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# Germline Genetic Variants Associated with Prostate Cancer and Potential Relevance to Clinical Practice

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## Abstract

The inherited link of prostate cancer predisposition has been supported using data from early epidemiological studies, as well as from familial and twin studies. Early linkage analyses and candidate gene approaches to identify these variants yielded mixed results. Since then, multiple genetic variants associated with prostate cancer susceptibility have now been found from genome-wide association studies (GWAS). Their clinical utility, however, remains unknown. It is recognised that collaborative efforts are needed to ensure adequate sample sizes are available to definitively investigate the genetic–clinical interactions. These could have important implications for public health as well as individualised prostate cancer management strategies. With the costs of genotyping decreasing and direct-to-consumer testing already offered for these common variants, it is envisaged that a lot of attention will be focussed in this area. These results will enable more refined risk stratification which will be important for targeting screening and prevention to higher risk groups. Ascertaining their clinical role remains an important goal for the GWAS community with international consortia now established, pooling efforts and resources to move this field forward.

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## 1 Introduction

Although prostate cancer (PrCa) remains a significant burden for health services across the world (Ferlay et al. 2010), little is known of its aetiology or triggers. Age, race and family history remain the major risk factors associated with the development of this disease (Crawford 2003). Epidemiological data showing the wide variation of PrCa incidence around the world as well as the cluster patterns observed amongst family members with PrCa imply a potential genetic link within families and/or populations (Center et al. 2012; Goh et al. 2012). Men of African ancestry have nearly twice the incidence rates of Caucasians and Asians, and these differences persist despite accounting for the movement of populations (Jemal et al. 2010).

The clues to a genetic link have been further supported in familial and twin studies. From risk modelling estimates, a positive family history of PrCa increases the risk for an unaffected male relative by two-fold (Lichtenstein et al. 2000). This risk increases the closer the relation is to the man with PrCa, i.e. higher risk if a first versus a second degree relative is affected. The risk also rises with the number of cases affected within the family. Lichtenstein et al. reported that in analyses based on Nordic twin registries, an estimated 42 % of PrCa risk can be explained through germline genetic variants. The higher risks found with monozygotic versus dizygotic twins support the hypothesis that familial aggregation results from shared genetic rather than environmental factors (Lichtenstein et al. 2000). Researchers in this field, therefore, focussed on the discovery of these genetic variants, which could have potentially important clinical utility in public health, both in terms of screening and the tailoring of more effective cancer therapy through personalised medicine.

This chapter aims to provide a brief overview of the evidence for genetic predisposition in PrCa and outline some potential clinical implications for these susceptibility loci as well as the future directions for research in this field.

## 2 Germline Genetic Models

The initial search for the genetic variants had mixed results. Various analytical methods were used to define this inherited link. Segregation analysis assesses the genetic models of inheritance (Houlston and Peto 2004). Initial studies suggested a major genetic component with an autosomal dominant inheritance, although others have since reported recessive or X-linked modes of inheritance (Carter et al. 1992; Gronberg et al. 1997; Schaid 1998, MacInnis et al. 2010; Cui et al. 2001). This depended heavily on the types of population studied. Nevertheless, these initial results provided further evidence of the inherited link and thus the impetus to search for these high-risk genes. To identify and characterise these genes, molecular analyses in the form of linkage and candidate gene analyses were performed.

Linkage is essentially the co-inheritance of genetic markers with a disease (Easton 2004). The concept of linkage was first described by Mendel who noted the co-inheritance of certain characteristics in his plants. Studies have implicated genes from numerous chromosomes associated with PrCa risk, but many were then refuted by other groups (Lange 2010). In 2005, the International Consortium for PrCa Genetics (ICPCG) reported the largest study to date, combining data from 1,233 families from 10 research groups worldwide (Xu et al. 2005). They identified several promising regions, but the replication of these regions has proved difficult and their status as susceptibility genes remains in doubt. This difficulty suggests that PrCa might be more genetically complex than once thought, involving a polygenic inheritance.

