Common genetic variation associated with increased susceptibility to prostate cancer does not increase risk of radiotherapy toxicity

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ABSTRACT

Background

Numerous germline single nucleotide polymorphisms increase susceptibility to prostate cancer, some lying near genes involved in cellular radiation response. This study investigated whether prostate cancer patients with a high genetic risk have increased toxicity following radiotherapy.

Methods

The study included 1,560 prostate cancer patients from four radiotherapy cohorts: RAPPER (n=533), RADIOGEN (n=597), GenePARE (n=290), CCI (n=150). Data from genome-wide association studies were imputed with the 1000 Genomes reference panel. Individuals were genetically similar with a European ancestry based on principal component analysis. Genetic risks were quantified using polygenic risk scores. Regression models tested associations between risk scores and 2-year toxicity (overall, urinary frequency, decreased stream, rectal bleeding). Results were combined across studies using standard inverse-variance fixed effects meta-analysis methods.

Results

75 variants were genotyped/ imputed successfully. Neither non-weighted nor weighted polygenic risk scores were associated with late radiation toxicity in individual studies ($p>0.11$) or after meta-analysis ($p>0.24$). No individual variant was associated with 2-year toxicity.

Conclusion

Patients with a high polygenic susceptibility for prostate cancer have no increased risk for developing late radiotherapy toxicity. . These findings suggest that patients with a genetic pre-disposition for prostate cancer, inferred by common variants, can be safely treated using current standard radiotherapy regimens.

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Introduction

Prostate carcinoma accounts for a quarter of cancer diagnoses in men in the UK and is the fourth most common cancer worldwide with an estimated 1.1 million men diagnosed in 2012 (Globocan, 2012, UK, 2014). It is estimated that approximately a third of patients with localised or locally advanced prostate cancer undergo external beam radiotherapy (RT) with curative intent (Foroudi et al., 2003). The use of RT in combination with androgen-deprivation prolongs survival (Martin and D'Amico, 2014), and has contributed to the increase in 5-year survival rate from 30% in the 1970s to 80% in 2009 (UK, 2014). Due to increased cure rates, cancer survivorship and late treatment toxicity have become increasingly important issues in healthcare provision (England, 2013).

Late toxicity following irradiation for prostate cancer includes damage to the bladder, bowel and erectile function (Peeters et al., 2005). The median rates of late gastrointestinal (GI) and genitourinary (GU) toxicity are reported to be 15% and 17% respectively (Ohri et al., 2012). The rates of severe GI and GU toxicity are reported to be 2% and 3% respectively (Ohri et al., 2012). There is now supporting evidence new techniques such as Intensity Modulated Radiotherapy (IMRT) reduce rates of long term GI and GU side effects compared to 3-D conformal RT, even with dose escalation (Dolezel et al., 2015, Wilkins et al., 2015). Despite these advances approximately one in five patients will experience some degree of late radiation toxicity (Dolezel et al., 2015).

Studies are attempting to identify the genetic variants that increase an individual's risk of radiation toxicity (Fachal et al., 2014, Barnett et al., 2014, Kerns et al., 2013b). This work has highlighted the need to increase the statistical power to identify individual common variants with small effects (Barnett et al., 2012a). To address this need the Radiogenomics Consortium (RGC) was established in 2009 to facilitate large scale collaborative research with sufficient power to detect genetic variants that predict a patient's risk of radiation toxicity (West et al., 2010). RGC groups have undertaken genome wide association studies

(GWAS) and are starting to identify replicated variants that increase a prostate cancer patient's risk of toxicity (Fachal et al., 2014).

In the cancer pre-disposition field, GWAS have identified 76 common single nucleotide polymorphisms (SNPs) associated with prostate cancer susceptibility (Eeles et al., 2013a). While the biologic role of these SNPs in the development of prostate cancer is an area of on-going investigation, their proximity to genes which are involved in DNA repair processes suggests that disruption of DNA damage response and repair mechanisms may have a key role (Hazelett et al., 2014, Eeles et al., 2013a). If a patient has an inherent compromised ability to repair DNA damage, they may be predisposed to both prostate cancer and toxicity following RT, as the same DNA repair pathways play a central role in cellular response to radiation. Also, recent epidemiological evidence suggests that radiation exposure increases the risk of developing prostate cancer (Schmitz-Feuerhake and Pflugbeil, 2011, Kondo et al., 2013, Myles et al., 2008). Therefore, the hypothesis underlying this study was that common genetic variants involved in cancer pre-disposition may have roles in both tumour formation and in the response of normal tissues to radiation-induced DNA damage. The aim of this study was to investigate the association between prostate cancer germline risk SNPs and likelihood of developing late radiation toxicity.

Methods

Patients

This prospective study involved four prostate cancer radiotherapy cohorts: RAPPER (N=533), RADIOGEN (N=597), GenePARE (N=290) and CCI (N=150). Informed consent was obtained from all patients. RAPPER was approved by the Cambridge South Research Ethics Committee (05/Q0108/365). RADIOGEN was approved by the Galician Ethical Committee. Gene-PARE was approved by the Mount Sinai Medical Center Institutional

Review Board. The CCI study was approved by the Health Research Ethics Board of Alberta (Cancer).

The UK RAPPER study (UKCRN1471) recruited patients who received neoadjuvant androgen suppression and external beam radiotherapy (EBRT) from two clinical trials RT01 (ISRCTN47772397) and CHHiP (ISRCTN97182923). A full description of the cohort is available elsewhere (Barnett et al., 2014). The RTO1 study was a randomised dose escalation study using 3D conformal radiotherapy comparing 64 Gy and 74 Gy in the treatment of localised prostate cancer (Dearnaley et al., 2014). The CHHiP study randomised between standard (74 Gy in 37 fractions) and hypofractionated (60 Gy in 20 fractions or 57 Gy in 19 fractions) intensity modulated radiotherapy (IMRT) (Dearnaley et al., 2012).

RADIOGEN comprised patients who received 3D conformal radical or post-prostatectomy EBRT at the Clinical University Hospital of Santiago de Compostela, Spain. 473 patients had adjuvant hormone therapy. Patients received radical EBRT using doses of between 70 Gy – 76 Gy in 2 Gy per fraction. The adjuvant EBRT doses used were 60 Gy – 66 Gy in 2 Gy per fraction. A full description of the cohort can be found elsewhere (Fachal et al., 2012).

GenePARE patients received brachytherapy with/without EBRT at the Mount Sinai Hospital, New York. Of the approximately 800 patients included in the initial Gene-PARE study, 290 individuals of European ancestry had high quality genome-wide SNP data available and were included in the present study. 147 of these received adjuvant hormone therapy. ^{125}I (160 Gy; TG-43) was used in patients undergoing brachytherapy alone and ^{103}Pd (100 Gy) in patients also receiving EBRT. The EBRT regimen was delivered using 3D conformal technique using 24 Gy - 50 Gy. EBRT alone was delivered using IMRT using 66.6 Gy – 81 Gy, and further full details can be found elsewhere (Kerns et al., 2013a).

The CCI cohort recruited patients from the Cross Cancer Institute in Edmonton and the Tom Baker Cancer Centre in Alberta, Canada. Patients underwent EBRT using a

hypofractionated (68 Gy in 25 fractions or 55 Gy in 16 fractions) or conventional (72 Gy – 82 Gy delivered in 2 Gy per fraction) schedule. Approximately 50% of patients received androgen suppression. Further treatment details can be found elsewhere (Kerns et al., 2013b).

Assessment of Late Radiotherapy Toxicity

Late toxicity data were collected prospectively and assessed using standardised scoring systems (Supplementary Table 1). Data collected at 2 years were used as in other RGC studies (Andreassen et al., 2012, Kerns et al., 2013b, Dearnaley et al., 2012). For rectal bleeding in GenePARE, a 1-5 year window was allowed, because the scoring system assigns grades based on whether rectal bleeding occurs as a single incident or intermittent symptoms over time.

Decreased stream, urinary frequency and rectal bleeding data were harmonized across the four cohorts to create comparable endpoints (see Supplementary Table 2). Toxicity endpoints were analysed as change from baseline rather than actual recorded grade such that the toxicity captured was due to radiotherapy only. Due to the low number of high grade toxicities (≥2) it was only possible to analyse toxicities as grade 0 versus ≥1 (Table 1). Scale-independent Standardized Total Average Toxicity (STAT) scores were derived, as described previously (Barnett et al., 2012b), from a range of individual toxicity endpoints to provide an overall measure of two-year toxicity that was comparable across the four cohorts.

Genotyping, Quality Control and Imputation

Samples were genotyped as part of previously completed GWAS (Kerns et al., 2013b, Fachal et al., 2014, Barnett et al., 2014). Standard quality control procedures were applied to remove variants that were missing in >5% of samples, had a minor allele frequency (MAF) <1%, or displayed genotype frequencies deviating from those expected under Hardy-Weinberg equilibrium (p-value<10^{-6}). Samples that had >3% of all variants missing were

removed. Allele frequencies are known to vary by ancestral background, so principle components analysis (PCA) was used to identify and exclude individuals with non-European ancestry in order to avoid false positive associations arising from population substructure because of the small number of participants with other ethnicities. Comparable sets of variants were produced through imputation using SHAPEIT (Delaneau et al., 2012) and IMPUTE2 (Howie et al., 2011) with the 1000 Genomes Phase I reference panel (Abecasis et al., 2010). Supplementary Table 3 lists the 76 known prostate cancer susceptibility SNPs. Genotype dosages for the prostate cancer risk alleles were extracted from the imputed data.

Statistical Analysis

Polygenic risk scores were created to quantify the patients' genetic risk of prostate cancer. For each patient, genotype dosages for the prostate cancer risk-increasing alleles were calculated and then summed across all the variants. Two types of risk score were calculated:

Non-weighted, for patient i: $risk\ score_i = \sum_1^j G_{ij}$

Weighted, for patient i: $weighted\ risk\ score_i = \sum_1^j \beta_j G_{ij}$

where j = variants 1..76

β_j = the per-allele log-odds ratio for risk of prostate cancer associated with variant j

G = risk allele dosage

The log-odds ratios used to weight the risk score were taken from the review paper by Eeles *et al* (Eeles et al., 2013a).

Within each cohort, logistic regression was used to test the association between each individual toxicity endpoint and polygenic risk score, adjusted for important non-genetic factors identified by QUANTEC (Bentzen et al., 2010). Total biologically effective dose (BED)

was calculated for individuals in all four studies as a measure of radiation dose exposure using an α/β=3. Other non-genetic risk factors included were age at treatment, diabetes (rectal bleeding only), rectal volume (rectal bleeding only), transurethral resection of the prostate (TURP) prior to radiotherapy (urinary endpoints only), and baseline toxicity (Table 1). Linear regression was used to test the association between STAT score and polygenic risk score, adjusted for all the non-genetic factors above. Logistic and linear regression was also used to test each genetic variant individually. Regression coefficients and their standard errors were then meta-analysed using standard inverse-variance weighted fixed effects meta-analysis methods.

Power Calculations

This study was well powered to detect significant associations between prostate cancer polygenic risk scores and common radiotherapy toxicity endpoints. Assuming a moderate difference of 0.34 in mean polygenic risk score between prostate cancer patients who experience toxicity and those who do not, with a significance level of α=0.05, the power to detect an association between toxicity (grade≥1) and polygenic risk score would be 99% for a toxicity endpoint with 15% prevalence (grade≥1) and 96% for a toxicity endpoint with 6% prevalence (grade≥1). This difference in mean risk would be equivalent to a relative risk of toxicity of 1.4 for the subset of patients with a higher mean polygenic risk of prostate cancer.

Results

The distributions of patient characteristics, toxicity endpoints and STAT scores are summarised in Table 1. Of the 76 germline prostate cancer risk SNPs, 75 were genotyped or imputed successfully (R^2>0.3) (Table 2). Histograms of the polygenic risk scores show an approximate normal distribution within each cohort (Figure 1). Brachytherapy slightly increases urinary toxicity compared with EBRT alone, which explains the higher urinary toxicity in Gene-PARE (Sutani et al., 2015).

The results of the association analyses are shown in Table 3 and Supplementary Tables 4-7. Neither the non-weighted nor the weighted polygenic risk score was associated with any late radiotherapy individual toxicity endpoints or STAT score in any of the individual studies or on meta-analysis (meta-analysis $p>0.35$ and $p>0.33$ for non-weighted and weighted scores respectively; Table 3). None of the individual SNPs were associated with late radiation toxicity at 2 years at the pre-specified significance level of p-value$<5\times10^{-4}$ in any of the individual studies or on meta-analysis (Supplementary Tables 4-7). There was no statistical evidence of heterogeneity between studies for any individual SNPs or the polygenic risk score.

Discussion

This study found no evidence that prostate cancer patients with a high polygenic risk score for susceptibility to the disease have an increased risk of developing late toxicity following RT. The study was well powered to detect an association between prostate cancer polygenic risk and radiotherapy toxicity endpoints with a prevalence ≥6% and a moderate effect of RR=1.4. There was also no evidence for individual SNPs to be associated with risk of toxicity, although the study was not sufficiently powered to detect associations with individual SNPs that are each likely to carry a very small risk for radiotherapy toxicity. Rare, highly penetrant variants like *BRCA1, BRCA2 and HOXB13* were not included in this analysis as they require sequencing in a much larger number of patients and different statistical analysis methods.

The biggest non-genetic determinant of radiotherapy toxicity is known to be dose (Kerns et al., 2015). In this study we calculated biologically effective dose [BED] to allow comparison across cohorts receiving external beam therapy only (RAPPER, RADIOGEN and CCI) and those receiving brachytherapy as well (Gene-PARE). Other important non-genetic factors such as age and co-morbidities were also adjusted for. Tests for heterogeneity in these factors across the cohorts were highly significant, suggesting that the cohorts are not homogeneous. However, none of the meta-analysis p-values for heterogeneity were statistically significant. Thus, although the heterogeneity of the cohorts may have reduced the power of the meta-analysis, it is unlikely to have biased the results for the SNPs.

