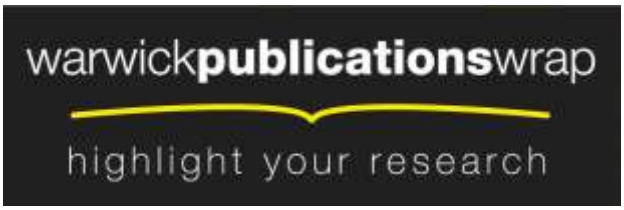

Common genetic variants associated with disease from genome-wide association studies are mutually exclusive in prostate cancer and rheumatoid arthritis

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What's known on the subject? and What does the study add?

- The link between inflammation and cancer has long been reported and inflammation is thought to play a role in the pathogenesis of many cancers, including prostate cancer (PrCa). Over the last 5 years, genome-wide association studies (GWAS) have reported numerous susceptibility loci that predispose individuals to many different traits.
- The present study aims to ascertain if there are common genetic risk profiles that might predispose individuals to both PrCa and the autoimmune inflammatory condition, rheumatoid arthritis. These results could have potential public heath impact in terms of screening and chemoprevention.

Objectives

- To investigate if potential common pathways exist for the pathogenesis of autoimmune disease and prostate cancer (PrCa).
- To ascertain if the single nucleotide polymorphisms (SNPs) reported by genome-wide association studies (GWAS) as being associated with susceptibility to PrCa are also associated with susceptibility to the autoimmune disease rheumatoid arthritis (RA).

Materials and Methods

- The original Wellcome Trust Case Control Consortium (WTCCC) UK RA GWAS study was expanded to include a total of 3221 cases and 5272 controls.
- In all, 37 germline autosomal SNPs at genome-wide significance associated with PrCa risk were identified from a UK/Australian PrCa GWAS.
- Allele frequencies were compared for these 37 SNPs between RA cases and controls using a chi-squared trend test and corrected for multiple testing (Bonferroni).

Results

- In all, 33 SNPs were able to be analysed in the RA dataset. Proxies could not be located for the SNPs in 3q26, 5p15 and for two SNPs in 17q12.
- After applying a Bonferroni correction for the number of SNPs tested, the SNP mapping to *CCHCR1* (rs130067) retained statistically significant evidence for association

  | 111, 1148–1155 | doi:10.1111/j.1464-410X.2012.11492.x

($P = 6 \times 10^{-4}$; odds ratio [OR] = 1.15, 95% CI: 1.06–1.24); this has also been associated with psoriasis.
- However, further analyses showed that the association of this allele was due to confounding by RA-associated *HLA-DRB1* alleles.

Conclusions

- There is currently no evidence that SNPs associated with PrCa at genome-wide significance are associated with the development of RA.
- Studies like this are important in determining if common genetic risk profiles might predispose individuals to many diseases, which could have implications for public health in terms of screening and chemoprevention.

Keywords

genetic variants, genome-wide association studies (GWAS), prostate cancer, rheumatoid arthritis

Introduction

Although prostate cancer (PrCa) is the most frequent non-cutaneous cancer among men in America and the UK, very little is known regarding the underlying aetiology [1–3]. Age, race and family history of PrCa remain the primary main risk factors for PrCa [4]. It has been shown to be one of the most heritable cancers [5,6] and a positive family history of PrCa increases the risk to first-degree relatives over twofold [6]. The estimates from Nordic twin studies suggest that 42% of the risk could be due to genetic factors [5,7]. The search for these genetic variants has led to genome-wide association studies (GWAS), which have so far reported 49 single nucleotide polymorphisms (SNPs) associated with PrCa risk [8–24]. Nevertheless, these variants alone cannot explain fully the variation of PrCa incidence seen amongst populations. Environmental factors are also thought to play a key role in PrCa aetiology. These factors include the immune system and inflammation [25].

The link between inflammation and cancer has long been established [26]. Chronic inflammation is thought to influence carcinogenesis of many tumour sites, including PrCa [27–29]. The role of the immune system in the aetiology of PrCa has been further enhanced by the results from the IMPACT study, which for the first time showed an improved survival for patients with PrCa using sipuleucel-T immunotherapy [30].