There are, however, genes that have been successfully identified and replicated through candidate studies. Deleterious mutations in both *BRCA1* and *BRCA2* genes have been associated with increased PrCa risk. Both have a moderate to high penetrance, with *BRCA2* conferring an estimated 8.6-fold increased risk in carriers  $\leq 65$  years (Kote-Jarai et al. 2011a), and *BRCA1* 4.5-fold in carriers  $\leq 65$  years (Leongamornlert et al. 2012). Consistent evidence is now emerging that *BRCA* mutation carriers who develop PrCa also develop worse disease and have a poorer survival (Castro et al. 2013). More recently, evidence has also emerged for another genetic syndrome, which has been shown to have a moderate effect on PrCa risk. These are the Lynch syndrome mutation carriers who have a germline mutation in the mismatch repair genes; *MLH1*, *MSH2* and *MSH6* (Grindedal et al. 2009; Engel et al. 2012; Barrow et al. 2013). Early data suggest that the risk can be up to 10-fold (Barrow et al. 2013), but further reports are awaited to assess its clinical implications in PrCa and whether all three genes confer an increased PrCa risk when mutated.

Other DNA repair genes have been studied as candidates for PrCa predisposition, and some have been shown to have apparent significant associations, including the *NBS1*, *CHEK2* and *PALB2* genes (Cybulski et al. 2004; Cybulski et al. 2006; Erkkö et al. 2007; Thompson et al. 2006; Tischkowitz et al. 2008, Eeles et al. 2010). However, like some of the linkage studies, it has also been

difficult to replicate these results and these may be population origin specific in their risks. More recently, thorough sequencing of a linkage region of interest on 17q has revealed a new locus associated with PrCa risk. Rare germline mutations in *HOXB13*, particularly *G84E*, have been reported to increase the risk of PrCa development of up to 10-fold in early-onset cases from certain populations (Ewing et al. 2012, Shang et al. 2013). Further reports have shown that the RR is nearer 3–4-fold in most populations, but is higher in those of Scandinavian origin (Shang et al. 2013).

Nevertheless, all the genes reported above are rare in the population and are unlikely to account for the vast majority of genetic predisposition for common diseases like PrCa. The difficulty in identifying definitive genes despite epidemiological evidence of the inherited component further supports the hypothesis that PrCa inheritance is unlikely to follow the Mendelian single gene approach, but comprise multiple lower penetrance genes.

Genome-wide association studies (GWAS) were developed to investigate this theory further. Their main advantage is the ability to offer an agnostic approach to identify low risk variants that occur more commonly and are therefore more applicable to a larger proportion of the population (Manolio 2010; Chung et al. 2010). GWAS compares the frequencies of single nucleotide polymorphisms (SNPs), which differ in a single DNA base pair, between cases and controls to look for an association with that particular genetic trait. The SNP is the most common form of genomic variation and the latest estimates for the number of SNPs are 4 million, with a minor-allele frequency of at least 5 % (Abecasis et al. 2012). A typical GWAS would genotype from 0.3 up to 2.5 million SNPs at a single time. Linkage mapping studies lacked power to detect loci that confer low to moderate risks. Given a large enough case–control study, GWAS have the ability to detect multiple loci conferring small risks with odds ratios of  $\leq 1.1$ .

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### 3 Results from Genome-Wide Association Studies

The first PrCa GWAS was published in 2006 (Amundadottir et al. 2006), and currently the National Human Research Genome Institute (NHGRI) catalogue lists over 25 GWAS published with 76 SNPs currently known to be associated with PrCa risk (Hindroff et al. 2009) (see Table 1). Although they individually confer a modest risk of PrCa, collectively they are estimated to explain approximately 30 % of the familial risk (Eeles et al. 2013). The genes identified could prove important in clinical use. Examples are the 8q24 loci, which are the first identified from GWAS and where there is the highest number of independently associated variants (Al Olama et al. 2009). 8q24 is in the vicinity of the *c-MYC* oncogene and chromatin conformation assays have shown that some of these SNPs exert long-range tissue-specific expression of *MYC* expression (Ahmadiyeh et al. 2010). 8q24 is also implicated in many other cancers and would be an important target for cancer management.