The prostate cancer risk SNPs are mostly located in intronic regions and the functional target genes through which they increase prostate cancer risk are not known. However, some SNPs associated with prostate cancer risk reside near genes that may influence the DNA repair process. The SNP rs817826, identified in a Han Chinese population, lies in an intergenic region between *RAD23B* and *KLF4* (Xu et al., 2012). RAD23B is a key protein involved in the nucleotide excision repair pathway which functions to repair single strand

DNA breaks from ionising radiation (Clement et al., 2010). Defects in this pathway have been associated with photosensitive conditions such as xeroderma pigmentosa (XP) and increase the likelihood of double strand breaks and late radiation toxicity (Feltes and Bonatto, 2015). Another SNP, rs1938781, found on chromosome 11q12 lies very close to *FAM111A* and *FAM111B (Akamatsu et al., 2012)*. Mutations in *FAM111B* have been associated with the development of hereditary fibrosing poililoderma with pulmonary fibrosis, tendon contracture, and myopathy (Mercier et al., 2013). The underlying mechanism in which *FAM111B* causes the above abnormalities is not known. One of the most interesting SNPs, rs7141529 on chromosome 14q24, is an intronic SNP in the DNA repair gene *RAD51B* (Eeles et al., 2013c). Though the functional effect of this SNP is unknown, *RAD51B* is involved in homologous recombination repair induced by double strand DNA breaks such as those caused by RT. SNPs in the *TERT* locus of 5p15 have been shown to affect prostate cancer risk by interfering with TERT expression (Amin Al Olama et al., 2013). The *TERT* gene functions by adding telomere repeat sequences at the end of chromosomes, which prevent cells undergoing telomere dependent senescence (Kote-Jarai et al., 2013). A number of proteins have been identified that are involved in telomere maintenance as well as being involved in repair of DNA double strand breaks by homologous recombination (Huda et al., 2009). Another SNP that has an association with aggressive prostate cancer is rs4245739 which is located in the 3' untranslated (UTR) of *MDM4* on chromosome 1q32 (Eeles et al., 2013c). When functioning normally *MDM4* is a critical negative regulator of the tumour suppressor gene *TP53*. *MDM4* is frequently overexpressed in many cancers that have wild type *TP53* (Wynendaele et al., 2010). *TP53* is involved in DNA repair (Merino and Malkin, 2014).

Studies investigating genetic variation in relation to risk of radiotherapy toxicity focused initially on *ATM*, because individuals with homozygote mutations are extremely sensitive to radiation. The first SNP studies were reported at the start of twenty-first century, and the most widely studied genes encoded proteins associated with DNA repair (e.g. *ATM*), the

development of fibrosis (e.g. *TGFB1*) and scavenging of reactive oxygen species (e.g. *SOD2*). Although significant associations were reported, replication was often unsuccessful (Andreassen et al 2006, Barnett et al 2012 Lancet Oncol). Since the establishment of the RGC, replicated associations have been found in both large candidate gene (Talbot et al 2012 BJC; Siebold et al 2015) and genome wide association (Fachal et al 2014) studies. It is interesting to note that the SNPs being identified through GWAS fall in or near genes associated with the function of the tissue irradiated (Kerns et al., 2015, Kerns et al., 2014a, Kerns et al., 2014b, Rosenstein et al., 2014,)Fachal et al 2014). Although DNA damage response gene products have a clear role in cancer eradication, other pathways are clearly important in the pathogenesis of late radiotherapy toxicity (Bentzen, 2006).

The study reported here had a number of limitations. First, the findings are limited to prostate cancer risk conferred by common variants only – many thousands of participants will need to be studied to assess a role for rare variants. Second, our analysis was limited to men who were genetically of European ancestry and therefore the conclusions may not be generalisable to men of other ethnicities. Third, many genes that predispose to prostate cancer have not yet been identified. Fourth, there are likely to be un-recorded toxicities in patients because under-reporting is a known issue of data collection in radiotherapy studies (Bentzen et al., 2010). For example, it was not possible to analyse sexual dysfunction as no data were available for two of the cohorts.

Only 33% of common germline variants that predict the familial risk of developing prostate cancer have so far been discovered (Eeles et al., 2014). The top 1% of the risk distribution have a 4.7 times increased risk of developing prostate cancer than the average population being profiled (Eeles et al., 2013c). The National Institute of Health funded GAME-ON initiative is a cross cancer genotyping project which will include 100,000 prostate cancer patient samples on a genotyping array of 500,000 SNPs. Through this expanded genotyping effort, additional risk SNPs for prostate cancer susceptibility are expected to be identified. Around 5,000 samples from the RGC are included in the OncoArray genotyping initiative,

and can be used to test associations between SNPs and radiotherapy toxicity in a future larger study with more SNPs covering a larger percentage of the familial risk. The larger sample size should allow for better testing of individual SNPs.

In summary, this work showed that there is no association between genetic susceptibility to developing prostate cancer and the development of late radiation toxicity.. The implication of this finding is that standard RT for prostate cancer can be given to patients with an increased genetic burden for prostate cancer without the risk of increased late radiotherapy toxicity.

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Table 1: Distributions of patient characteristics and toxicity

	RAPPER (N=533)	**RADIOGEN** (N=597)	**GenePARE** (N=290)	**CCI** (N=150)	**p-value**[4]
Age					
Mean (SD)	67.2 (5.7)	71.0 (6.5)	64.0 (7.5)	66.7 (7.4)	p<0.00005
Diabetes					
Yes n(%)	39 (7.3)	144 (24.1)	16 (5.5)	24 (16.0)	
No n(%)	493 (92.5)	453 (75.9)	274 (94.5)	122 (81.3)	p<0.00005
Missing n(%)	1 (0.2)	0	0	4 (2.7)	
Prior TURP[1]					
Yes n(%)	56 (10.5)	45 (7.5)	6 (2.1)	6 (4.0)	
No n(%)	472 ((88.6)	552 (92.5)	284 (97.9)	144 (96.0)	p=0.0002
Missing n(%)	5 (0.9)	0	0	0	
BED[2]					
Mean (SD)	120.5 (6.2)	120.5 (5.6)	191.9 (22.4)	125.5 (6.2)	p<0.00005
STAT 2 years[3]					
Mean (SD)	-0.01 (0.5)	0.02 (0.8)	0.12 (0.7)	-0.01 (0.7)	0.06
Decreased Stream					
Grade 0 n(%)	483 (90.6)	472 (79.1)	189 (65.2)	NA	
Grade ≥1 n(%)	29 (5.5)	6 (1.0)	66 (22.7)	NA	p<0.00005
Missing n(%)	21 (3.9)	119 (19.9)	35 (12.1)	NA	
Urine frequency					
Grade 0 n(%)	482 (90.5)	423 (70.9)	179 (61.7)	120 (80)	
Grade ≥1 n(%)	45 (8.4)	54 (9.0)	76 (26.2)	30 (20)	p<0.00005
Missing n(%)	6 (1.1)	120 (20.1)	35 (12.1)	0	
Rectal bleeding					
Grade 0 n(%)	446 (83.7)	522 (87.4)	208 (71.7)	110 (73.3)	
Grade ≥1 n(%)	81 (15.2)	74 (12.4)	82 (28.3)	40 (26.7)	p<0.00005
Missing n(%)	6 (1.1)	1 (0.2)	0	0	

[1]TURP trans-urethral resection of the prostate
[2]BED biologically effective dose
[3]STAT standardized total average toxicity
[4]p-value for test of heterogeneity across cohorts

Table 2: SNPs associated with prostate cancer

SNP	Chromosome	Position	Alleles major/minor	RAPPER		RADIOGEN		GenePARE		CCI	
				MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$
rs1218582	1	154834183	A/G	0.45	0.94	0.50	0.87	0.43	0.96	0.48	0.96
rs4245739	1	204518842	A/C	0.24	0.99	0.30	0.99	0.28	1	0.23	1
rs11902236	2	10117868	G/A	0.27	0.93	0.29	1	0.27	0.91	0.28	1
rs13385191	2	20888265	G/A[d]	0.25	0.99	0.24	1	0.27	1	0.26	1
rs1465618	2	43553949	G/A	0.22	0.98	0.26	0.98	0.23	0.98	0.22	1
rs721048	2	63131731	G/A	0.22	1	0.22	1	0.18	0.94	0.17	0.93
rs10187424	2	85794297	A/G	0.37	1	0.44	0.99	0.42	0.99	0.42	1
rs12621278	2	173311553	A/G	0.04	0.97	0.04	1	-	-	-	-
rs2292884	2	238443226	A/G	0.28	1	0.23	0.97	0.24	0.99	0.22	0.99
rs3771570	2	242382864	G/A	0.18	0.99	0.16	0.96	0.14	1	0.15	1
rs2660753	3	87110674	C/T	0.11	1	0.16	1	0.19	0.96	0.08	0.98
rs2055109	3	87467332	C/T[d]	0.26	1	0.28	0.99	0.24	0.86	0.22	0.99
rs7611694	3	113275624	A/C	0.41	1	0.37	0.98	0.36	1	0.39	1
rs10934853	3	128038373	C/A	0.29	0.98	0.29	0.94	0.32	1	0.34	1
rs6763931	3	141102833	C/T	0.45	0.98	0.39	1	0.40	0.96	0.39	1
rs10936632	3	170130102	A/C	0.49	0.94	0.45	0.95	0.46	0.94	0.47	0.95
rs1894292	4	74349158	G/A	0.47	0.86	0.47	1	0.40	0.91	0.44	1
rs12500426	4	95514609	C/A	0.48	0.96	0.48	0.98	0.49	0.98	0.49	0.99
rs17021918	4	95562877	C/T	0.31	0.99	0.31	0.99	0.35	1	0.37	1
rs7679673	4	106061534	C/A	0.34	1	0.38	0.99	0.49	0.99	0.38	1
rs2242652	5	1280028	G/A	0.19	0.91	0.15	0.45	0.22	0.62	0.19	0.62
rs12653946	5	1895829	C/T	0.45	1	0.46	0.58	0.48	0.90	0.44	0.90
rs2121875	5	44365545	T/G	0.35	1	0.37	1	0.41	0.99	0.34	1
rs6869841	5	172939426	G/A	0.23	0.98	0.21	0.99	0.24	0.99	0.23	0.99
rs130067[a]	6	31118511	T/G	0.21	1	0.19	1	NA	NA	NA	NA

SNP	Chromosome	Position	Alleles major/minor	RAPPER		RADIOGEN		GenePARE		CCI	
				MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$
rs3096702[b]	6	32192331	G/A	0.42	0.97	0.28	1	NA	NA	NA	NA
rs1983891	6	41536427	C/T	0.29	0.95	0.35	0.98	0.31	1	0.31	1
rs2273669	6	109285189	A/G	0.15	0.99	0.16	0.97	0.12	0.97	0.14	0.99
rs339331	6	117210052	T/C[d]	0.27	0.97	0.25	1	0.19	1	0.32	1
rs1933488	6	153441079	A/G	0.38	0.99	0.41	1	0.44	1	0.41	1
rs9364554	6	160833664	C/T	0.33	0.99	0.25	1	0.25	1	0.29	1
rs12155172	7	20994491	G/A	0.22	0.82	0.21	1	0.21	0.97	0.22	0.97
rs10486567	7	27976563	G/A[d]	0.19	0.97	0.20	1	0.25	0.99	0.21	0.98
rs6465657	7	97816327	T/C	0.49	1	0.47	1	0.41	1	0.49	1
rs2928679	8	23438975	C/T	0.48	1	0.45	0.99	0.49	0.97	0.46	1
rs1512268	8	23526463	G/A	0.45	0.99	0.50	0.98	0.49	0.99	0.42	1
rs11135910	8	25892142	G/A	0.2	0.93	0.15	1	0.16	0.97	0.18	0.99
rs12543663	8	127924659	A/C	0.35	0.94	0.26	0.97	0.31	0.94	0.33	0.94
rs10086908	8	128011937	T/C	0.27	1	0.31	1	0.26	1	0.26	0.99
rs16901979	8	128124916	C/A	0.05	0.99	0.05	1	0.05	1	0.05	1
rs620861	8	128335673	C/T	0.34	1	0.36	0.99	0.36	0.99	0.31	0.99
rs6983267	8	128413305	G/T[d]	0.43	0.95	0.40	1	0.48	0.98	0.45	1
rs1447295	8	128485038	C/A	0.14	0.97	0.07	1	0.09	0.99	0.10	0.99
rs817826	9	110156300	T/C	0.17	0.64	0.17	0.94	0.21	1	0.12	1
rs1571801	9	124427373	C/A	0.28	0.76	0.23	1	0.22	1	0.32	1
rs10993994	10	51549496	C/T	0.46	0.79	0.43	1	0.47	0.92	0.43	0.92
rs3850699	10	104414221	A/G	0.28	0.99	0.28	0.96	0.29	0.97	0.26	0.97
rs2252004	10	122844709	G/T[d]	0.09	0.99	0.09	0.99	0.11	1	0.09	1
rs4962416	10	126696872	T/C	0.28	0.93	0.31	1	0.31	0.98	0.24	0.98
rs7127900	11	2233574	G/A	0.22	0.98	0.23	0.91	0.27	0.59	0.22	0.96
rs1938781	11	58915110	T/C	0.21	1	0.21	1	0.20	0.99	0.19	1
rs7931342	11	68994497	G/T	0.46	1	0.41	1	0.36	1	0.41	1
rs11568818	11	102401661	A/G	0.44	0.89	0.46	0.99	0.42	0.91	0.42	0.93

