<td>rs3775291 (TLR3 c.1234C&gt;T)</td>
<td>2924</td>
<td>536</td>
<td>186</td>
<td>1.15 (0.95 to 1.40)</td>
<td>.15</td>
<td>1.07 (0.77 to 1.49)</td>
<td>.67</td>
<td>1.19 (0.99 to 1.45)</td>
<td>.07</td>
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<tr>
<td>rs4986790 (TLR4 c.896A&gt;G)</td>
<td>2929</td>
<td>538</td>
<td>186</td>
<td>1.01 (0.85 to 1.19)</td>
<td>.50</td>
<td>1.04 (0.84 to 1.49)</td>
<td>.46</td>
<td>1.16 (0.73 to 1.87)</td>
<td>.53</td>
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<tr>
<td>Additive</td>
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*Both univariate and multivariable analyses use all informative cases. Hazard ratios show risk associated with reported LOF allele (underscored) for each SNP as follows: rs687228: FPR1 c.1037A>G; rs3775291: TLR3 c.1234C>T; rs4986790: TLR4 c.896A>G. Corresponding associations from rs4986791 (TLR4 c.1196C>T; p.Thr399Ile), which is tightly linked to rs4986790, were essentially identical to those obtained from analysis of rs4986790 and are not shown. Multivariable-adjusted HRs were adjusted for age, sex, disease site (colon vs rectum), primary tumor stage (pT1–2 vs pT3 vs pT4), nodal status (N0 vs N1 vs N2), treatment regimen (FOLFOX or CAPOX), and treatment duration (24 vs 12 weeks). Prognostic associations of covariables are shown in Table 2 (available online). CI — confidence interval; DFS — disease-free survival; HR — hazard ratio; LOF — loss of function; OS — overall survival; pT — pathological tumor (T) stage; SCOT — Short Course in Oncology Therapy.†P values were calculated by two-sided Wald test.

Pattern Recognition SNPs, Clinical Outcome, and Oxaliplatin Response in the COIN/COIN-B Cohort

An additional analysis according to radiological response to oxaliplatin-based chemotherapy after 12 weeks of therapy...
Corresponding results for OS are shown in Oncology Therapy (SCOT) cohort. Kaplan Meier curves showing DFS for patients in SCOT cohort by pattern recognition receptor SNPs rs867228 (FPR1), rs4986790 (TLR3), rs3775291 (TLR4), and rs4986790 (TLR4 c.1196C>T, p. Thr399Ile) polymorphism, which is strongly linked with rs4986790, were essentially identical to C and F and are provided as Supplementary Figure 1 (available online). Shaded areas represent 95% confidence intervals. P values indicate comparison of all groups by the two-sided log-rank test.

Discussion

Previous studies have suggested that LOF polymorphisms in the pattern recognition receptors FPR1 (rs867228), TLR3 (rs3775291), and TLR4 (rs4986790/rs4986791) decrease the presentation of [complete or partial response vs stable or progressive disease by RECIST 1.0 (31)] revealed no difference in the proportions of functional and LOF alleles between responders and nonresponders for rs867228 (P = .90, χ² test), rs3775291 (P = .68, χ² test), or rs4986790 (P = .64, Fisher exact test).
ligand to the innate immune system by dying cells (3–7). This, in turn, is proposed to reduce the efficacy of anthracycline and oxaliplatin chemotherapy, the activities of which depend in part on the induction of immunogenic cell death (3–5,7). In this study of nearly 5000 patients with CRC treated with oxaliplatin, we failed to confirm any of these associations. The 95% confidence intervals for the association of each SNP with DFS and OS in the SCOT cohort and OS in the COIN/COIN-B cohort all included the estimate of no effect. Although our data by no means exclude an immunomodulatory effect of these SNPs, they suggest that they are very unlikely to be clinically useful as predictive biomarkers for oxaliplatin benefit in CRC. The discordance between our results and those from previous studies may be explained by the increased risk of false-positive associations in the smaller cohorts they used, and in the case of rs867228, an apparent misclassification of the functional and LOF alleles in the survival analyses (the functional FPR1 allele c.1037A, p.346Glu appeared to be incorrectly classified as LOF in all analyses in the study by Vacchelli et al.) (5). Our results underscore the importance of validation of encouraging findings from modestly sized studies in large, meticulously curated trial cohorts, even where preclinical data provide a plausible mechanism for an association.

Strengths of our study include its large size, defined clinical trial cohorts, standardized therapy, comprehensively annotated clinicopathological variables, and, in the case of the COIN/COIN-B cohort, molecular variables and mature outcome data. Consequently, our analyses were powered to detect even a modest association of most SNPs with clinical outcome and had a power of greater than 0.95 to detect an association of similar strength to that previously reported for the rs867228 and rs4986790 LOF variants (4,6). Limitations include the lack of molecular profiling in the SCOT trial, which meant that we were unable to test for an association of the SNPs with clinical outcome in specific tumor subgroups such as those with enhanced immunogenicity due to defective DNA mismatch repair or POLE exomeulce domain mutation.

In summary, in this study of two large clinical trial cohorts, we find no evidence that LOF SNPs in the pattern recognition receptors FPR1, TLR3, and TLR4 are associated with differential benefit from oxaliplatin in CRC. Future studies may better define the complex relationship between cytotoxic therapeutic-induced cell death, pattern recognition SNPs, and the innate immune system.

**Figure 3.** FPR1, TLR3, and TLR4 loss of function (LOF) single nucleotide polymorphisms (SNPs) and overall survival (OS) in COIN/COIN-B cohort. Kaplan–Meier curves showing OS for patients in combined COIN/COIN-B cohort by pattern recognition receptor SNPs rs867228 (FPR1 c.1037A>C, p.Glu346Lys (A)), rs3775291 (TLR3 c.1234C>T, p.Leu412Phe) (B), and rs4986790 (TLR4 c.896A>C, p.Asp299Gly) (C) (LOF allele/amino acid underscored in each case). Analyses of the rs4986790 (TLR4 c.1196C>T, p.Thr399Ile) polymorphism, which is strongly linked with rs4986790, were essentially identical to C and are not shown. Shaded areas represent 95% confidence intervals. P values indicate comparison of all groups by the two-sided log-rank test.

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were coordinated by the Medical Research Council Clinical Trials Unit and conducted with the support of the National Institutes of Health Research Council. COIN and COIN-B translational studies were supported by the Bobby Moore Fund from Cancer Research UK, Tenovus, the Kidani Trust, Cancer Research Wales, and the National Institute for Social Care and Health Research Cancer Genetics Biomedical Research Unit.

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