**Table 1** Common susceptibility loci for PrCa

Locus	SNP	Effect allele frequency <sup>a</sup>	Per allele OR <sup>a</sup>	Nearby genes	References
1q21	rs1218582	0.45	1.06 (1.03–1.09)	<i>KCNN3</i>	(Eeles et al. 2013)
1q32	rs4245739	0.25	0.91 (0.88–0.95)	<i>MDM4</i> , <i>PIK3C2B</i>	(Eeles et al. 2013)
2p11	rs10187424	0.41	0.92 (0.89–0.94)	<i>GGCX/VAMP8</i>	(Kote-Jarai et al. 2011b)
2p15	rs721048	0.19	1.15 (1.10–1.21)	<i>EHBPI</i>	(Gudmundsson et al. 2008)
2p21	rs1465618	0.23	1.08 (1.03–1.12)	<i>THADA</i>	(Eeles et al. 2009)
2p24	rs13385191	0.56	1.15 (1.10–1.21)	<i>C2orf43</i>	(Takata et al. 2010)
2p25	rs11902236	0.27	1.07 (1.03–1.10)	<i>TAF1B:GRHL1</i>	(Eeles et al. 2013)
2q31	rs12621278	0.06	0.75 (0.70–0.80)	<i>ITGA6</i>	(Eeles et al. 2009)
2q37	rs2292884	0.25	1.14 (1.09–1.19)	<i>MLPH</i>	(Kote-Jarai et al. 2011b; Schumacher et al. 2011)
2q37	rs3771570	0.15	1.12 (1.08–1.17)	<i>FARP2</i>	(Eeles et al. 2013)
3p11	rs2055109	0.9	1.20 (1.13–1.29)		(Akamatsu et al. 2012)
3p12	rs2660753	0.11	1.18 (1.06–1.31)		(Eeles et al. 2008)
3q13	rs7611694	0.41	0.91 (0.88–0.93)	<i>SIDT1</i>	(Eeles et al. 2013)
3q21	rs10934853	0.28	1.12 (1.08–1.16)	<i>EEFSEC</i>	(Gudmundsson et al. 2009)
3q23	rs6763931	0.45	1.04 (1.01–1.07)	<i>ZBTB38</i>	(Kote-Jarai et al. 2011b)
3q26	rs10936632	0.48	0.90 (0.88–0.93)	<i>CLDN11/SKIL</i>	(Kote-Jarai et al. 2011b)
4q13	rs1894292	0.48	0.91 (0.89–0.94)	<i>AFM</i> , <i>RASSF6</i>	(Kote-Jarai et al. 2013)
4q22	rs17021918	0.34	0.90 (0.87–0.93)	<i>PDLIM5</i>	(Eeles et al. 2009)
4q22	rs12500426	0.46	1.08 (1.05–1.12)	<i>PDLIM5</i>	(Eeles et al. 2009)
4q24	rs7679673	0.45	0.91 (0.88–0.94)	<i>TET2</i>	(Eeles et al. 2009)

(continued)