SNP	Chromosome	Position	Alleles major/minor	RAPPER		RADIOGEN		GenePARE		CCI	
				MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$	MAF	$R^{2\,e}$
rs902774	12	53273904	G/A	0.16	0.98	0.14	1	0.17	0.99	0.18	1
rs1270884	12	114685571	G/A	0.48	0.93	0.49	0.98	0.48	0.98	0.48	1
rs10875943	12	49676010	T/C	0.32	0.86	0.28	1	0.32	0.93	0.29	0.95
rs9600079	13	73728139	G/T	0.46	0.86	0.47	1	0.43	0.89	0.46	0.95
rs8008270	14	53372330	G/A	0.15	1	0.19	0.99	0.19	1	0.16	1
rs7141529	14	69126744	G/A[d]	0.47	1	0.45	1	0.46	0.99	0.49	0.99
rs4430796	17	36098040	G/A	0.47	0.94	0.49	0.88	0.49	0.90	0.45	0.93
rs7210100[c]	17	47436749	A/G	-	-	-	-	-	-	-	-
rs11649743	17	36074979	G/A[d]	0.2	1	0.19	1	0.15	1	0.16	1
rs11650494	17	47345186	G/A	0.09	0.99	0.08	0.93	0.13	0.99	0.09	0.99
rs684232	17	618965	A/G	0.35	0.99	0.33	0.98	0.34	0.98	0.39	0.99
rs1859962	17	69108753	T/G	0.5	0.99	0.45	1	0.43	1	0.47	1
rs7241993	18	76773973	G/A	0.28	0.94	0.28	0.91	0.32	0.51	0.32	0.56
rs8102476	19	38735613	C/T[d]	0.42	0.99	0.34	0.96	0.38	0.97	0.43	0.97
rs11672691	19	41985587	A/G[d]	0.24	0.87	0.21	0.93	0.23	0.93	0.27	0.93
rs103294[f]	19	54797848	T/C	0.23	1	0.20	1	0.22	0.30	-	-
rs2735839	19	51364623	G/A	0.12	1	0.15	1	0.17	0.93	0.16	0.97
rs2427345	20	61015611	G/A	0.35	0.99	0.35	0.37	0.39	0.91	0.40	0.96
rs6062509	20	62362563	A/C	0.32	1	0.26	0.99	0.27	0.98	0.28	0.98
rs5759167	22	43500212	G/T	0.47	1	0.45	0.90	0.46	0.80	0.47	1
rs2405942	23	9814135	A/G	0.17	1	0.20	0.95	0.21	0.94	0.23	0.93
rs5919432	23	67021550	A/G	0.14	0.98	0.18	1	0.21	1	0.18	1
rs5945619	23	51241672	T/C	0.41	0.92	0.44	1	0.38	1	0.33	1

[a]merged SNP rs115664826
[b]merged SNP rs114376585
[c]rs7210100 MAF=0, R^2=0, excluded from RAPPER analyses; RADIOGEN R^2= 0.005; not imputed in GenePARE or CCI datasets
[d]major allele is associated with increased risk of prostate cancer

[e]R^2 refers to the “imputation info” metric produced by IMPUTE2, which represents the certainty with which the SNP has been imputed and lies between 0 (no certainty) and 1 (high certainty; R^2=1 for genotyped SNPs).
[f]rs103294 poorly imputed in CCI

Table 3: Polygenic risk score analyses results

	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
	beta (95% CI)	p[1]	beta (95% CI)	p	beta (95% CI)	p	beta (95% CI)	P	beta (95% CI)	p	Q, p-het[2]
STAT[3] score											
Unweighted risk score	0.003 (-0.006, 0.01)	0.49	0.003 (-0.008, 0.01)	0.61	-0.01 (-0.03, 0.01)	0.15	-0.01 (-0.04, 0.01)	0.25	0.00002 (-0.01, 0.01)	0.99	3.88, 0.28
Weighted risk score	0.04 (-0.02, 0.10)	0.19	0.03 (-0.05, 0.10)	0.44	-0.06 (-0.17, 0.05)	0.28	-0.09 (-0.26, 0.08)	0.29	0.01 (-0.03, 0.06)	0.49	4.15, 0.25
Decreased stream											
Unweighted risk score	0.01 (-0.06, 0.08)	0.78	0001 (-0.001, 0.003)	0.36	0.004 (-0.06, 0.06)	0.91	NA	NA	0.001 (-0.001, 0.003)	0.35	0.08, 0.96
Weighted risk score	0.34 (-0.15, 0.83)	0.17	0.01 (-0.01, 0.02)	0.36	0.04 (-0.35, 0.43)	0.86	NA	NA	0.01 (-0.01, 0.02)	0.33	1.84, 0.40
Urine frequency											
Unweighted risk score	-0.004 (-0.06, 0.06)	0.90	-0.001 (-0.01, 0.004)	0.66	-0.04 (-0.10, 0.02)	0.18	-0.03 (-0.12, 0.05)	0.45	-0.002 (-0.007, 0.004)	0.54	2.19, 0.53
Weighted risk score	-0.003 (-0.40, 0.40)	0.99	-0.01 (-0.05, 0.02)	0.50	-0.31 (-0.72, 0.08)	0.12	0.04 (-0.56, 0.62)	0.89	-0.01 (-0.05, 0.02)	0.42	2.18, 0.54
Rectal bleeding											
Unweighted risk score	0.04 (-0.009, 0.08)	0.11	-0.002 (-0.01, 0.003)	0.47	-0.02 (-0.08, 0.04)	0.48	-0.0003 (-0.07, 0.07)	0.99	-0.002 (-0.01, 0.003)	0.55	3.22, 0.36
Weighted risk score	0.28 (-0.03, 0.59)	0.08	-0.01 (-0.04, 0.03)	0.78	-0.06 (-0.45, 0.32)	0.75	-0.05 (-0.57, 0.47)	0.86	-0.002 (-0.04, 0.03)	0.90	3.32, 0.34

[1]p-value corresponding to beta estimate
[2]p-value for test of heterogeneity between studies
[3]Standardized total average toxicity

Titles and legends to figures

Figure 1: Histograms showing the approximate normal distributions for the unweighted and the weighted polygenic risk scores in A) the RAPPER cohort, B) the RADIOGEN cohort, C) the GenePARE cohort, D) the CCI cohort

Supplementary Table 1: Standardized scoring systems for toxicity data collection

Study/trial	Toxicity endpoint and scale	Grade
RT01, CHHiP, GenePARE	Clinical assessment (RTOG) of late toxicity Proctitis	0 = No toxicity 1 = Minor symptoms requiring no treatment 2 = Symptoms responding to simple OPD management; lifestyle & PS unaffected 3 = Distressing symptoms altering lifestyle & PS. Hospitalisation for diagnosis or minor surgical intervention may be required 4 = Major surgical intervention (e.g. laparotomy, colostomy) or prolonged hospitalisation
RT01, CHHiP	Clinical assessment (RMH) of late toxicity Rectal bleeding	0 = No toxicity 1 = Occasional (no treatment) 2 = Moderate (simple OPD treatment) 3 = Severe (blood transfusion, surgery)
RT01, CHHiP	Nocturnal frequency	0 = 0-1 times 1 = 2-3 times 2 = 4-5 times 3 = 6-8 times 4 = >8 times
RT01, CHHiP	Clinical assessment (LENT-SOM) of late toxicity Sphincter control	0 = No toxicity 1 = Occasional 2 = Intermittent 3 = Persistent 4 = Refractory
RT01, CHHiP	Stool frequency	0 = < 2 per day 1 = 2-4 per day 2 = 5-8 per day 3 = >8 per day 4 = Uncontrolled diarrhoea
RT01, CHHiP	Urinary frequency	0 = >4 hour intervals 1 = 3-4 hour intervals 2 = 2-3 hour intervals

Study/trial	Toxicity endpoint and scale	Grade
		3 = 1-2 hour intervals 4 = Hourly
RT01, CHHiP	Urine incontinence	0 = No toxicity 1 = < weekly episodes 2 = < daily episodes 3 = <2 pads / undergarments / day 4 = Refractory
RT01, CHHiP	Decreased stream	0 = No toxicity 1 = Occasionally weak 2 = Intermittent 3 = Persistent but incomplete 4 = Complete obstruction
RADIOGEN	Clinical assessment (CTCAEv3.0) of late toxicity Rectal bleeding	0 = None 1 = Minimal (simple OPD treatment) 2 = Moderate (simple OPD treatment) 3 = Severe (blood transfusion, surgery)
RADIOGEN	Proctitis	0 = No toxicity 1 = Rectal discomfort, intervention not indicated 2 = Symptoms not interfering with ADL; medical intervention indicated 3 = Stool incontinence or other symptoms interfering with ADL; operative intervention indicated 4 = Life-threatening consequences (e.g., perforation)
RADIOGEN	Sphincter control	0 = No toxicity 1 = Occasional use of pads required 2 = Daily use of pads required 3 = Interfering with ADL; operative intervention indicated 4 = Permanent bowel diversion indicated
RADIOGEN	Diarrhoea	0 = No toxicity 1 = Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline 2 = Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in stoma output compared to baseline; not interfering with ADL 3 = Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in stoma output compared to baseline; interfering with ADL 4 = Uncontrolled diarrhea
RADIOGEN	Urinary frequency	0 = No toxicity

Study/trial	Toxicity endpoint and scale	Grade
		1 = Increase in frequency or nocturia up to 2 x normal; enuresis 2 = Increase >2 x normal but <hourly 3 = ≥1 x/hr; urgency; catheter indicated
RADIOGEN	Nocturnal frequency	0 = No toxicity 1 = Increase in frequency or nocturia up to 2 x normal; enuresis 2 = Increase >2 x normal but <hourly 3 = ≥1 x/hr; urgency; catheter indicated
RADIOGEN	Urine incontinence	0 = No toxicity 1 = Occasional (e.g., with coughing, sneezing, etc.), pads not indicated 2 = Spontaneous, pads indicated 3 = Interfering with ADL; intervention indicated (e.g., clamp, collagen injections) 4 = Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)
RADIOGEN	Decreased stream	0 = No toxicity 1 = Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period 2 = Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks 3 = More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy) 4 = Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated
GenePARE	Patient-reported outcome (IPSS) Nocturnal frequency	In the last month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you get up in the morning? 0 = None 1 = 1 time 2 = 2 times 3 = 3 times 4 = 4 times 5 = 5 times or more
GenePARE	Decreased stream	In the last month or so, how often have you had to push or strain to urinate? 0 = Not at all 1 = Less than 1 time in 5 2 = Less than ½ the time 3 = About ½ the time 4 = More than ½ the time 5 = Almost always

Study/trial	Toxicity endpoint and scale	Grade
GenePARE	Urinary frequency	In the last month or so, how often have you had to urinate again less than 2 hours after you have urinated? 1 = Less than 1 time in 5 2 = Less than ½ the time 3 = About ½ the time 4 = More than ½ the time 5 = Almost always

Supplementary Table 2: Harmonization of toxicity scoring systems across studies.

Toxicity endpoint	Study-Specific Toxicity Grade			Harmonized Grade
	RAPPER (LENT SOMA)	RADIOGEN, CCI (CTCAE v3.0)	GenePARE (IPSS)	
Nocturia	0	0	0 1	0
	1	1	2 3	1
	2	2	4	2
	3 4	3	5	3
Daytime urinary frequency	0	0	0 1	0
	1 2	1	2 3	1
	3	2	4	2
	4	3	5	3
Decreased urine stream	0	0	0 1	0
	1	1	2	1
	2	2	3 4	2
	3	3	5	3

Supplementary Table 3: Common susceptibility loci for prostate cancer identified through GWAS

Locus	SNP	Reference allele	Effect allele	Effect allele frequency*	Per allele OR* (95% CI)	Nearby genes	Reference
1q21	rs1218582	A	G	0.45	1.06 (1.03–1.09)	*KCNN3*	(Amin Al Olama et al.)
1q32	rs4245739	A	C	0.25	0.91 (0.88–0.95)	*MDM4, PIK3C2B*	(Amin Al Olama et al.)
2p11	rs10187424	A	G	0.41	0.92 (0.89–0.94)	*GGCX/VAMP8*	(Eeles et al., 2013b)
2p15	rs721048	G	A	0.19	1.15 (1.10–1.21)	*EHBP1*	(Gudmundsson et al., 2008)
2p21	rs1465618	G	A	0.23	1.08 (1.03–1.12)	*THADA*	(Al Olama et al., 2009)
2p24	rs13385191	A	G	0.56	1.15 (1.10–1.21)	*C2orf43*	(Takata et al., 2010)
2p25	rs11902236	G	A	0.27	1.07 (1.03–1.10)	*TAF1B:GRHL1*	(Amin Al Olama et al.)
2q31	rs12621278	A	G	0.06	0.75 (0.70–0.80)	*ITGA6*	(Al Olama et al., 2009)
2q37	rs2292884	A	G	0.25	1.14 (1.09–1.19)	*MLPH*	(Eeles et al., 2013b)
2q37	rs3771570	G	A	0.15	1.12 (1.08–1.17)	*FARP2*	(Amin Al Olama et al.)
3p11	rs2055109	T	C	0.9	1.20 (1.13–1.29)	None	(Akamatsu et al., 2012)
3p12	rs2660753	C	T	0.11	1.18 (1.06–1.31)	None	(Eeles et al., 2008)
3q13	rs7611694	A	C	0.41	0.91 (0.88–0.93)	*SIDT1*	(Amin Al Olama et al.)
3q21	rs10934853	C	A	0.28	1.12 (1.08–1.16)	*EEFSEC*	(Gudmundsson et al., 2009)
3q23	rs6763931	C	T	0.45	1.04 (1.01–1.07)	*ZBTB38*	(Eeles et al., 2013b)
3q26	rs10936632	A	C	0.48	0.90 (0.88–0.93)	*CLDN11/SKIL*	(Eeles et al., 2013b)
4q13	rs1894292	G	A	0.48	0.91 (0.89–0.94)	*AFM, RASSF6*	(Amin Al Olama et al.)
4q22	rs17021918	C	T	0.34	0.90 (0.87–0.93)	*PDLIM5*	(Al Olama et al., 2009)
4q22	rs12500426	C	A	0.46	1.08 (1.05–	*PDLIM5*	(Al Olama et