There have also been attempts to investigate the relationship between autoimmune diseases and PrCa. Reports from longitudinal studies looking at the incidence of cancers in cohorts with autoimmune diseases have been conflicting. Cohorts with Crohn's or ulcerative colitis have been reported to have a slightly increased incidence of PrCa, but this was not statistically significant [31,32]. A group from the National Cancer Institute in the USA reported no difference in the incidence of PrCa in a scleroderma cohort [33]. Conversely, cohorts with rheumatoid arthritis (RA), psoriasis and systemic lupus erythematosus seemed to have a decreased risk of PrCa [34–36]. This seems to go against the previously reported studies showing inflammation as a cause of carcinogenesis. Furthermore there is an increased incidence of non-Hodgkin's lymphoma in relatives of patients with PrCa [37,38]. There are, however, potential confounding factors that might account for these findings, such as the medication usage in these cohorts. The chemopreventive effects of aspirin and NSAIDs have been reported in many longitudinal studies [39]. The increased intake of NSAIDs in the cohorts with RA could have skewed the results, leading to the perceived protective effect.

The interest in the effects of autoimmunity and inflammation on PrCa has also led to groups exploring the association of PrCa risk with genes in these pathways. A candidate gene approach was initially adopted, with conflicting results [25,27]. Zheng et al. [40] then conducted a pathway analysis approach looking at sets of inflammatory pathways genes and their association with PrCa. There were some positive associations with PrCa risk, but further validation is still awaited. More recently, GWAS identified a coding SNP associated with PrCa risk at *CCHCR1* (coding for coiled-coil alpha-helical rod protein 1), which is also associated with the autoimmune disease psoriasis [17]. This is encouraging as it highlights a potential autoimmune aetiology for PrCa. The question that arises from this is: could there still be other susceptibility loci that are common to both PrCa and autoimmune diseases? It is known that the functions for most PrCa GWAS SNPs have not been established, as they are non-coding, lying in intronic or intergenic regions [41]. It would be important to determine if there are any associations between these PrCa-risk SNPs and autoimmune diseases, as it could improve our understanding of the biology of these SNPs, as well as potentially offering a chemopreventive and/or therapeutic target. The present study aims to evaluate this further by investigating if the GWAS SNPs associated with

susceptibility to PrCa are also associated with susceptibility to the autoimmune disease RA.

Rheumatoid arthritis is a chronic autoimmune disease affecting 0.5–1% of the population worldwide. The inherited link has been established in twin studies, where the genetic contribution to risk is estimated to be between 50% and 60% [42]. As with PrCa, significant progress has been made recently with the advent of GWAS to identify the genetic factors that contribute to this disease, with over 33 SNPs reported [42,43]. However, it is still estimated that more than 50% of the genetic risks remain unaccounted for [43]. The present study could also potentially highlight new susceptibility loci for RA. RA was chosen as the autoimmune disease to compare with PrCa as the former also occurs in males, whereas many other autoimmune diseases are predominant in females.

Materials and Methods

We expanded the original Wellcome Trust Case Control Consortium (WTCCC) UK RA GWAS study [44] by adding a further 2334 controls and 1361 cases (G. Orozco et al., unpublished). All RA patients satisfied the 1987 American College of Rheumatology criteria for RA modified for genetic studies [45,46]. All samples were collected with ethical committee approval and all individuals provided informed consent.

The additional RA and control samples were genotyped on a range of GWAS platforms as different RA cohorts (Table 1). The first stage for combining these data was to impute all the genotypes. Each RA case cohort was imputed using IMPUTE, v2 (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html), using two reference panels, 1000 genomes project pilot data and Hapmap3. Controls were imputed using the same 1000 genomes project reference panel using MACH software (http://www.sph.umich.edu/csg/abecasis/MACH/index.html). Stringent quality control thresholds were applied to both individual cohorts and then the merged cohorts. Imputed SNP genotypes were dropped if the calling probability was <90%; samples and SNPs were removed if they had a missingness >5%; and SNPs were dropped either if their minor allele frequency (MAF) was <5% or if they had a Hardy–Weinberg equilibrium (HWE) P value $<10^{-6}$.

A panel of 37 autosomal SNPs was selected for investigation from recent large-scale GWAS and meta-analysis studies of PrCa-associated loci [8–23]. Proxy SNPs ($r^2 > 0.8$) were included where the original SNP tested in PrCa was not present in our RA dataset.