**Table 1** (continued)

Locus	SNP	Effect allele frequency <sup>a</sup>	Per allele OR <sup>a</sup>	Nearby genes	References
5p12	rs2121875	0.34	1.05 (1.02–1.08)	<i>FGF10</i>	(Kote-Jarai et al. <a href="#">2011b</a> )
5p15	rs2242652	0.19	0.87 (0.84–0.90)	<i>TERT</i>	(Kote-Jarai et al. <a href="#">2011b</a> )
5p15	rs12653946	0.44	1.26 (1.20–1.33)	<i>IRX4</i>	(Takata et al. <a href="#">2010</a> )
5q35	rs6869841	0.21	1.07 (1.04–1.11)	<i>FAM44B</i> ( <i>BOD1</i> )	(Eeles et al. <a href="#">2013</a> )
6p21	rs130067	0.21	1.05 (1.02–1.09)	<i>CCHCR1</i>	(Kote-Jarai et al. <a href="#">2011b</a> )
6p21	rs1983891	0.41	1.15 (1.09–1.21)	<i>FOXP4</i>	(Takata et al. <a href="#">2010</a> )
6p21	rs3096702	0.4	1.07 (1.04–1.10)	<i>NOTCH4</i>	(Eeles et al. <a href="#">2013</a> )
6p21	rs2273669	0.15	1.07 (1.03–1.11)	<i>ARMC2</i> , <i>SESNI</i>	(Eeles et al. <a href="#">2013</a> )
6q22	rs339331	0.63	1.22 (1.15–1.28)	<i>RFX6</i>	(Takata et al. <a href="#">2010</a> )
6q25	rs9364554	0.29	1.17 (1.08–1.26)	<i>SLC22A3</i>	(Eeles et al. <a href="#">2008</a> )
6q25	rs1933488	0.41	0.89 (0.87–0.92)	<i>RSG17</i>	(Eeles et al. <a href="#">2013</a> )
7p15	rs10486567	0.77	0.74 (0.66–0.83)	<i>JAZF1</i>	(Thomas et al. <a href="#">2008</a> )
7p21	rs12155172	0.23	1.11 (1.07–1.15)	<i>SP8</i>	(Eeles et al. <a href="#">2013</a> )
7q21	rs6465657	0.46	1.12 (1.05–1.20)	<i>LMTK2</i>	(Eeles et al. <a href="#">2008</a> )
8p21	rs2928679	0.42	1.05 (1.01–1.09)	<i>SLC25A37</i>	(Eeles et al. <a href="#">2009</a> )
8p21	rs1512268	0.45	1.18 (1.14–1.22)	<i>NKX3.1</i>	(Eeles et al. <a href="#">2009</a> )
8p21	rs11135910	0.16	1.11 (1.07–1.16)	<i>EBF2</i>	(Eeles et al. <a href="#">2013</a> )
8q24	rs1447295	0.13	1.62		(Amundadottir et al. <a href="#">2006</a> )
8q24	rs6983267	0.5	1.26 (1.13–1.41)		(Yeager et al. <a href="#">2007</a> )
8q24	rs16901979	0.09	1.79 (1.36–2.34)		(Gudmundsson et al. <a href="#">2007a</a> )

(continued)

**Table 1** (continued)

Locus	SNP	Effect allele frequency <sup>a</sup>	Per allele OR <sup>a</sup>	Nearby genes	References
8q24	rs10086908	0.3	0.87 (0.81–0.94)		(Al Olama et al. 2009)
8q24	rs12543663	0.31	1.08 (1.00–1.16)		(Al Olama et al. 2009)
8q24	rs620861	0.39	0.90 (0.84–0.96)		(Al Olama et al. 2009)
9q31	rs817826	0.08	1.41 (1.29–1.54)	<i>RAD23B-KLF4</i>	(Xu et al. 2012)
9q33	rs1571801	0.25	1.27 (1.10–1.48)	<i>DAB2IP</i>	(Duggan et al. 2007)
10q11	rs10993994	0.4	1.25 (1.17–1.34)	<i>MSMB</i>	(Eeles et al. 2008; Thomas et al. 2008)
10q24	rs3850699	0.29	0.91 (0.89–0.94)	<i>TRIM8</i>	(Eeles et al. 2013)
10q26	rs4962416	0.27	1.20 (1.07–1.34)	<i>CTBP2</i>	(Thomas et al. 2008)
10q26	rs2252004	0.77	1.16 (1.10–1.22)		(Akamatsu et al. 2012)
11p15	rs7127900	0.2	1.22 (1.17–1.27)		(Eeles et al. 2009)
11q12	rs1938781	0.3	1.16 (1.11–1.21)	<i>FAM111A</i>	(Akamatsu et al. 2012)
11q13	rs7931342	0.49	0.84 (0.79–0.90)		(Eeles et al. 2008; Thomas et al. 2008)
11q22	rs11568818	0.44	0.91 (0.88–0.94)	<i>MMP7</i>	(Eeles et al. 2013)
12q13	rs10875943	0.31	1.07 (1.04–1.10)	<i>TUBA1C/PRPH</i>	(Kote-Jarai et al. 2011b)
12q13	rs902774	0.15	1.17 (1.11–1.24)	<i>KRT8</i>	(Schumacher et al. 2011)
12q24	rs1270884	0.49	1.07 (1.04–1.10)	<i>TBX5</i>	(Eeles et al. 2013)
13q22	rs9600079	0.38	1.18 (1.12–1.24)		(Takata et al. 2010)
14q22	rs8008270	0.18	0.89 (0.86–0.93)	<i>FERMT2</i>	(Eeles et al. 2013)
14q24	rs7141529	0.5	1.09 (1.06–1.12)	<i>RAD51LI</i>	(Eeles et al. 2013)
17p13	rs684232	0.36	1.10 (1.07–1.14)	<i>VPS53, FAM57A</i>	(Eeles et al. 2013)