Locus	SNP	Reference allele	Effect allele	Effect allele frequency*	Per allele OR* (95% CI)	Nearby genes	Reference
					1.12)		al., 2009)
4q24	rs7679673	C	A	0.45	0.91 (0.88–0.94)	*TET2*	(Al Olama et al., 2009)
5p12	rs2121875	T	G	0.34	1.05 (1.02–1.08)	*FGF10*	(Eeles et al., 2013b)
5p15	rs2242652	G	A	0.19	0.87 (0.84–0.90)	*TERT*	(Eeles et al., 2013b)
5p15	rs12653946	C	T	0.44	1.26 (1.20–1.33)	*IRX4*	(Takata et al., 2010)
5q35	rs6869841	G	A	0.21	1.07 (1.04–1.11)	*FAM44B (BOD1)*	(Amin Al Olama et al.)
6p21	rs130067	T	G	0.21	1.05 (1.02–1.09)	*CCHCR1*	(Eeles et al., 2013b)
6p21	rs1983891	C	T	0.41	1.15 (1.09–1.21)	*FOXP4*	(Takata et al., 2010)
6p21	rs3096702	G	A	0.4	1.07 (1.04–1.10)	*NOTCH4*	(Amin Al Olama et al.)
6p21	rs2273669	A	G	0.15	1.07 (1.03–1.11)	*ARMC2, SESN1*	(Amin Al Olama et al.)
6q22	rs339331	C	T	0.63	1.22 (1.15–1.28)	*RFX6*	(Takata et al., 2010)
6q25	rs9364554	C	T	0.29	1.17 (1.08–1.26)	*SLC22A3*	(Eeles et al., 2008)
6q25	rs1933488	A	G	0.41	0.89 (0.87–0.92)	*RSG17*	(Amin Al Olama et al.)
7p15	rs10486567	A	G	0.77	0.74 (0.66–0.83)	*JAZF1*	(Thomas et al., 2008)
7p21	rs12155172	G	A	0.23	1.11 (1.07–1.15)	*SP8*	(Amin Al Olama et al.)
7q21	rs6465657	T	C	0.46	1.12 (1.05–1.20)	*LMTK2*	(Eeles et al., 2008)
8p21	rs2928679	C	T	0.42	1.05 (1.01–1.09)	*SLC25A37*	(Al Olama et al., 2009)
8p21	rs1512268	G	A	0.45	1.18 (1.14–1.22)	*NKX3.1*	(Al Olama et al., 2009)
8p21	rs11135910	G	A	0.16	1.11 (1.07–1.16)	*EBF2*	(Amin Al Olama et al., 2015)
8q24	rs1447295	C	A	0.13	1.62 (NR)	None	(Amundadottir et al., 2006)

Locus	SNP	Reference allele	Effect allele	Effect allele frequency*	Per allele OR* (95% CI)	Nearby genes	Reference
8q24	rs6983267	T	G	0.5	1.26 (1.13–1.41)	None	(Yeager et al., 2007)
8q24	rs16901979	C	A	0.09	1.79 (1.36–2.34)	None	(Gudmundsson et al., 2007a)
8q24	rs10086908	T	C	0.3	0.87 (0.81–0.94)	None	(Al Olama et al., 2009)
8q24	rs12543663	A	C	0.31	1.08 (1.00–1.16)	None	(Al Olama et al., 2009)
8q24	rs620861	C	T	0.39	0.90 (0.84–0.96)	None	(Al Olama et al., 2009)
9q31	rs817826	T	C	0.08	1.41 (1.29–1.54)	*RAD23B-KLF4*	(Amin Al Olama et al., 2013)
9q33	rs1571801	C	A	0.25	1.27 (1.10–1.48)	*DAB21P*	(Duggan et al., 2007)
10q11	rs10993994	C	T	0.4	1.25 (1.17–1.34)	*MSMB*	(Eeles et al., 2008, Thomas et al., 2008)
10q24	rs3850699	A	G	0.29	0.91 (0.89–0.94)	*TRIM8*	(Amin Al Olama et al.)
10q26	rs4962416	T	C	0.27	1.20 (1.07–1.34)	*CTBP2*	(Thomas et al., 2008)
10q26	rs2252004	T	G	0.77	1.16 (1.10–1.22)	None	(Akamatsu et al., 2012)
11p15	rs7127900	G	A	0.2	1.22 (1.17–1.27)	None	(Al Olama et al., 2009)
11q12	rs1938781	T	C	0.3	1.16 (1.11–1.21)	*FAM111A*	(Akamatsu et al., 2012)
11q13	rs7931342	G	T	0.49	0.84 (0.79–0.90)	None	(Eeles et al., 2008, Thomas et al., 2008)
11q22	rs11568818	A	G	0.44	0.91 (0.88–0.94)	*MMP7*	(Amin Al Olama et al., 2015)
12q13	rs10875943	T	C	0.31	1.07 (1.04–1.10)	*TUBA1C/PRPH*	(Eeles et al., 2013b)
12q13	rs902774	G	A	0.15	1.17 (1.11–1.24)	*KRT8*	(Eeles et al., 2013b)
12q24	rs1270884	G	A	0.49	1.07 (1.04–1.10)	*TBX5*	(Amin Al Olama et al., 2015)
13q22	rs9600079	G	T	0.38	1.18 (1.12–1.24)	None	(Takata et al., 2010)

Locus	SNP	Reference allele	Effect allele	Effect allele frequency*	Per allele OR* (95% CI)	Nearby genes	Reference
14q22	rs8008270	G	A	0.18	0.89 (0.86–0.93)	*FERMT2*	(Amin Al Olama et al., 2015)
14q24	rs7141529	A	G	0.5	1.09 (1.06–1.12)	*RAD51L1*	(Amin Al Olama et al., 2015)
17p13	rs684232	A	G	0.36	1.10 (1.07–1.14)	*VPS53, FAM57A*	(Amin Al Olama et al., 2015)
17q12	rs4430796	G	A	0.49	1.22 (1.15–1.30)	*HNF1B*	(Gudmundsson et al., 2007b)
17q12	rs11649743	A	G	0.8	1.28 (1.07–1.52)	*HNF1B*	(Al-Shibli et al., 2008)
17q21	rs7210100	A	G	0.05	1.51 (1.35–1.69)	*ZNF652*	(Eeles et al., 2013b)
17q21	rs11650494	G	A	0.08	1.15 (1.09–1.22)	*SPOP, HOXB13*	(Amin Al Olama et al., 2015)
17q24	rs1859962	T	G	0.46	1.20 (1.14–1.27)	None	(Gudmundsson et al., 2007b)
18q23	rs7241993	G	A	0.3	0.92 (0.89–0.95)	*SALL3*	(Amin Al Olama et al., 2015)
19q13	rs2735839	G	A	0.15	0.83 (0.75–0.91)	*KLK2/KLK3*	(Eeles et al., 2008)
19q13	rs8102476	T	C	0.54	1.12 (1.08–1.15)	None	(Gudmundsson et al., 2009)
19q13	rs11672691	G	A	0.76	1.12 (1.03–1.21)	None	(Amin Al Olama et al., 2013)
19q13	rs103294	T	C	0.24	1.28 (1.21–1.36)	*LILRA3*	(Amin Al Olama et al., 2013)
20q13	rs2427345	G	A	0.37	0.94 (0.91–0.97)	*GATAS, CABLES2*	(Amin Al Olama et al., 2015)
20q13	rs6062509	A	C	0.3	0.89 (0.66–0.92)	*ZGPAT*	(Amin Al Olama et al., 2015)
22q13	rs5759167	G	T	0.47	0.86 (0.83–0.88)	*BIL/TTLL1*	(Al Olama et al., 2009)
Xp11	rs5945619	T	C	0.36	1.19 (1.07–1.31)	*NUDT11*	(Gudmundsson et al., 2008, Eeles et al., 2008)
Xp22	rs2405942	A	G	0.21	0.88 (0.83–0.92)	*SHROOM2*	(Amin Al Olama et al., 2015)
Xq12	rs5919432	A	G	0.19	0.94 (0.89–0.98)	*AR*	(Eeles et al., 2013b)

*Data taken from the original publications
NR – Not Reported

Supplementary Table 4: Individual SNP analysis results for STAT endpoint

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs1218582	G	0.06 (0.03)	0.08	-0.06 (0.05)	0.22	-0.10 (0.07)	0.19	-0.17 (0.09)	0.05	-0.01 (0.03)	0.70	0.02
rs4245739	A	-0.05 (0.04)	0.24	-0.06 (0.05)	0.23	-0.07 (0.07)	0.33	-0.05 (0.10)	0.62	-0.05 (0.03)	0.05	0.99
rs11902236	A	0.03 (0.04)	0.50	-0.02 (0.05)	0.70	-0.06 (0.07)	0.36	-0.09 (0.10)	0.39	-0.01 (0.03)	0.81	0.59
rs13385191	G	-0.04 (0.04)	0.33	-0.01 (0.05)	0.89	0.06 (0.07)	0.37	0.10 (0.10)	0.30	-0.01 (0.03)	0.83	0.47
rs1465618	A	-0.04 (0.04)	0.28	0.04 (0.05)	0.45	0.003 (0.08)	0.51	-0.03 (0.10)	0.78	-0.01 (0.03)	0.67	0.66
rs721048	A	0.006 (0.04)	0.88	0.07 (0.05)	0.21	-0.03 (0.09)	0.48	-0.06 (0.13)	0.61	0.02 (0.03)	0.53	0.66
rs10187424	A	0.05 (0.03)	0.13	-0.05 (0.04)	0.22	0.07 (0.07)	0.31	-0.14 (0.09)	0.10	0.01 (0.02)	0.78	0.07
rs12621278	A	0.05 (0.08)	0.58	0.19 (0.11)	0.58	-	-	-	-	0.09 (0.07)	0.15	0.3
rs2292884	G	-0.01 (0.04)	0.83	-0.01 (0.05)	0.80	-0.02 (0.08)	0.49	0.02 (0.10)	0.87	-0.01 (0.03)	0.74	0.99
rs3771570	A	-0.05 (0.04)	0.23	0.04 (0.06)	0.51	-0.06 (0.10)	0.41	0.12 (0.13)	0.34	-0.02 (0.03)	0.61	0.41
rs2660753	T	0.06 (0.05)	0.30	-0.06 (0.06)	0.29	-0.01 (0.08)	0.50	-0.08 (0.15)	0.58	-0.01 (0.04)	0.89	0.47
rs2055109	C	0.06 (0.04)	0.08	-0.04 (0.05)	0.46	0.08 (0.08)	0.30	-0.06 (0.11)	0.59	0.03 (0.03)	0.27	0.29
rs7611694	A	0.03 (0.03)	0.38	0.06 (0.05)	0.17	-0.03 (0.07)	0.45	0.12 (0.09)	0.17	0.04 (0.02)	0.12	0.53
rs10934853	A	-0.02 (0.04)	0.59	0.05 (0.05)	0.31	0.10 (0.08)	0.21	-0.16 (0.09)	0.08	0.002 (0.03)	0.93	0.11
rs6763931	T	0.05 (0.03)	0.18	-0.03 (0.05)	0.57	-0.07 (0.07)	0.27	-0.05 (0.10)	0.57	0.003 (0.02)	0.91	0.31

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs10936632	A	0.07 (0.03)	0.03	-0.03 (0.04)	0.43	0.01 (0.07)	0.50	0.03 (0.09)	0.73	0.03 (0.02)	0.18	0.27
rs1894292	G	-0.07 (0.03)	0.05	0.02 (0.04)	0.59	0.04 (0.07)	0.42	-0.03 (0.09)	0.77	-0.02 (0.02)	0.36	0.31
rs12500426	A	-0.002 (0.04)	0.96	0.008 (0.04)	0.85	0.11 (0.07)	0.15	-0.04 (0.09)	0.69	0.01 (0.03)	0.61	0.51
rs17021918	C	-0.02 (0.03)	0.53	0.002 (0.05)	0.97	0.003 (0.07)	0.51	-0.10 (0.10)	0.29	-0.02 (0.03)	0.5	0.8
rs7679673	C	-0.03 (0.03)	0.35	0.04 (0.04)	0.35	-0.07 (0.06)	0.27	0.08 (0.10)	0.42	-0.01 (0.02)	0.71	0.33
rs2242652	G	-0.09 (0.05)	0.06	-0.01 (0.10)	0.89	0.02 (0.11)	0.49	0.11 (0.15)	0.43	-0.05 (0.04)	0.17	0.48
rs12653946	T	0.01 (0.03)	0.78	-0.03 (0.06)	0.59	-0.17 (0.07)	0.03	-0.14 (0.09)	0.12	-0.03 (0.03)	0.21	0.09
rs2121875	G	-0.03 (0.03)	0.41	0.03 (0.05)	0.45	-0.03 (0.07)	0.47	0.02 (0.09)	0.79	-0.01 (0.03)	0.8	0.7
rs6869841	A	-0.006 (0.04)	0.88	0.02 (0.05)	0.67	0.02 (0.08)	0.49	-0.19 (0.11)	0.08	-0.01 (0.03)	0.83	0.37
rs130067[1]	G	-0.004 (0.04)	0.93	-0.006 (0.06)	0.92	-	-	-	-	-0.004 (0.03)	0.9	0.98
rs3096702[2]	A	-0.03 (0.04)	0.44	-0.05 (0.05)	0.31	-	-	-	-	-0.04 (0.03)	0.22	0.72
rs1983891	T	-0.001 (0.04)	0.98	0.05 (0.05)	0.24	-0.11 (0.07)	0.15	0.16 (0.09)	0.06	0.02 (0.03)	0.54	0.08
rs2273669	G	0.03 (0.05)	0.55	0.11 (0.06)	0.06	-0.06 (0.11)	0.44	0.12 (0.13)	0.35	0.05 (0.03)	0.13	0.47
rs339331	T	-0.03 (0.04)	0.47	0.09 (0.05)	0.10	0.10 (0.09)	0.27	0.03 (0.10)	0.78	0.02 (0.03)	0.45	0.26
rs1933488	A	0.03 (0.03)	0.40	-0.08 (0.05)	0.06	-0.02 (0.07)	0.48	-0.13 (0.09)	0.15	-0.02 (0.02)	0.37	0.14
rs9364554	T	0.004 (0.03)	0.90	0.05 (0.05)	0.27	-0.01 (0.08)	0.50	-0.10 (0.10)	0.34	0.01 (0.03)	0.71	0.57
rs12155172	A	0.02 (0.05)	0.72	0.04 (0.05)	0.44	-0.01 (0.09)	0.50	-0.03 (0.11)	0.77	0.02 (0.03)	0.58	0.91
rs10486567	A	0.08 (0.04)	0.07	-0.06 (0.05)	0.28	0.10 (0.08)	0.21	-0.11 (0.11)	0.28	0.03 (0.03)	0.41	0.09
rs6465657	C	-0.02 (0.03)	0.54	-0.01 (0.04)	0.83	0.05 (0.07)	0.37	-0.10 (0.10)	0.32	-0.01 (0.02)	0.61	0.64