Allele frequencies were compared between RA cases and controls using the chi-squared trend test implemented in PLINK software (http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml). $P < 1.4 \times 10^{-3}$ was considered to be statistically significant after correcting for multiple testing (37 tests) applying the Bonferroni correction.

Finally, an analysis of the carriage of PrCa alleles in patients with RA was carried out using STATA version 9.2 to determine if there is an overall enrichment of PrCa susceptibility variants in patients with RA. Carriage of PrCa risk alleles was coded as 1 and absence of the risk allele was coded as 0. A PrCa loci carriage score was calculated by summing the number of PrCa risk alleles carried by each individual, and differences in the mean score between RA cases and controls was tested using the Wilcoxon rank-sum test.

Results

Of the 37 autosomal PrCa loci identified to date, we could not find proxies for rs10936632 in 3q26, rs2242652 in 5p15, and rs11649743 and rs4430796 in 17q12. Association with RA was tested for the remaining 33 PrCa-associated markers (Table 2). Control allele frequencies for all SNPs tested conformed to Hardy–Weinberg expectations ($P > 0.05$) and were similar to those described for population of European ancestry by the HapMap project (http://hapmap.ncbi.nlm.nih.gov/).

Three SNPs – rs2121875 mapping to the *FGF10* locus, rs130067 mapping to *CCHCR1* and rs10993994 mapping to the *MSMB* locus – showed nominal evidence for association ($P < 0.05$). After applying a Bonferroni correction for the number of SNPs tested, only the SNP

Table 1 Patients with RA and controls included in the study and genotyping platforms used.

	WTCCC GWAS		Additional 2334 controls and 1361 cases with RA				
			WTCCC2 controls	Cases with RA			
	Controls	Cases with RA		POCEMON	BRAGGSS1	BRAGGSS2	BRAGGSS3
Number of individuals	2938	1860	2334	766	271	141	185
Genotyping platform	Affymetrix 500K	Affymetrix 500K	Affymetrix v6.0 + Illumina 1.2M	Illumina CNV370	Affymetrix v6.0	Affymetrix v6.0	Omni Express
Number of SNPs	500 000	500 000	906 600 + 1 200 000	318 000	906 600	906 600	700 000

Table 2 Case–control association results of confirmed prostate cancer susceptibility loci in RA.

Locus	SNP	Proxy	r^2	MAF cases	MAF controls	*P* value	OR (95% CI)
2p11	rs10187424			0.43	0.42	0.13	1.05 (0.99–1.12)
2p15	rs721048			0.22	0.20	0.07	1.11 (0.99–1.24)
2p21	rs1465618			0.20	0.21	0.44	0.96 (0.86–1.07)
2q31	rs12621278			0.06	0.06	0.70	1.03 (0.90–1.17)
2q37 (*MLPH*)	rs7584330			0.25	0.25	0.83	0.99 (0.92–1.07)
3p12	rs2660753			0.09	0.10	0.27	0.94 (0.84–1.05)
3q21 (*EEFSEC*)	rs10934853			0.27	0.27	0.62	1.02 (0.95–1.09)
3q23 (*ZBTB38*)	rs6763931			0.44	0.44	0.94	0.99 (0.94–1.06)
4q22	rs12500426	rs10019505	0.97	0.46	0.46	0.99	1.00 (0.94–1.07)
4q22	rs17021918			0.35	0.35	0.55	0.98 (0.92–1.05)
4q24	rs7679673	rs7663401	0.81	0.34	0.33	0.47	1.03 (0.96–1.10)
5p12 (*FGF10*)	rs2121875			0.32	0.33	0.02	0.93 (0.87–0.99)
6p21 (*CCHCR1*)	rs130067			0.22	0.20	6×10^{-4}	1.15 (1.06–1.24)
6q25	rs9364554			0.30	0.30	0.89	0.99 (0.93–1.07)
7p15 (*JAZF1*)	rs10486567	rs11982766	0.96	0.23	0.22	0.17	1.05 (0.98–1.14)
7q21	rs6465657			0.47	0.47	0.39	0.97 (0.91–1.04)
8p21	rs1512268			0.43	0.42	0.49	1.02 (0.96–1.09)
8p21	rs2928679	rs7009914	1.00	0.47	0.47	0.89	0.99 (0.93–1.06)
8q24	rs10086908			0.31	0.30	0.70	1.01 (0.95–1.09)
8q24	rs12543663	rs6984837	0.86	0.33	0.33	0.81	0.99 (0.90–1.08)
8q24	rs1447295			0.11	0.10	0.33	1.05 (0.95–1.17)
8q24	rs16901979	rs1551512	1.00	0.03	0.03	0.73	0.97 (0.81–1.16)
8q24	rs620861			0.37	0.37	0.86	1.01 (0.94–1.08)
8q24	rs6983267	rs10505477	0.88	0.48	0.48	0.89	0.99 (0.93–1.06)
9q33 (*DAB2IP*)	rs1571801			0.26	0.27	0.06	0.93 (0.87–1.00)
10q11 (*MSMB*)	rs10993994			0.37	0.40	0.03	0.90 (0.82–0.99)
10q26 (*CTBP2*)	rs4962416			0.29	0.29	0.84	1.01 (0.91–1.12)
11p15	rs7127900	rs10840606	0.95	0.19	0.17	0.08	1.12 (0.99–1.27)
11q13	rs7931342	rs9787877	0.97	0.49	0.50	0.32	0.97 (0.91–1.03)
12q13	rs10875943			0.27	0.27	0.97	1.002 (0.90–1.12)
17q24	rs1859962			0.46	0.47	0.20	0.96 (0.90–1.02)
19q13 (*KLK3*)	rs17632542			0.08	0.08	0.79	1.03 (0.83–1.29)
22q13	rs5759167			0.50	0.50	0.87	0.99 (0.88–1.12)