(continued)

**Table 1** (continued)

Locus	SNP	Effect allele frequency <sup>a</sup>	Per allele OR <sup>a</sup>	Nearby genes	References
17q12	rs4430796	0.49	1.22 (1.15–1.30)	<i>HNF1B</i>	(Gudmundsson et al. 2007b)
17q12	rs11649743	0.8	1.28 (1.07–1.52)	<i>HNF1B</i>	(Sun et al. 2008)
17q21	rs7210100	0.05	1.51 (1.35–1.69)	<i>ZNF652</i>	(Haiman et al. 2011)
17q21	rs11650494	0.08	1.15 (1.09–1.22)	<i>HOXB13</i> , <i>SPOP</i>	(Eeles et al. 2013)
17q24	rs1859962	0.46	1.20 (1.14–1.27)		(Gudmundsson et al. 2007b)
18q23	rs7241993	0.3	0.92 (0.89–0.95)	<i>SALL3</i>	(Eeles et al. 2013)
19q13	rs2735839	0.15	0.83 (0.75–0.91)	<i>KLK2/KLK3</i>	(Eeles et al. 2008)
19q13	rs8102476	0.54	1.12 (1.08–1.15)		(Gudmundsson et al. 2009)
19q13	rs11672691	0.76	1.12 (1.03–1.21)		(Amin Al Olama et al. 2013)
19q13	rs103294	0.24	1.28 (1.21–1.36)	<i>LILRA3</i>	(Xu et al. 2012)
20q13	rs2427345	0.37	0.94 (0.91–0.97)	<i>GATAS</i> , <i>CABLES2</i>	(Eeles et al. 2013)
20q13	rs6062509	0.3	0.89 (0.66–0.92)	<i>ZGPAT</i>	(Eeles et al., 2013)
22q13	rs5759167	0.47	0.86 (0.83–0.88)	<i>BIL/TTL1</i>	(Eeles et al. 2009)
Xp11	rs5945619	0.36	1.19 (1.07–1.31)	<i>NUDT11</i>	(Gudmundsson et al. 2008; Eeles et al. 2008)
Xp22	rs2405942	0.21	0.88 (0.83–0.92)	<i>SHROOM2</i>	(Eeles et al. 2013)
Xq12	rs5919432	0.19	0.94 (0.89–0.98)	<i>AR</i>	(Kote-Jarai et al. 2011b)

<sup>a</sup>Data for effect allele frequency and per allele OR (odds ratio) are taken from the original publications. 95 % confidence intervals are given in brackets where available. Modified and updated from Goh et al. (2012)



Other sites of potential clinical significance are the SNP rs4245739 on chromosome 1 near the *MDM4* gene, which is a negative regulator of *TP53*, or rs11568818, which is in linkage disequilibrium with the gene *MMP7*, encoding a matrix metalloproteinase. *MMP7* has been reported to be associated with metastasis and poor prognosis (Eeles et al. 2013). These variants could perhaps play a role in the ability to differentiate low- and high-risk disease. Further work is needed in this area.