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs2928679	T	0.03 (0.03)	0.36	-0.01 (0.04)	0.74	-0.02 (0.06)	0.48	-0.02 (0.09)	0.85	0.007 (0.02)	0.75	0.81
rs1512268	A	0.01 (0.03)	0.82	-0.01 (0.04)	0.73	0.02 (0.07)	0.48	-0.02 (0.09)	0.77	0.0002 (0.02)	0.99	0.95
rs11135910	A	0.06 (0.04)	0.15	-0.07 (0.06)	0.28	-0.16 (0.09)	0.09	0.01 (0.12)	0.93	-0.004 (0.03)	0.89	0.09
rs12543663	C	0.04 (0.04)	0.31	-0.03 (0.05)	0.54	-0.05 (0.07)	0.39	0.10 (0.11)	0.33	0.01 (0.03)	0.68	0.45
rs10086908	T	-0.01 (0.04)	0.82	0.04 (0.05)	0.44	-0.20 (0.08)	0.01	-0.10 (0.10)	0.29	-0.03 (0.03)	0.33	0.04
rs16901979	A	0.15 (0.08)	0.07	-0.04 (0.10)	0.67	0.11 (0.15)	0.38	0.29 (0.21)	0.16	0.09 (0.06)	0.1	0.35
rs620861	C	0.05 (0.04)	0.17	-0.01 (0.05)	0.86	0.14 (0.07)	0.07	0.10 (0.09)	0.28	0.05 (0.03)	0.07	0.33
rs6983267	G	0.04 (0.03)	0.28	0.02 (0.04)	0.67	0.04 (0.07)	0.44	-0.01 (0.09)	0.89	0.03 (0.02)	0.24	0.96
rs1447295	A	0.07 (0.05)	0.15	0.11 (0.09)	0.21	-0.21 (0.11)	0.09	-0.11 (0.15)	0.45	0.04 (0.04)	0.36	0.08
rs817826	C	0.04 (0.05)	0.44	0.07 (0.06)	0.26	-0.08 (0.08)	0.28	-0.17 (0.14)	0.21	0.01 (0.04)	0.74	0.21
rs1571801	A	-0.03 (0.04)	0.53	-0.01 (0.05)	0.78	0.14 (0.07)	0.06	0.12 (0.09)	0.18	0.02 (0.03)	0.54	0.12
rs10993994	T	-0.05 (0.04)	0.19	0.02 (0.04)	0.72	-0.05 (0.07)	0.39	0.02 (0.09)	0.84	-0.02 (0.03)	0.38	0.66
rs3850699	A	-0.06 (0.04)	0.12	0.01 (0.05)	0.84	-0.05 (0.08)	0.41	0.09 (0.10)	0.34	-0.03 (0.03)	0.31	0.43
rs2252004	G	0.01 (0.05)	0.85	0.01 (0.07)	0.94	-0.07 (0.11)	0.40	-0.25 (0.15)	0.09	-0.02 (0.04)	0.63	0.39
rs4962416	C	-0.01 (0.04)	0.80	-0.07 (0.05)	0.15	0.14 (0.08)	0.09	-0.06 (0.11)	0.59	-0.01 (0.03)	0.63	0.13
rs7127900	A	0.01 (0.04)	0.81	-0.04 (0.05)	0.50	-0.03 (0.08)	0.48	-0.08 (0.11)	0.47	-0.01 (0.03)	0.63	0.83
rs1938781	C	-0.05 (0.04)	0.19	-0.03 (0.05)	0.53	0.07 (0.08)	0.37	-0.14 (0.11)	0.18	-0.04 (0.03)	0.17	0.46
rs7931342	G	-0.04 (0.03)	0.29	0.03 (0.04)	0.49	-0.05 (0.07)	0.40	-0.01 (0.09)	0.92	-0.02 (0.02)	0.54	0.64
rs11568818	A	-0.02 (0.03)	0.66	0.08 (0.04)	0.07	-0.05 (0.07)	0.40	0.10 (0.10)	0.29	0.02 (0.02)	0.46	0.21

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs10875943	C	-0.01 (0.04)	0.87	0.06 (0.05)	0.20	0.02 (0.07)	0.49	0.04 (0.10)	0.65	0.02 (0.03)	0.43	0.73
rs902774	A	-0.001 (0.05)	0.99	-0.01 (0.06)	0.94	0.02 (0.10)	0.49	0.03 (0.11)	0.75	0.004 (0.03)	0.91	0.99
rs1270884	A	0.01 (0.03)	0.72	0.01 (0.04)	0.90	-0.09 (0.07)	0.20	-0.07 (0.09)	0.39	-0.01 (0.02)	0.69	0.47
rs9600079	T	-0.02 (0.03)	0.51	-0.01 (0.04)	0.83	-0.04 (0.07)	0.44	0.02 (0.09)	0.78	-0.02 (0.03)	0.5	0.95
rs8008270	G	-0.001 (0.04)	0.99	-0.06 (0.06)	0.26	-0.05 (0.08)	0.42	0.12 (0.13)	0.32	-0.02 (0.03)	0.54	0.53
rs7141529	G	0.03 (0.03)	0.31	-0.03 (0.04)	0.55	0.06 (0.07)	0.34	-0.09 (0.09)	0.30	0.01 (0.02)	0.65	0.39
rs684232	G	0.02 (0.04)	0.65	-0.004 (0.05)	0.93	-0.16 (0.07)	0.04	-0.03 (0.09)	0.76	-0.02 (0.03)	0.53	0.17
rs11649743	G	-0.04 (0.04)	0.30	0.01 (0.06)	0.90	-0.11 (0.09)	0.22	-0.13 (0.11)	0.23	-0.04 (0.03)	0.15	0.57
rs4430796	A	0.002 (0.03)	0.95	-0.01 (0.05)	0.78	0.03 (0.07)	0.47	-0.01 (0.09)	0.94	0.0004 (0.02)	0.99	0.97
rs11650494	A	0.02 (0.06)	0.77	-0.02 (0.08)	0.78	-0.03 (0.11)	0.49	-0.14 (0.16)	0.36	-0.01 (0.04)	0.79	0.81
rs1859962	G	-0.002 (0.03)	0.94	0.03 (0.04)	0.57	-0.06 (0.07)	0.33	0.11 (0.09)	0.21	0.01 (0.02)	0.82	0.46
rs7241993	G	-0.04 (0.04)	0.30	-0.07 (0.05)	0.14	0.08 (0.10)	0.38	0.04 (0.12)	0.72	-0.04 (0.03)	0.18	0.53
rs8102476	C	0.01 (0.03)	0.68	-0.001 (0.05)	0.98	-0.02 (0.07)	0.49	0.03 (0.09)	0.77	0.01 (0.03)	0.78	0.97
rs11672691	A	-0.02 (0.04)	0.64	0.06 (0.05)	0.31	0.03 (0.08)	0.47	0.02 (0.10)	0.88	0.01 (0.03)	0.7	0.73
rs2735839	G	-0.06 (0.05)	0.20	-0.04 (0.06)	0.57	-0.03 (0.09)	0.48	-0.03 (0.14)	0.81	-0.05 (0.04)	0.16	0.98
rs103294	C	0.08 (0.04)	0.06	0.08 (0.05)	0.16	-0.13 (0.11)	0.24	-	-	0.06 (0.03)	0.05	0.18
rs2427345	G	0.03 (0.03)	0.39	0.01 (0.08)	0.93	0.03 (0.07)	0.46	-0.18 (0.09)	0.04	0.01 (0.03)	0.76	0.19
rs6062509	A	0.002 (0.03)	0.95	0.01 (0.05)	0.88	-0.05 (0.07)	0.39	-0.01 (0.10)	0.90	-0.003 (0.03)	0.89	0.92
rs5759167	G	-0.01 (0.03)	0.81	0.02 (0.05)	0.70	-0.07 (0.07)	029	0.20 (0.09)	0.03	0.01 (0.03)	0.82	0.13

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs2405942	A	-0.02 (0.03)	0.56	0.01 (0.04)	0.78	0.13 (0.06)	0.04	0.06 (0.08)	0.44	0.02 (0.02)	0.45	0.16
rs5945619	C	0.02 (0.02)	0.33	-0.001 (0.03)	0.98	-0.004 (0.05)	0.50	-0.04 (0.07)	0.53	0.01 (0.02)	0.63	0.78
rs5919432	A	-0.01 (0.03)	0.70	0.02 (0.04)	0.68	0.02 (0.06)	0.47	0.08 (0.08)	0.32	0.01 (0.02)	0.69	0.74

[1]data shown for rs115664826 (merged with rs130067)
[2]data shown for rs114376585 (merged with rs3096702) for RAPPER only

Supplementary Table 5: Individual SNP analysis results for decreased stream toxicity

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs1218582	G	-0.10 (0.29)	0.72	-0.01 (0.01)	0.25	-0.09 (0.24)	0.84	NA	NA	-0.01 (0.01)	0.24	0.90
rs4245739	A	-0.06 (0.33)	0.87	-0.01 (0.01)	0.31	-0.07 (0.25)	0.88	NA	NA	-0.01 (0.01)	0.30	0.96
rs11902236	A	-0.08 (0.31)	0.79	-0.01 (0.01)	0.29	0.19 (0.25)	0.83	NA	NA	-0.01 (0.01)	0.30	0.72
rs13385191	G	-0.56 (0.36)	0.12	-0.002 (0.01)	0.81	-0.24 (0.26)	0.35	NA	NA	-0.003 (0.01)	0.76	0.19
rs1465618	A	0.23 (0.30)	0.45	0.01 (0.01)	0.34	-0.12 (0.28)	0.31	NA	NA	0.01 (0.01)	0.34	0.69
rs721048	A	0.14 (0.34)	0.67	0.01 (0.01)	0.35	-0.72 (0.34)	0.67	NA	NA	0.01 (0.01)	0.37	0.10
rs10187424	A	0.05 (0.29)	0.85	-0.002 (0.01)	0.74	0.30 (0.26)	0.37	NA	NA	-0.002 (0.01)	0.77	0.48
rs12621278	A	1.29 (1.11)	0.25	0.01 (0.02)	0.44	-	-	NA	NA	0.01 (0.02)	0.43	0.25
rs2292884	G	0.05 (0.30)	0.86	-0.01 (0.01)	0.56	0.10 (0.26)	0.54	NA	NA	-0.01 (0.01)	0.58	0.90
rs3771570	A	-0.59 (0.44)	0.18	-0.01 (0.01)	0.48	0.23 (0.33)	0.71	NA	NA	-0.01 (0.01)	0.47	0.32
rs2660753	T	0.01 (0.46)	0.98	-0.01 (0.01)	0.49	0.08 (0.28)	0.15	NA	NA	-0.01 (0.01)	0.50	0.95
rs2055109	C	0.29 (0.28)	0.31	0.003 (0.01)	0.69	0.22 (0.25)	0.55	NA	NA	0.004 (0.01)	0.65	0.41
rs7611694	A	0.02 (0.28)	0.94	-0.01 (0.01)	0.34	-0.21 (0.24)	0.70	NA	NA	-0.01 (0.01)	0.33	0.69
rs10934853	A	-0.10 (0.31)	0.74	-0.01 (0.01)	0.12	-0.25 (0.26)	0.52	NA	NA	-0.01 (0.01)	0.11	0.65
rs6763931	T	-0.01 (0.28)	0.96	0.002 (0.01)	0.83	-0.17 (0.23)	0.55	NA	NA	0.002 (0.01)	0.85	0.74
rs10936632	A	0.38 (0.28)	0.17	-0.01 (0.01)	0.12	-0.39 (0.24)	0.82	NA	NA	-0.01 (0.01)	0.12	0.10
rs1894292	G	-0.34 (0.29)	0.24	0.003 (0.01)	0.72	0.18 (0.23)	0.71	NA	NA	0.003 (0.01)	0.72	0.37
rs12500426	A	-0.23 (0.29)	0.42	0.01 (0.01)	0.20	0.44 (0.25)	0.08	NA	NA	0.01 (0.01)	0.18	0.15
rs17021918	C	0.0003 (0.29)	1.00	0.01 (0.01)	0.35	0.10 (0.24)	0.52	NA	NA	0.01 (0.01)	0.35	0.93
rs7679673	C	-0.26 (0.28)	0.35	-0.01 (0.01)	0.47	-0.09 (0.22)	0.17	NA	NA	-0.01 (0.01)	0.45	0.61
rs2242652	G	-0.37 (0.35)	0.29	-0.02 (0.02)	0.21	-0.11 (0.37)	0.05	NA	NA	-0.02 (0.02)	0.19	0.59
rs12653946	T	-0.02 (0.27)	0.95	0.003 (0.01)	0.79	-0.11 (0.25)	0.11	NA	NA	0.002 (0.01)	0.81	0.90
rs2121875	G	0.05 (0.29)	0.87	0.002 (0.01)	0.77	0.01 (0.24)	0.04	NA	NA	0.002 (0.01)	0.76	0.99