mapping to *CCHCR1* retained statistically significant evidence for association ($P = 6 \times 10^{-4}$; OR = 1.15, 95% CI: 1.06–1.24).

CCHCR1 maps to the human leucocyte antigen (HLA) region, around 100 kb from the *HLA-C* gene. The major RA susceptibility locus, *HLA-DRB1*, and a number of additional RA loci also map to the HLA. The region is characterized by the presence of strong linkage disequilibrium, and therefore the association of rs130067 with RA might be due to linkage disequilibrium with previously known RA loci. We carried out a study aimed at identifying *HLA-DRB1*-independent RA susceptibility loci by pairwise matching WTCCC cases and controls on *DRB1* genotypes [47]. A perfect proxy ($r^2 = 1$) of rs130067, rs1265074, was included in the above-mentioned analysis. When we compared non-matched cases and controls, this SNP was associated with RA with a *P* value of 0.03. However, when we repeated the analysis using case–control pairs with identical *DRB1* genotypes, the SNP was no longer significant ($P = 0.91$). This suggests that the association of rs130067 was due to confounding by RA-associated *HLA-DRB1* alleles.

Additionally, we explored what the total burden of PrCa susceptibility alleles was in RA. For this analysis, we included the markers for which we had genotype data across all the cohorts included in the study (rs10187424, rs12621278, rs7584330, rs2660753, rs10934853, rs6763931, rs10019505, rs17021918, rs7663401, rs2121875, rs130067, rs9364554, rs11982766, rs6465657, rs7009914, rs1512268, rs10086908, rs1551512, rs10505477, rs1447295, rs1571801, rs9787877, rs1859962). We found that the mean number of PrCa risk alleles carried by RA patients was similar to that found in controls (14.39 vs 14.30, $P = 0.82$).

Discussion

This is the first study exploring the association between the common genetic variants associated with PrCa and RA. The inflammation pathways remain an important factor in PrCa biology, especially with the improved survival reported with the use of the immunotherapy drug sipuleucel-T in castration-resistant PrCa [30]. The main aim of the present study was to ascertain if PrCa is related to autoimmunity with shared genetic variants that could predispose individuals to both diseases.

For the present study, a large sample size was used, including 3221 cases and 5272 controls. However, no PrCa risk SNPs were found to be significantly associated in the RA cohorts. This suggests that PrCa is not genetically linked to autoimmune diseases, at least for those SNPs at highest significance on GWAS.