The SNP rs10993994, located upstream of the microseminoprotein beta (*MSMB*) gene could potentially play a role in screening (Eeles et al. 2008). *MSMB* is a seminal fluid protein and has been shown to be either lost or decreased in PrCa (Whitaker et al. 2010). The association between a reduced level of *MSMB* and PrCa risk has also been consistently replicated in multi-ethnic cohorts, indicating a potential utility in screening, which is applicable across different populations and is independent of serum PSA level (Haiman et al. 2013). SNPs within the kallikrein regions have also been associated with PSA level (Eeles et al. 2008). These could be incorporated in risk prediction models and would warrant further testing.

Other SNPs have been found in regions of interest including the androgen receptor gene (Kote-Jarai et al. 2011b), DNA repair *RAD51B* (Eeles et al. 2013) and the *CCHCR1* (coding for coiled-coil alpha-helical rod protein 1), which is also associated with psoriasis (Kote-Jarai et al. 2011b). All these could suggest potential targets for therapy.

Nevertheless, despite some evidence of coding SNPs, the majority of these SNPs are non-coding, lying in intronic or intergenic regions. Freedman et al. presented a hypothesis that these trait-associated alleles exert their effects by influencing transcriptional output, for example transcript levels and splicing, through multiple mechanisms. They further emphasise that appropriate assays and models are needed to test the functional effects of these SNPs (Freedman et al. 2011). A better understanding of their functional effects would improve our understanding of the pathogenesis of this disease and potentially lead to better clinical application and utility.

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## 4 Potential Clinical Implications

PrCa mortality has decreased steadily over the past few decades. Over the past 25 years, the 5-year survival rate for all stages combined has increased from 68.3 to 99 % (Siegel et al. 2012). Nevertheless, there are still a large number of men who die from this disease. In the US, it is the second commonest cause of male cancer-related death (Jemal et al. 2010). The ability to differentiate men who are likely to succumb to this disease is therefore of major public health interest. Research is now underway to investigate the use of common germline genetic variants as potential biomarkers.

## 4.1 Individual Risk Profiling

One of the potential roles for the GWAS risk SNPs is risk profiling. As mentioned before, the SNPs individually exert a modest effect. However, these SNPs act multiplicatively. Antoniou et al. in the paper by Eeles et al., proposed a risk model using the currently known SNPs, where men at the top 1 % of the highest risk distribution have a 4.7-fold relative risk compared with the population average and the top 10 % of men have a 2.7-fold increased risk in comparison (Eeles et al. 2013). MacInnis et al. presented a model that incorporated SNPs and family history, which could stratify men better with regard to their risk of developing PrCa (Macinnis et al. 2011). These models could be used to counsel patients with regard to their individual risk of developing PrCa and have public health implications in terms of targeted screening. Those at higher risk could also be targeted for chemoprevention. Nevertheless, these models do not address the potential interaction between genetic variants and environmental factors. The question that needs to be answered is: do certain genotypes increase the susceptibility risk when exposed to certain environmental stimuli, and vice versa? The BPC3 (Breast PrCa Cohort Consortium) did not report any significant association between 36 GWAS risk SNPs and environmental factors including alcohol, BMI and smoking (Lindstrom et al. 2011). Potential limitations of their study include the low power to detect modest differences. Large consortia are needed to potentially power these sorts of analyses, and until then the gene–environmental interaction question remains unanswered.

## 4.2 Public Health Screening Implications

There currently exist controversies in the US and Europe with regard to the benefits of population-based PSA screening for PrCa (Chou et al. 2011; Basch et al. 2012). Whether the harms of screening are justified by the benefits in terms of the reports of reduction in PrCa mortality remain hotly debated. The recent publication of the Prostate Cancer Intervention Versus Observational Trial (PIVOT) casts further doubt, since men with PSA screen-detected localised PrCa who underwent radical prostatectomy did not have a significantly improved PrCa specific survival (Wilt Chou et al. 2012). It is without doubt that PSA screening may identify cancer earlier, but we need better screening approaches that can identify clinically significant disease. The usage of the GWAS risk SNPs to potentially individualise PrCa risk and identify men at higher risk for targeted screening should be evaluated further. Several groups have reported the use of varying numbers of GWAS risk SNPs, incorporating these in screening models using PSA and family history. These methods could improve the positive predictive value of PSA screening but further validation is needed. Pashayan et al. proposed a screening model utilising 31 PrCa risk SNPs to stratify men into risk groups according to their genetic profiles. If a polygenic risk score was generated and screening the bottom 1 % of the genetic risk distribution was avoided, 16 % of

men who would currently be offered screening based on an age threshold of >55 years would avoid screening (Pashayan et al. 2011). Importantly their model estimates that only 3 % of cases will be missed, but it is unknown if these would be clinically significant tumours. Further investigation is needed in this area also.