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs6869841	A	-0.79 (0.42)	0.06	0.016 (0.01)	0.07	0.14 (0.27)	0.49	NA	NA	0.02 (0.01)	0.07	0.14
rs130067[1]	G	0.32 (0.32)	0.32	0.01 (0.01)	0.18	-	-	NA	NA	0.01 (0.01)	0.17	0.34
rs3096702[2]	A	-0.15 (0.30)	0.60	-0.001 (0.01)	0.91	-	-	NA	NA	-0.001 (0.01)	0.92	0.62
rs1983891	T	0.03 (0.30)	0.91	0.01 (0.01)	0.07	0.03 (0.25)	0.16	NA	NA	0.01 (0.01)	0.07	1.00
rs2273669	G	-0.01 (0.38)	0.99	0.02 (0.01)	0.02	-0.34 (0.42)	0.40	NA	NA	0.02 (0.01)	0.02	0.68
rs339331	T	-0.09 (0.30)	0.78	0.02 (0.01)	0.04	-0.20 (0.31)	0.09	NA	NA	0.02 (0.01)	0.04	0.74
rs1933488	A	0.22 (0.29)	0.45	-0.01 (0.01)	0.21	0.32 (0.24)	0.64	NA	NA	-0.01 (0.01)	0.23	0.27
rs9364554	T	0.35 (0.27)	0.19	0.01 (0.01)	0.52	0.08 (0.25)	0.35	NA	NA	0.01 (0.01)	0.49	0.42
rs12155172	A	0.11 (0.36)	0.76	-0.003 (0.01)	0.73	-0.05 (0.29)	0.09	NA	NA	-0.003 (0.01)	0.73	0.94
rs10486567	A	0.07 (0.37)	0.84	-0.02 (0.01)	0.08	0.67 (0.26)	0.50	NA	NA	-0.01 (0.01)	0.10	0.03
rs6465657	C	-0.13 (0.28)	0.64	0.001 (0.01)	0.93	0.18 (0.22)	0.42	NA	NA	0.001 (0.01)	0.92	0.65
rs2928679	T	0.11 (0.26)	0.67	0.002 (0.01)	0.76	-0.05 (0.22)	0.53	NA	NA	0.002 (0.01)	0.76	0.89
rs1512268	A	0.26 (0.28)	0.35	-0.004 (0.01)	0.60	0.003 (0.24)	0.42	NA	NA	-0.004 (0.01)	0.62	0.63
rs11135910	A	0.34 (0.34)	0.33	0.002 (0.01)	0.85	-0.08 (0.30)	0.38	NA	NA	0.002 (0.01)	0.84	0.60
rs12543663	C	0.18 (0.28)	0.52	-0.01 (0.01)	0.49	-0.37 (0.26)	0.86	NA	NA	-0.01 (0.01)	0.47	0.31
rs10086908	T	-0.31 (0.29)	0.29	0.01 (0.01)	0.07	0.02 (0.26)	0.07	NA	NA	0.01 (0.01)	0.08	0.54
rs16901979	A	0.87 (0.51)	0.09	0.01 (0.02)	0.63	0.13 (0.50)	0.69	NA	NA	0.01 (0.02)	0.59	0.24
rs620861	C	0.20 (0.30)	0.52	-0.001 (0.01)	0.88	0.29 (0.26)	0.57	NA	NA	-0.001 (0.01)	0.92	0.42
rs6983267	G	0.65 (0.30)	0.03	0.01 (0.01)	0.24	-0.08 (0.24)	0.69	NA	NA	0.01 (0.01)	0.22	0.09
rs1447295	A	0.36 (0.36)	0.31	0.01 (0.01)	0.74	-0.06 (0.41)	0.03	NA	NA	0.01 (0.01)	0.72	0.60
rs817826	C	0.58 (0.39)	0.14	0.01 (0.01)	0.60	0.01 (0.27)	0.42	NA	NA	0.01 (0.01)	0.58	0.34
rs1571801	A	-0.59 (0.38)	0.12	0.01 (0.01)	0.52	0.26 (0.24)	0.52	NA	NA	0.01 (0.01)	0.52	0.16
rs10993994	T	0.17 (0.31)	0.58	0.00004 (0.01)	0.99	-0.46 (0.23)	0.35	NA	NA	-0.0004 (0.01)	0.95	0.11
rs3850699	A	-0.15 (0.30)	0.62	0.01 (0.01)	0.15	0.01 (0.27)	0.52	NA	NA	0.01 (0.01)	0.15	0.86
rs2252004	G	0.29 (0.52)	0.58	0.001 (0.01)	0.97	-0.18 (0.37)	0.06	NA	NA	0.001 (0.01)	0.97	0.77

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs4962416	C	-0.09 (0.31)	0.77	0.01 (0.01)	0.46	0.47 (0.26)	0.63	NA	NA	0.01 (0.01)	0.43	0.18
rs7127900	A	-0.06 (0.34)	0.85	0.001 (0.01)	0.94	-0.29 (0.28)	0.95	NA	NA	0.0003 (0.01)	0.97	0.58
rs1938781	C	0.26 (0.31)	0.40	-0.02 (0.01)	0.06	-0.14 (0.29)	0.77	NA	NA	-0.02 (0.01)	0.06	0.62
rs7931342	G	-0.14 (0.29)	0.61	0.004 (0.01)	0.57	-0.09 (0.24)	0.76	NA	NA	0.004 (0.01)	0.59	0.81
rs11568818	A	-0.48 (0.29)	0.10	0.01 (0.01)	0.13	-0.01 (0.24)	0.39	NA	NA	0.01 (0.01)	0.14	0.23
rs10875943	C	-0.23 (0.32)	0.48	0.01 (0.01)	0.31	0.23 (0.24)	0.28	NA	NA	0.01 (0.01)	0.30	0.50
rs902774	A	0.25 (0.36)	0.48	-0.01 (0.01)	0.52	-0.13 (0.33)	0.22	NA	NA	-0.01 (0.01)	0.53	0.72
rs1270884	A	0.15 (0.29)	0.59	0.0004 (0.01)	1.00	-0.01 (0.24)	0.40	NA	NA	0.0001 (0.01)	0.99	0.87
rs9600079	T	-0.36 (0.30)	0.23	-0.002 (0.01)	0.76	-0.41 (0.26)	0.71	NA	NA	-0.003 (0.01)	0.70	0.13
rs8008270	G	-0.05 (0.37)	0.90	-0.004 (0.01)	0.66	-0.22 (0.29)	0.79	NA	NA	-0.004 (0.01)	0.64	0.75
rs7141529	G	0.58 (0.29)	0.05	0.01 (0.01)	0.40	-0.27 (0.24)	0.61	NA	NA	0.01 (0.01)	0.39	0.07
rs684232	G	0.19 (0.30)	0.52	0.01 (0.01)	0.23	-0.37 (0.25)	0.67	NA	NA	0.01 (0.01)	0.24	0.27
rs11649743	G	0.10 (0.36)	0.79	-0.01 (0.01)	0.56	-0.26 (0.30)	0.37	NA	NA	-0.01 (0.01)	0.55	0.66
rs4430796	A	-0.08 (0.27)	0.78	0.002 (0.01)	0.79	0.21 (0.24)	0.45	NA	NA	0.002 (0.01)	0.78	0.67
rs11650494	A	-0.41 (0.53)	0.44	-0.01 (0.01)	0.60	-0.29 (0.41)	0.39	NA	NA	-0.01 (0.01)	0.57	0.59
rs1859962	G	0.17 (0.27)	0.54	-0.01 (0.01)	0.36	-0.06 (0.22)	0.60	NA	NA	-0.01 (0.01)	0.36	0.79
rs7241993	G	0.03 (0.31)	0.92	-0.01 (0.01)	0.18	0.27 (0.35)	0.47	NA	NA	-0.01 (0.01)	0.18	0.73
rs8102476	C	0.14 (0.28)	0.61	-0.001 (0.01)	0.89	-0.05 (0.25)	0.30	NA	NA	-0.001 (0.01)	0.89	0.86
rs11672691	A	0.13 (0.32)	0.68	0.01 (0.01)	0.56	-0.04 (0.27)	0.77	NA	NA	0.01 (0.01)	0.55	0.91
rs2735839	G	0.01 (0.41)	0.99	0.01 (0.01)	0.56	-0.28 (0.29)	0.22	NA	NA	0.01 (0.01)	0.58	0.63
rs103294	C	0.55 (0.40)	0.17	0.01 (0.01)	0.29	-0.19 (0.35)	0.71	NA	NA	0.01 (0.01)	0.29	0.34
rs2427345	G	0.11 (0.28)	0.71	-0.01 (0.01)	0.39	0.29 (0.25)	0.35	NA	NA	-0.01 (0.01)	0.43	0.43
rs6062509	A	-0.03 (0.29)	0.92	0.01 (0.01)	0.13	-0.25 (0.25)	0.00	NA	NA	0.01 (0.01)	0.14	0.57
rs5759167	G	-0.27 (0.28)	0.34	-0.01 (0.01)	0.26	0.32 (0.25)	0.55	NA	NA	-0.01 (0.01)	0.26	0.28
rs2405942	A	-0.34 (0.22)	0.12	-0.01 (0.01)	0.36	0.11 (0.21)	0.02	NA	NA	-0.01 (0.01)	0.34	0.27

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs5945619	C	-0.01 (0.20)	0.96	0.001 (0.01)	0.78	0.25 (0.16)	0.73	NA	NA	0.002 (0.01)	0.75	0.32
rs5919432	A	-0.27 (0.24)	0.26	0.001 (0.01)	0.83	0.44 (0.23)	0.43	NA	NA	0.002 (0.01)	0.81	0.08

[1]data shown for rs115664826 (merged with rs130067)
[2]data shown for rs114376585 (merged with rs3096702) for RAPPER only

Supplementary Table 6: Individual SNP analysis results for urine frequency endpoint

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs1218582	G	-0.17 (0.24)	0.48	-0.01 (0.02)	0.67	-0.05 (0.24)	0.84	-0.32 (0.30)	0.28	-0.01 (0.02)	0.56	0.68
rs4245739	A	0.19 (0.29)	0.52	-0.05 (0.02)	0.03	0.04 (0.25)	0.88	-0.33 (0.35)	0.35	-0.04 (0.02)	0.03	0.70
rs11902236	A	-0.03 (0.26)	0.92	-0.001 (0.02)	0.97	0.06 (0.26)	0.83	-0.44 (0.37)	0.22	-0.002 (0.02)	0.92	0.69
rs13385191	G	-0.12 (0.27)	0.67	-0.01 (0.02)	0.82	0.22 (0.24)	0.35	0.39 (0.35)	0.28	-0.002 (0.02)	0.92	0.51
rs1465618	A	-0.19 (0.28)	0.49	-0.01 (0.02)	0.83	0.27 (0.27)	0.31	-0.45 (0.33)	0.18	-0.01 (0.02)	0.78	0.35
rs721048	A	-0.05 (0.29)	0.88	0.04 (0.02)	0.07	-0.13 (0.30)	0.67	-0.03 (0.44)	0.94	0.04 (0.02)	0.08	0.93
rs10187424	A	0.21 (0.24)	0.38	-0.02 (0.02)	0.23	-0.23 (0.25)	0.37	-0.48 (0.33)	0.14	-0.03 (0.02)	0.20	0.32
rs12621278	A	-0.19 (0.51)	0.70	0.01 (0.05)	0.91	-	-	-	-	0.004 (0.05)	0.94	0.70
rs2292884	G	0.49 (0.27)	0.07	-0.05 (0.02)	0.05	-0.16 (0.26)	0.54	0.25 (0.36)	0.49	-0.04 (0.02)	0.07	0.18
rs3771570	A	-0.07 (0.33)	0.84	-0.02 (0.03)	0.59	-0.13 (0.33)	0.71	0.66 (0.42)	0.12	-0.01 (0.03)	0.63	0.44
rs2660753	T	0.23 (0.38)	0.55	0.03 (0.03)	0.30	-0.42 (0.29)	0.15	0.48 (0.46)	0.31	0.03 (0.03)	0.32	0.32
rs2055109	C	0.05 (0.26)	0.86	0.01 (0.02)	0.67	0.15 (0.26)	0.55	-0.47 (0.43)	0.27	0.01 (0.02)	0.66	0.67
rs7611694	A	0.28 (0.25)	0.27	0.03 (0.02)	0.22	-0.09 (0.24)	0.70	-0.16 (0.30)	0.59	0.03 (0.02)	0.21	0.66
rs10934853	A	-0.07 (0.27)	0.81	0.04 (0.02)	0.12	0.16 (0.26)	0.52	-0.17 (0.31)	0.59	0.04 (0.02)	0.12	0.85
rs6763931	T	0.25 (0.24)	0.31	0.003 (0.02)	0.87	-0.14 (0.23)	0.55	-0.14 (0.33)	0.68	0.003 (0.02)	0.87	0.67
rs10936632	A	0.18 (0.23)	0.43	0.004 (0.02)	0.82	0.05 (0.23)	0.82	0.16 (0.31)	0.61	0.01 (0.02)	0.72	0.84
rs1894292	G	-0.45 (0.25)	0.07	0.01 (0.02)	0.65	0.09 (0.23)	0.71	-0.34 (0.31)	0.27	0.01 (0.02)	0.80	0.19
rs12500426	A	0.06 (0.25)	0.80	0.01 (0.02)	0.55	0.43 (0.25)	0.08	0.06 (0.30)	0.84	0.02 (0.02)	0.44	0.42
rs17021918	C	-0.11 (0.24)	0.65	-0.02 (0.02)	0.46	0.15 (0.23)	0.52	-0.49 (0.33)	0.15	-0.02 (0.02)	0.42	0.46
rs7679673	C	-0.20 (0.24)	0.42	0.01 (0.02)	0.77	-0.31 (0.22)	0.17	0.05 (0.33)	0.89	0.002 (0.02)	0.92	0.45
rs2242652	G	-0.63 (0.30)	0.04	0.01 (0.04)	0.88	0.78 (0.41)	0.05	-0.06 (0.51)	0.91	0.001 (0.04)	0.97	0.05
rs12653946	T	-0.05 (0.23)	0.82	0.01 (0.03)	0.86	-0.40 (0.25)	0.11	-0.54 (0.33)	0.09	-0.004 (0.03)	0.89	0.15
rs2121875	G	0.19 (0.24)	0.42	-0.01 (0.02)	0.70	-0.51 (0.25)	0.04	1.06 (0.39)	0.00	-0.01 (0.02)	0.74	0.01