There could be several possible reasons for the lack of association found. Firstly, we have still yet to discover the full extent of the genetic inheritability of PrCa and GWAS continue to report new SNPs. So far 18 GWAS have been reported in PrCa [48], with new studies due to be published, such as the Collaborative Oncological Gene-environment Study (COGS) analysis [49]. These undiscovered genes might yet uncover potential links. Different papers have reported a chronic inflammatory pathogenesis for many cancers, which include PrCa [26–29]. Epidemiological studies have also shown a correlation between PrCa incidence and autoimmune diseases, which lead to chronic inflammation and hence cancer [31,32]. It is therefore still possible that we might be missing genetic variants common to both diseases. Future analyses should be done to include a newer risk SNP profile. Conversely, analyses of the published RA risk loci in PrCa case–control cohorts should also be performed to determine any associations.

The second possible reason for the lack of association is that the present study design only allows us to explore common germline genetic variants identified from the PrCa GWAS. Rarer variants, which are not evaluated here, could be important in RA. The rare variants associated with PrCa risk have so far only been identified in DNA repair genes and the *HOX* gene, *HOXB13* [50–52]. More recently, PrCa has also been shown to be a feature of Lynch syndrome, which is an autosomal condition caused by germline mutations in the DNA mismatch repair (MMR) genes [53]. Rare variants like these could also be important in autoimmune diseases such as RA. Previous groups have shown the association of defects in DNA repair genes with diseases involving the immune system, for example in severe common immunodeficiency (SCID). There have also been reports of polymorphisms in the DNA repair gene *XRCC1* associated with the risk of developing RA [54,55]. GWAS have not been designed to study the contribution of rare or structural variants that the current next generation sequencing studies are targeting, and where it is likely that more genetic variants relating to PrCa risk will be discovered [56]. Future analyses should include these other forms of heritability. Furthermore, as only the SNP identified in PrCa GWAS was tested in RA, it could be that a different variant in the same gene/region is responsible for risk in the second disease.

In addition, although this is a relatively large study, it still has limited power to detect all the associations (averaged power across SNPs with MAF > 5% is 47% for OR = 1.1 and >90% for OR > 1.2), so failure to detect a signal could just be the result of stochastic variations.

Lastly, it could transpire that the autoimmune inflammatory pathogenesis pathways for both diseases are actually mutually exclusive. Most of the SNPs reported in RA are unsurprisingly associated with immune-related pathways [42], which relate to its pathogenesis. Unlike RA, the molecular basis for the aetiology of SNPs associated with PrCa risk remains unknown and it is possible that they exert their effect on other pathways via promoter or enhancer elements, leading to control of gene expression in genes located elsewhere [41]. Evaluating how the genetic variants initiate disease would allow a better understanding of the pathogenesis of PrCa. Currently, the only GWAS-risk SNP found to be potentially linked with autoimmunity is on chromosome 6p21, coding for *CCHCR1* [17], which was not significantly associated with the RA cohorts in the present study after correction of confounding variables. The discovery of the functional elements of the other risk SNPs might feature common pathways in the future, which could be evaluated further to ascertain any true associations between PrCa and RA.

Studies like this are important to determine if common genetic risk profiles might predispose individuals to many diseases. The results could have implications for public health in terms of screening and chemoprevention. Future research is therefore warranted to investigate this link further.

In conclusion, there is currently no evidence that SNPs associated with PrCa at genome-wide significance are associated with the development of RA. Further work should be done using an updated profile to potentially include rare or structural variants.

Acknowledgements

This work was funded by The European Community's Seventh Framework Programme under the grant agreement 223175; (grant number Health-F2-2009-223175-COGS), the Genetic Associations and Mechanisms in Oncology (GAME-ON) Initiative (ELLIPSE grant: U19CA148537) and CRUK (Cancer Research United Kingdom grant C5047/A10692). GO is funded by the Wellcome Trust (Research Career Development Fellowship 095684/Z/11/A). We acknowledge support from the Wellcome Trust, National Institute for Health Research (NIHR) and the Biomedical Research Centre at The Institute of Cancer Research and Royal Marsden Foundation NHS Trust. We are grateful for the support from the Institute of Cancer Research Everyman Campaign and Prostate Action.

Conflict of Interest

None declared.

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Abbreviations: GWAS, genome-wide association studies; HLA, human leucocyte antigen; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; PrCa, prostate cancer; RA, rheumatoid arthritis; SNPs, single nucleotide polymorphisms; WTCCC, Wellcome Trust Case Control Consortium.