### 4.3 Disease Aggressiveness and Prostate Cancer Treatment Outcomes

As mentioned before, rare mutations like *BRCA1/2* have been associated with worse prognosis. It is therefore becoming increasingly recognised that mutation carriers with PrCa should be treated more aggressively and early screening studies are currently under investigation, e.g. the IMPACT (The Identification of Men with a genetic Predisposition to Prostate Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) trial (Mitra et al. 2011). However, the clinical utility of the more common GWAS variants to predict aggressive disease is not yet clear.

Like the screening approach, the ability to stratify men into more refined risk groups for treatment is needed. Staging information and nomograms currently in existence do give some indication of prognosis but these do not predict accurately the response to particular treatment or toxicity. There are also unexpected early deaths and long-term survivors that remain unexplained in good and poor prognosis groups, respectively (Mac Manus et al. 2006). If we can use germline genetic variants to predict men with poorer prognosis or those who respond better/worse to different treatment modalities, we might be better able to tailor treatment. Several groups have reported some association of the GWAS variants with disease aggressiveness including the 8q24 region (Cussenot et al. 2008), 15q13 (Fitzgerald et al. 2011), and the androgen receptor gene (Kote-Jarai et al. 2011b). However, these have not been consistently replicated (Xu et al. 2008). Szulkin et al. published a study looking at association of the GWAS SNPs with disease progression in men with clinically localised PrCa regardless of treatment administered (Szulkin et al. 2012). No significant association was found in the 23 SNPs studied. Further work is still needed to incorporate the updated list of SNPs in analyses of cohorts of patients with treatment outcome data.

Other groups have investigated the utility of genetic variants in specific PrCa treatment cohorts. Prostatectomy cohorts have been the most investigated. Different groups have reported in single centre studies, several candidate genes that are associated with disease aggressiveness. These include, amongst others, the *MMP* (Matrix Metallo-proteinases) (Jaboin et al. 2011), *KLK* (kallikrein) (Morote et al. 2010), *RNASEL* (encoding ribonuclease L) (Larson et al. 2008), *Wnt* signalling pathway genes (Huang et al. 2010), *IGF1* (*Insulin-like growth factor-1*) (Chang et al. 2013), *cyclin D1* (Yu et al. 2013), *SRD5A* (steroid 5-alpha reductase polypeptide) (Audet-Walsh et al. 2011), *IL10* (Interleukin-10) (Dluzniewski et al. 2012), androgen pathway (Strom et al. 2004) and *EGFR* (epidermal growth factor receptor) genes (Perez et al. 2010). For some of these genes, conflicting results

have been reported and further validation is needed to ascertain their true utility. The utility of some of the GWAS risk SNPs have also been reported by different groups in surgical cohorts. SNPs in chromosome 8q24 and the *MSMB* SNP have been reported to be associated with worse pathological tumour stage and biochemical relapse post-prostatectomy, respectively (Huang et al. 2009; Whitman et al. 2010). However, some groups reported no associations (Kader et al. 2009). The true impact of the risk SNPs in this cohort is, therefore, still unclear.