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs6869841	A	-0.40 (0.31)	0.20	-0.01 (0.02)	0.77	-0.19 (0.28)	0.49	-1.23 (0.51)	0.01	-0.01 (0.03)	0.57	0.05
rs130067[1]	G	-0.80 (0.36)	0.03	0.01 (0.03)	0.81	-	-	-	-	0.002 (0.03)	0.94	0.02
rs3096702[2]	A	-0.17 (0.25)	0.48	-0.01 (0.02)	0.846	-	-	-	-	-0.01 (0.02)	0.62	0.52
rs1983891	T	-0.15 (0.26)	0.56	0.02 (0.02)	0.38	-0.35 (0.25)	0.16	0.36 (0.29)	0.23	0.02 (0.02)	0.43	0.27
rs2273669	G	0.14 (0.32)	0.66	0.04 (0.03)	0.15	-0.35 (0.42)	0.40	-0.72 (0.52)	0.14	0.04 (0.03)	0.18	0.38
rs339331	T	0.07 (0.27)	0.80	0.02 (0.02)	0.54	-0.52 (0.31)	0.09	0.62 (0.36)	0.07	0.02 (0.02)	0.54	0.11
rs1933488	A	0.34 (0.25)	0.17	-0.02 (0.02)	0.46	0.11 (0.23)	0.64	-0.40 (0.31)	0.19	-0.01 (0.02)	0.51	0.27
rs9364554	T	0.16 (0.24)	0.49	0.01 (0.02)	0.52	-0.25 (0.26)	0.35	0.13 (0.35)	0.72	0.01 (0.02)	0.52	0.69
rs12155172	A	-0.16 (0.33)	0.63	0.03 (0.02)	0.28	-0.49 (0.30)	0.09	0.17 (0.36)	0.65	0.02 (0.02)	0.35	0.33
rs10486567	A	0.62 (0.29)	0.03	-0.07 (0.02)	0.01	0.18 (0.26)	0.50	0.31 (0.34)	0.37	-0.06 (0.02)	0.02	0.06
rs6465657	C	-0.15 (0.24)	0.53	0.001 (0.02)	0.96	0.18 (0.23)	0.42	-0.60 (0.35)	0.08	-0.001 (0.02)	0.97	0.25
rs2928679	T	0.19 (0.22)	0.39	-0.02 (0.02)	0.24	0.14 (0.22)	0.53	-0.002 (0.30)	1.00	-0.02 (0.02)	0.31	0.70
rs1512268	A	-0.47 (0.25)	0.06	-0.02 (0.02)	0.42	0.19 (0.24)	0.42	0.44 (0.31)	0.15	-0.02 (0.02)	0.43	0.11
rs11135910	A	0.27 (0.29)	0.35	0.001 (0.03)	0.96	-0.28 (0.32)	0.38	0.10 (0.40)	0.82	0.002 (0.03)	0.94	0.64
rs12543663	C	0.32 (0.24)	0.18	0.01 (0.02)	0.63	0.04 (0.25)	0.86	0.05 (0.37)	0.89	0.01 (0.02)	0.53	0.65
rs10086908	T	-0.25 (0.25)	0.32	-0.04 (0.02)	0.08	-0.46 (0.26)	0.07	-0.35 (0.33)	0.29	-0.05 (0.02)	0.04	0.24
rs16901979	A	0.12 (0.53)	0.82	-0.03 (0.04)	0.51	0.20 (0.50)	0.69	0.96 (0.63)	0.14	-0.02 (0.04)	0.62	0.43
rs620861	C	0.02 (0.26)	0.93	0.02 (0.02)	0.36	0.14 (0.25)	0.57	-0.03 (0.33)	0.92	0.02 (0.02)	0.34	0.97
rs6983267	G	0.34 (0.24)	0.16	-0.004 (0.02)	0.85	0.09 (0.24)	0.69	-0.13(0.31)	0.66	-0.001 (0.02)	0.95	0.51
rs1447295	A	0.18 (0.32)	0.58	0.03 (0.04)	0.47	-0.96 (0.46)	0.03	0.17 (0.51)	0.74	0.03 (0.04)	0.53	0.19
rs817826	C	-0.35 (0.40)	0.38	-0.003 (0.03)	0.91	-0.21 (0.26)	0.42	-0.30 (0.52)	0.55	-0.01 (0.03)	0.77	0.65
rs1571801	A	0.15 (0.28)	0.60	-0.03 (0.02)	0.23	0.16 (0.25)	0.52	0.39 (0.30)	0.19	-0.02 (0.02)	0.33	0.41
rs10993994	T	-0.03 (0.27)	0.92	0.02 (0.02)	0.46	-0.21 (0.23)	0.35	0.02 (0.31)	0.95	0.01 (0.02)	0.51	0.80
rs3850699	A	-0.10 (0.25)	0.68	0.001 (0.02)	0.98	0.17 (0.27)	0.52	-0.02 (0.34)	0.95	0.001 (0.02)	0.97	0.90

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs2252004	G	0.27 (0.45)	0.55	0.02 (0.03)	0.48	-0.70 (0.38)	0.06	-0.29 (0.57)	0.59	0.02 (0.03)	0.58	0.23
rs4962416	C	-0.86 (0.31)	0.01	-0.04 (0.02)	0.05	0.13 (0.26)	0.63	0.21 (0.37)	0.58	-0.04 (0.02)	0.04	0.06
rs7127900	A	-0.16 (0.29)	0.58	-0.01 (0.03)	0.77	-0.02 (0.27)	0.95	-0.17 (0.41)	0.68	-0.01 (0.03)	0.71	0.93
rs1938781	C	-0.01 (0.29)	0.97	0.0002 (0.02)	0.99	0.08 (0.28)	0.77	-0.45 (0.40)	0.25	-0.001 (0.02)	0.97	0.72
rs7931342	G	-0.05 (0.24)	0.85	-0.01 (0.02)	0.48	0.08 (0.24)	0.76	-0.19 (0.32)	0.56	-0.01 (0.02)	0.47	0.93
rs11568818	A	-0.14 (0.25)	0.57	-0.002 (0.02)	0.92	-0.21 (0.24)	0.39	0.03 (0.34)	0.92	-0.004 (0.02)	0.84	0.79
rs10875943	C	0.17 (0.26)	0.50	-0.01 (0.02)	0.70	-0.27 (0.25)	0.28	0.53 (0.33)	0.10	-0.01 (0.02)	0.76	0.23
rs902774	A	-0.27 (0.36)	0.46	-0.001 (0.03)	0.97	0.40 (0.32)	0.22	-0.21 (0.42)	0.62	-0.001 (0.03)	0.99	0.51
rs1270884	A	0.42 (0.25)	0.09	0.02 (0.02)	0.28	-0.20 (0.24)	0.40	-0.21 (0.30)	0.47	0.02 (0.02)	0.27	0.25
rs9600079	T	-0.09 (0.25)	0.72	-0.01 (0.02)	0.63	-0.09 (0.25)	0.71	-0.57 (0.32)	0.07	-0.01 (0.02)	0.52	0.36
rs8008270	G	-0.21 (0.30)	0.49	-0.02 (0.03)	0.37	-0.08 (0.29)	0.79	0.27 (0.44)	0.53	-0.02 (0.03)	0.35	0.84
rs7141529	G	0.17 (0.23)	0.46	0.002 (0.02)	0.94	0.12 (0.24)	0.61	-0.08 (0.30)	0.80	0.003 (0.02)	0.87	0.84
rs684232	G	0.09 (0.25)	0.71	-0.03 (0.02)	0.19	-0.10 (0.24)	0.67	-0.08 (0.31)	0.80	-0.03 (0.02)	0.19	0.95
rs11649743	G	-0.08 (0.31)	0.81	0.04 (0.03)	0.11	0.30 (0.33)	0.37	-0.30 (0.36)	0.41	0.04 (0.03)	0.11	0.65
rs4430796	A	0.33 (0.24)	0.16	-0.05 (0.02)	0.03	0.18 (0.24)	0.45	0.29 (0.31)	0.34	-0.04 (0.02)	0.06	0.20
rs11650494	A	-0.10 (0.40)	0.80	0.01 (0.04)	0.80	-0.35 (0.42)	0.39	-0.43 (0.56)	0.42	0.004 (0.04)	0.92	0.70
rs1859962	G	0.14 (0.24)	0.56	0.02 (0.02)	0.30	-0.12 (0.22)	0.60	0.14 (0.32)	0.67	0.02 (0.02)	0.30	0.86
rs7241993	G	-0.43 (0.25)	0.08	0.02 (0.02)	0.33	0.25 (0.35)	0.47	0.02 (0.41)	0.97	0.02 (0.02)	0.39	0.29
rs8102476	C	0.30 (0.25)	0.23	-0.01 (0.02)	0.79	-0.25 (0.25)	0.30	0.29 (0.32)	0.36	-0.004 (0.02)	0.85	0.34
rs11672691	A	-0.14 (0.29)	0.65	-0.02 (0.02)	0.48	0.08 (0.27)	0.77	-0.08 (0.35)	0.82	-0.02 (0.03)	0.46	0.96
rs2735839	G	0.16 (0.40)	0.69	0.004 (0.03)	0.89	-0.38 (0.30)	0.22	0.92 (0.53)	0.06	0.004 (0.03)	0.89	0.19
rs103294	C	-0.21 (0.27)	0.45	0.02 (0.03)	0.53	-0.13 (0.36)	0.71	-	-	0.01 (0.03)	0.60	0.66
rs2427345	G	0.15 (0.25)	0.55	0.01 (0.04)	0.80	0.23 (0.24)	0.35	-0.36 (0.31)	0.23	0.01 (0.03)	0.74	0.46
rs6062509	A	-0.17 (0.24)	0.48	-0.01 (0.02)	0.73	-0.73 (0.26)	0.004	0.02 (0.34)	0.95	-0.01 (0.02)	0.52	0.04
rs5759167	G	-0.28 (0.24)	0.25	0.02 (0.02)	0.36	-0.15 (0.25)	0.55	0.48 (0.33)	0.14	0.02 (0.02)	0.40	0.26

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs2405942	A	-0.05 (0.22)	0.83	-0.01 (0.02)	0.53	0.50 (0.23)	0.02	-0.13 (0.25)	0.60	-0.01 (0.02)	0.61	0.17
rs5945619	C	0.05 (0.17)	0.77	0.01 (0.01)	0.50	-0.06 (0.16)	0.73	-0.10 (0.25)	0.69	0.01 (0.01)	0.53	0.94
rs5919432	A	-0.06 (0.23)	0.78	0.01 (0.02)	0.58	0.16 (0.20)	0.43	0.29 (0.31)	0.33	0.01 (0.02)	0.52	0.70

[1]data shown for rs115664826 (merged with rs130067)
[2]data shown for rs114376585 (merged with rs3096702) for RAPPER only

Supplementary Table 7: Individual SNP analysis results for rectal bleeding toxicity

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs1218582	G	0.35 (0.18)	0.05	-0.01 (0.02)	0.56	-0.34 (0.23)	0.14	-0.53 (0.29)	0.06	-0.01 (0.02)	0.53	0.02
rs4245739	A	0.01 (0.21)	0.95	0.05 (0.02)	0.03	-0.21 (0.24)	0.38	0.07 (0.34)	0.83	0.04 (0.02)	0.04	0.76
rs11902236	A	0.34 (0.19)	0.08	-0.02 (0.02)	0.25	-0.08 (0.24)	0.73	0.27 (0.32)	0.40	-0.02 (0.02)	0.35	0.22
rs13385191	G	-0.07 (0.20)	0.71	-0.02 (0.02)	0.49	0.19 (0.23)	0.41	0.26 (0.32)	0.42	-0.01 (0.02)	0.55	0.66
rs1465618	A	-0.33 (0.22)	0.14	0.02 (0.02)	0.30	-0.28 (0.28)	0.30	0.79 (0.37)	0.02	0.02 (0.02)	0.35	0.05
rs721048	A	0.11 (0.21)	0.62	-0.03 (0.02)	0.22	-0.15 (0.29)	0.61	-0.52 (0.42)	0.20	-0.03 (0.02)	0.20	0.59
rs10187424	A	0.20 (0.19)	0.28	0.01 (0.02)	0.66	-0.07 (0.23)	0.76	0.03 (0.29)	0.92	0.01 (0.02)	0.60	0.76
rs12621278	A	0.06 (0.46)	0.90	0.11 (0.05)	0.03	-	-	-	-	0.11 (0.05)	0.03	0.91
rs2292884	G	-0.26 (0.20)	0.20	0.02 (0.02)	0.30	0.47 (0.25)	0.06	-0.23 (0.34)	0.50	0.02 (0.02)	0.31	0.12
rs3771570	A	-0.18 (0.24)	0.46	0.01 (0.03)	0.58	-0.12 (0.33)	0.71	0.34 (0.39)	0.39	0.01 (0.03)	0.63	0.69
rs2660753	T	0.30 (0.27)	0.25	0.02 (0.03)	0.52	0.27 (0.26)	0.31	-0.43 (0.50)	0.38	0.02 (0.03)	0.42	0.41
rs2055109	C	0.06 (0.19)	0.75	-0.02 (0.02)	0.36	0.09 (0.24)	0.71	-0.04 (0.36)	0.91	-0.02 (0.02)	0.40	0.95
rs7611694	A	-0.03 (0.18)	0.86	0.01 (0.02)	0.47	-0.09 (0.22)	0.70	0.80 (0.31)	0.01	0.02 (0.02)	0.41	0.09
rs10934853	A	0.20 (0.19)	0.30	0.03 (0.02)	0.14	0.41 (0.24)	0.09	-0.28 (0.29)	0.33	0.04 (0.02)	0.10	0.23
rs6763931	T	0.24 (0.18)	0.18	-0.02 (0.02)	0.25	-0.18 (0.22)	0.41	-0.35 (0.31)	0.26	-0.02 (0.02)	0.26	0.29
rs10936632	A	0.04 (0.17)	0.83	-0.006 (0.02)	0.78	0.09 (0.22)	0.68	0.06 (0.28)	0.84	-0.004 (0.02)	0.84	0.96
rs1894292	G	-0.05 (0.19)	0.79	-0.02 (0.02)	0.32	-0.12 (0.22)	0.58	0.01 (0.28)	0.98	-0.02(0.02)	0.29	0.97
rs12500426	A	0.06 (0.19)	0.77	-0.03 (0.02)	0.09	-0.03 (0.23)	0.89	-0.43 (0.28)	0.12	-0.03 (0.02)	0.08	0.52
rs17021918	C	-0.19 (0.18)	0.28	-0.004 (0.02)	0.84	-0.35 (0.23)	0.12	-0.22 (0.31)	0.47	-0.01 (0.02)	0.61	0.27
rs7679673	C	0.13 (0.19)	0.49	0.01 (0.02)	0.52	0.23 (0.21)	0.27	0.14 (0.31)	0.66	0.02 (0.02)	0.40	0.66
rs2242652	G	0.17 (0.25)	0.49	0.06 (0.04)	0.13	-0.70 (0.34)	0.04	0.33 (0.48)	0.48	0.06 (0.04)	0.16	0.14
rs12653946	T	0.07 (0.17)	0.68	-0.02 (0.03)	0.42	-0.15 (0.23)	0.51	-0.18 (0.29)	0.52	-0.02 (0.03)	0.39	0.82
rs2121875	G	-0.13 (0.19)	0.49	-0.003 (0.02)	0.90	0.21 (0.23)	0.36	-0.31 (0.28)	0.26	-0.004 (0.02)	0.84	0.46

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs6869841	A	0.01 (0.21)	0.96	-0.01 (0.02)	0.58	-0.17 (0.27)	0.53	0.14 (0.36)	0.69	-0.01 (0.02)	0.57	0.91
rs130067[1]	G	-0.08 (0.22)	0.71	-0.01 (0.03)	0.76	-	-	-	-	-0.01 (0.03)	0.73	0.74
rs3096702[2]	A	0.02 (0.19)	0.93	0.003 (0.02)	0.90	-	-	-	-	0.003 (0.02)	0.88	0.93
rs1983891	T	-0.05 (0.20)	0.82	-0.04 (0.02)	0.03	-0.34 (0.25)	0.15	0.35 (0.27)	0.18	-0.04 (0.02)	0.03	0.29
rs2273669	G	0.13 (0.24)	0.57	-0.01 (0.03)	0.77	0.77 (0.34)	0.02	0.19 (0.41)	0.65	-0.001 (0.03)	0.99	0.12
rs339331	T	-0.19 (0.19)	0.32	0.004 (0.02)	0.86	0.20 (0.30)	0.52	-0.10 (0.29)	0.74	0.002 (0.02)	0.93	0.67
rs1933488	A	0.12 (0.18)	0.53	0.01 (0.02)	0.71	-0.06 (0.22)	0.77	-0.26 (0.28)	0.36	0.01 (0.02)	0.73	0.71
rs9364554	T	-0.03 (0.19)	0.88	-0.004 (0.02)	0.84	-0.02 (0.25)	0.93	-0.35 (0.32)	0.28	-0.01 (0.02)	0.77	0.77
rs12155172	A	-0.05 (0.24)	0.84	-0.03 (0.02)	0.25	0.11 (0.28)	0.70	0.09 (0.35)	0.81	-0.03 (0.02)	0.27	0.95
rs10486567	A	0.40 (0.22)	0.07	-0.04 (0.02)	0.14	-0.31 (0.26)	0.23	-0.42 (0.35)	0.22	-0.03 (0.02)	0.15	0.10
rs6465657	C	-0.05 (0.18)	0.77	-0.03 (0.02)	0.17	0.23 (0.21)	0.28	0.32 (0.31)	0.30	-0.02 (0.02)	0.22	0.44
rs2928679	T	0.06 (0.17)	0.73	-0.01 (0.02)	0.44	0.12 (0.21)	0.58	0.05 (0.28)	0.87	-0.01 (0.02)	0.51	0.90
rs1512268	A	0.09 (0.18)	0.63	0.01 (0.02)	0.67	0.31 (0.22)	0.16	0.01 (0.27)	0.97	0.01 (0.02)	0.56	0.58
rs11135910	A	0.14 (0.23)	0.52	-0.04 (0.03)	0.15	-0.03 (0.28)	0.92	-0.16 (0.37)	0.67	-0.04 (0.03)	0.17	0.86
rs12543663	C	-0.10 (0.19)	0.62	-0.01 (0.02)	0.60	-0.32 (0.25)	0.18	0.48 (0.36)	0.18	-0.01 (0.02)	0.54	0.30
rs10086908	T	0.25 (0.21)	0.24	0.03 (0.02)	0.23	-0.61 (0.25)	0.01	-0.12 (0.30)	0.69	0.02 (0.02)	0.28	0.05
rs16901979	A	0.64 (0.37)	0.08	0.03 (0.04)	0.47	0.02 (0.49)	0.97	0.67 (0.63)	0.30	0.04 (0.04)	0.33	0.30
rs620861	C	0.01 (0.19)	0.96	-0.02 (0.02)	0.38	0.29 (0.24)	0.23	0.27 (0.28)	0.34	-0.01 (0.02)	0.49	0.45
rs6983267	G	-0.01 (0.17)	0.95	0.01 (0.02)	0.76	-0.01 (0.22)	0.97	-0.02 (0.28)	0.94	0.01 (0.02)	0.78	0.99
rs1447295	A	0.29 (0.23)	0.22	0.04 (0.04)	0.30	-0.36 (0.42)	0.38	-0.65 (0.54)	0.20	0.04 (0.04)	0.29	0.30
rs817826	C	-0.002 (0.29)	0.99	0.03 (0.03)	0.28	0.02 (0.25)	0.93	-0.73 (0.52)	0.13	0.03 (0.03)	0.31	0.54
rs1571801	A	-0.20 (0.23)	0.37	-0.03 (0.02)	0.20	0.09 (0.24)	0.71	0.23 (0.28)	0.41	-0.03 (0.02)	0.21	0.64
rs10993994	T	-0.29 (0.2)	0.15	-0.01 (0.02)	0.72	0.32 (0.22)	0.15	-0.01 (0.28)	0.98	-0.01 (0.02)	0.71	0.25
rs3850699	A	-0.32 (0.19)	0.08	-0.01 (0.02)	0.84	-0.12 (0.25)	0.62	0.05 (0.32)	0.88	-0.01 (0.02)	0.66	0.38
rs2252004	G	0.11 (0.29)	0.71	-0.02 (0.03)	0.48	-0.41 (0.34)	0.23	-0.99 (0.64)	0.08	-0.03 (0.03)	0.39	0.29

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs4962416	C	0.30 (0.19)	0.11	-0.002 (0.02)	0.92	0.19 (0.25)	0.44	-0.13 (0.34)	0.71	0.002 (0.02)	0.90	0.35
rs7127900	A	0.35 (0.20)	0.09	-0.02 (0.02)	0.39	0.12 (0.26)	0.64	0.11 (0.34)	0.74	-0.01 (0.02)	0.56	0.30
rs1938781	C	-0.23 (0.22)	0.31	-0.01 (0.02)	0.61	-0.12 (0.28)	0.67	-0.09 (0.34)	0.79	-0.02 (0.02)	0.50	0.77
rs7931342	G	-0.21 (0.18)	0.26	0.02 (0.02)	0.25	0.12 (0.23)	0.59	0.05 (0.30)	0.86	0.02 (0.02)	0.28	0.62
rs11568818	A	0.23 (0.19)	0.22	0.04 (0.02)	0.03	-0.23 (0.24)	0.34	-0.12 (0.31)	0.69	0.04 (0.02)	0.03	0.46
rs10875943	C	0.37 (0.19)	0.06	0.04 (0.02)	0.06	0.32 (0.23)	0.16	-0.41 (0.32)	0.19	0.04 (0.02)	0.03	0.10
rs902774	A	0.15 (0.24)	0.52	0.004 (0.03)	0.88	0.35 (0.29)	0.24	0.30 (0.33)	0.37	0.01 (0.03)	0.68	0.48
rs1270884	A	-0.05 (0.19)	0.80	-0.02 (0.02)	0.29	-0.32 (0.23)	0.16	-0.16 (0.28)	0.58	-0.02 (0.02)	0.22	0.58
rs9600079	T	-0.04 (0.18)	0.83	-0.02 (0.02)	0.44	0.06 (0.23)	0.81	0.73 (0.30)	0.01	-0.01 (0.02)	0.54	0.11
rs8008270	G	-0.07 (0.23)	0.76	0.01 (0.03)	0.68	-0.11 (0.27)	0.69	-0.09 (0.38)	0.81	0.01 (0.03)	0.74	0.94
rs7141529	G	0.20 (0.18)	0.26	0.01 (0.02)	0.70	-0.18 (0.22)	0.41	-0.31 (0.29)	0.27	0.01 (0.02)	0.72	0.36
rs684232	G	-0.03 (0.19)	0.86	-0.01 (0.02)	0.80	-0.14 (0.23)	0.54	0.10 (0.28)	0.72	-0.01 (0.02)	0.76	0.92
rs11649743	G	-0.04 (0.22)	0.87	-0.01 (0.02)	0.82	0.06 (0.29)	0.83	0.05 (0.34)	0.89	-0.01 (0.02)	0.83	0.99
rs4430796	A	-0.10 (0.17)	0.56	0.02 (0.02)	0.30	-0.21 (0.23)	0.37	0.07 (0.28)	0.81	0.02 (0.02)	0.38	0.69
rs11650494	A	0.19 (0.28)	0.49	0.01 (0.04)	0.84	0.34 (0.34)	0.32	-0.32 (0.52)	0.52	0.01 (0.04)	0.73	0.62
rs1859962	G	-0.08 (0.17)	0.66	0.02 (0.02)	0.35	-0.03 (0.22)	0.88	0.06 (0.29)	0.84	0.02 (0.02)	0.38	0.95
rs7241993	G	0.04 (0.20)	0.85	-0.04 (0.02)	0.10	0.19 (0.34)	0.58	0.06 (0.37)	0.88	-0.03 (0.02)	0.12	0.89
rs8102476	C	0.09 (0.18)	0.63	-0.01 (0.02)	0.55	0.03 (0.24)	0.88	0.02 (0.29)	0.96	-0.01 (0.02)	0.61	0.95
rs11672691	A	-0.26 (0.22)	0.24	0.04 (0.02)	0.10	0.20 (0.25)	0.43	-0.07 (0.31)	0.82	0.04 (0.02)	0.12	0.50
rs2735839	G	-0.27 (0.24)	0.26	-0.06 (0.03)	0.02	0.33 (0.31)	0.28	-0.33 (0.41)	0.43	-0.06 (0.03)	0.02	0.43
rs103294	C	0.27 (0.23)	0.25	-0.01 (0.02)	0.64	0.40 (0.39)	0.29	-	-	-0.01 (0.02)	0.77	0.28
rs2427345	G	0.17 (0.18)	0.35	-0.04 (0.03)	0.26	-0.44 (0.23)	0.06	-0.39 (0.29)	0.16	-0.04 (0.03)	0.18	0.12
rs6062509	A	0.04 (0.18)	0.84	0.01 (0.02)	0.80	-0.33 (0.24)	0.17	-0.16 (0.30)	0.59	0.002 (0.02)	0.91	0.51
rs5759167	G	-0.002 (0.18)	0.99	0.02 (0.02)	0.36	-0.11 (0.23)	0.64	0.18 (0.29)	0.53	0.02 (0.02)	0.37	0.89
rs2405942	A	0.07 (0.17)	0.70	0.002 (0.02)	0.91	-0.18 (0.18)	0.33	0.57 (0.28)	0.03	0.003 (0.02)	0.85	0.16

SNP	Effect Allele	RAPPER		RADIOGEN		GenePARE		CCI		Meta-analysis		
		Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	p-het[1]
rs5945619	C	0.12 (0.13)	0.35	-0.01 (0.01)	0.47	-0.07 (0.16)	0.67	-0.03 (0.22)	0.89	-0.01 (0.01)	0.50	0.77
rs5919432	A	0.06 (0.18)	0.74	0.01 (0.02)	0.46	0.02 (0.19)	0.91	0.30 (0.27)	0.26	0.01 (0.02)	0.39	0.76

[1]data shown for rs115664826 (merged with rs130067)
[2]data shown for rs114376585 (merged with rs3096702) for RAPPER only