With regard to androgen deprivation therapy, variants in candidate genes like the androgen transporter genes (*SLCO2B1* and *SLCO1B3*) (Yang et al. 2011), *MEGALIN* (low density lipoprotein-related protein 2) (Holt et al. 2008), *SRC* (sarcoma) (Maki et al. 2006) and genes involved in the steroid hormone pathway (Kohli et al. 2012), have been linked with treatment resistance. Bao et al. in 2011 investigated the association of 19 GWAS risk SNPs with PrCa survival in an androgen deprivation therapy cohort (Bao et al. 2012). They reported that only the risk SNP rs169001979 was associated with survival. However, further validation is needed. The same group also published the association of genetic variations in oestrogen and androgen-binding sites as well as microRNA and microRNA target sites (Huang et al. 2012a; Bao et al. 2011; Huang et al. 2012b). These results are encouraging, but again further confirmatory studies are needed.

There have been no published studies to date analysing the impact of risk SNPs in radiotherapy outcomes. However, four genome-wide association studies have been published investigating the association between genotypes and the development of radiation toxicity. Kerns et al. reported the first GWAS, which found an SNP on the *FSHR* (Follicle Stimulating Hormone Receptor) gene associated with increased rates of erectile dysfunction in African-American men post-radiotherapy (Kerns et al. 2010). Two further GWAS reported by the same group published several SNPs in chromosome 9p21 associated with the development of urinary toxicity, and several SNPs approaching GWAS significance associated with erectile dysfunction, but these need to be validated (Kerns et al. 2013a, Kerns et al. 2013b). Another GWAS by Barnett et al. did not report any SNP that was significantly associated with radiotoxicity (Barnett et al. 2012). It was acknowledged that the low number of patients could have resulted in reduced power to detect any significant difference. These groups are in the radiogenomics consortium and we await further results (West et al. 2010).

To investigate the clinical utility of the risk SNPs in PrCa active surveillance cohorts, a recent study investigated the use of risk scores in predicting adverse outcomes (Goh et al. 2013). No significant association was found but low patient numbers is the main limitation of this good prognosis cohort. For PrCa chemotherapy outcomes, groups have investigated the association of genetic variations in drug metabolism pathways. They report that some polymorphisms are associated with treatment resistance (Sissung et al. 2008). Another gene of interest in this area is the chromosome 8p21 *CLUSTERIN* gene (Chi et al. 2010). Increased expression is thought to predict chemotherapy resistance. There have been as yet no published chemotherapy studies utilising the risk SNPs and this remains an unmet need.

## 5 Future Directions

The clinical utility of the GWAS risk SNPs remains unclear and needs to be established. It has been clear that despite encouraging results from groups reporting some clinical associations, further validation is needed for most studies. Small numbers currently existing in single centre cohorts worldwide will limit the power to detect true differences. It is clear that collaborations are needed to establish larger sample sizes to answer both genetic-clinical and genetic-environmental questions.

International consortia have now been established to not only address these questions but to potentially validate published results. An example is the NIH (National Institute of Health) funded post-GWAS initiatives with the establishment of ELLIPSE (ELucidating Loci Involved in Prostate cancer SuscEptibility) (National Institute of Health 2010). As part of this, the Clinical ELLIPSE Consortium (CEC) was formed to develop risk models, analyse risk profiles and investigate clinical application. Other consortia include The PRACTICAL (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome) Consortium. PRACTICAL, which interacts with ELLIPSE, bringing together researchers interested in the genetic predisposition of PrCa to discover and validate these genetic variants (PRACTICAL 2008).

Efforts are also underway to fully discover the functional aspects of these SNPs within these consortia. A better understanding of this would in turn bring about a better understanding of the pathogenesis and could potentially lead to therapeutic targets and drug discovery as well as chemoprevention options.

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## 6 Conclusions

Technological advancements with improved high-throughput genome sequencing and better analytical as well as computational tools have escalated our discovery of genes associated with PrCa. The common variants could potentially play a major public health role in many different aspects of management. These include better risk stratification in the general population to identify men for targeted screening or to counsel individuals better regarding their own personal risk of cancer. Determining their effect in predicting treatment outcomes or toxicity would also enable clinicians to personalise and tailor specific treatments according to their genetic profile. With the costs of genotyping decreasing and direct-to-consumer testing already offered for the common variants, it is envisaged that a lot of attention will be focussed on this in the coming years. Ascertaining their clinical role remains an important goal for the GWAS community with consortia now established, pooling efforts and resources to move this field forward.

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