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## Refining the prostate cancer genetic association within the *JAZF1* gene on chromosome 7p15.2

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## Abstract

**Background**—Genome-wide association studies (GWAS) have identified multiple genetic variants associated with susceptibility to prostate cancer (PrCa). In the two-stage Cancer Genetic Markers of Susceptibility (CGEMS) prostate cancer scan, a single-nucleotide polymorphism (SNP) rs10486567 located within intron 2 of *JAZF1* gene on chromosome 7p15.2 showed a promising association with PrCa overall ( $p = 2.14 \times 10^{-6}$ ) with a suggestion of stronger association with aggressive disease ( $p = 1.2 \times 10^{-7}$ ).

**Methods**—In the third stage of GWAS, we genotyped 106 *JAZF1* SNPs in 10,286 PrCa cases and 9,135 controls of European ancestry.

**Results**—The strongest association was observed with the initial marker, rs10486567, which now achieves genome-wide significance ( $p = 7.79 \times 10^{-11}$ ,  $OR_{HET}$  1.19; 95%CI = 1.12 – 1.27 and  $OR_{HOM}$  1.37; 95%CI = 1.20 – 1.56). We did not confirm a previous suggestion of a stronger association of rs10486567 with aggressive disease ( $p = 1.60 \times 10^{-4}$  for aggressive cancer,  $n=4,597$ ;  $p = 3.25 \times 10^{-8}$  for non-aggressive cancer,  $n=4,514$ ). Based on a multi-locus model with adjustment for rs10486567, no additional independent signals were observed at chromosome 7p15.2. There was no association between PrCa risk and SNPs in *JAZF1* previously associated with height (rs849140,  $p = 0.587$ ), body stature (rs849141, tagged by rs849136,  $p = 0.171$ ), risk of type 2 diabetes and systemic lupus erythematosus (rs864745, tagged by rs849142,  $p = 0.657$ ).

**Conclusions**—rs10486567 remains the most significant marker for PrCa risk within *JAZF1* in individuals of European ancestry.

**Impact**—Future studies should identify all variants in high LD with rs10486567 and evaluate their functional significance for PrCa.

## INTRODUCTION

Prostate cancer (PrCa) is the most common non-cutaneous cancer in the developed world and the second leading cause of cancer death in men (1,2). The disease is highly treatable when detected early, with an encouraging 5-year survival rate (3). The established risk factors for PrCa are age, ethnicity and family history (3). Heritable factors have been estimated to explain 42% (29–50%) of PrCa risk in individuals of European ancestry (4). PrCa diagnostics based on the blood level of prostate-specific antigen (PSA) can result in 23–45% of overdiagnosis, that is in detection of disease with mild or insignificant clinical manifestations that don't require treatment (5). Several genome-wide association studies (GWAS) have been performed to determine genetic factors that can identify individuals with increased risk of PrCa. More than 25 genomic regions that harbor genetic risk factors for PrCa have been identified to date (6–10).

The discovery component of the Cancer Genetic Markers of Susceptibility project (CGEMS) has reported a two-stage GWAS for PrCa (6). In the first stage, 1,172 individuals with PrCa and 1,157 controls of European ancestry were genotyped for 527,869 SNPs. In the second stage, 26,958 SNPs selected based on their association in stage 1 ( $p < 0.068$ ), were genotyped in a total of 4,020 cases and 4,028 controls (6). The second stage of CGEMS identified SNPs within the 8q24 region, *HNF1B* (*TCF2*) gene, *MSMB* gene and the 11q13 region to be significantly associated with PrCa (6). An observed association for markers in the C-terminal binding protein 2 (*CTBP2*) gene, as well as in the juxtaposed with another zinc finger protein 1 (*JAZF1*), did not reach the threshold of genome-wide significance ( $p = 1.7 \times 10^{-7}$  for *CTBP2* and  $p = 2.14 \times 10^{-6}$  for *JAZF1*). For both genes there was a suggestion that the signal was more strongly associated with the risk of aggressive cancer, defined as Gleason score  $>7$  or disease stage III ( $p = 2.7 \times 10^{-8}$  for *CTBP2* and  $p = 1.2 \times 10^{-7}$  for *JAZF1*) (6).

The goals of the third stage of CGEMS GWAS have expanded to include testing for the presence of independent signals within established candidate regions and conducting a first order mapping of regions identified in CGEMS stage 2. Similar approach has resulted in identification of independent signals within the 8q24 region (10), chromosome 11q13 (11) and *HNF1B* gene on chromosome 17q12 (12). As a part of stage 3, we genotyped 106 *JAZF1* tag SNPs in 10,286 PrCa patients and 9,135 controls of European ancestry. We aimed to confirm the suggestive association observed in stage 2 in a larger data set and to test for presence of stronger or independent association signals within *JAZF1*. We tested for association of rs10486567 with age of cancer diagnosis, family history and aggressiveness of disease. Additionally, we tested whether the variants of *JAZF1* associated with other traits, were also associated with risk of PrCa.

## MATERIALS AND METHODS

### Subjects

Subjects were prostate cancer patients and controls drawn from 10 studies conducted in the US and Europe: Prostate, Lung, Colon and Ovarian (PLCO) (13); American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II) (6); Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (6); CeRePP French Prostate Case-Control Study (CeRePP) (6); Health Professionals Follow-up Study (HPFS) (6); The European Prospective Investigation into Cancer and Nutrition (EPIC)(14); Cohort of Norway (CONOR) (15); The Multiethnic Cohort Study (MEC) (16); Johns Hopkins University (JHU) (17); The Cancer Prostate in Sweden study (CAPS) (18). The counts and characteristics of each study are presented in Supplementary Table 1. The two main PrCa subtypes were defined as non-aggressive (Gleason score < 7 and stage < III) and aggressive (Gleason score  $\geq$  7 or stage  $\geq$  III) cancer at the time of diagnosis.

### SNP selection

The design, SNP selection and analysis of the study were described in details in Supplementary Material, Yeager et al. 2009 (10). In brief, of 7,034 SNPs were selected based on the previous GWAS results (6), and 115 of these SNPs were from *JAZF1* gene. The *JAZF1* targeted region was selected based on 0.2 cM HapMap recombination map centered on rs10486567 (chr7: 27290918–27826082). A preliminary set of 7 tags was selected using rs10486567 as an obligate-include and tagging the region at a  $D^2 > 0.6$  based on genotypes from HapMap CEU (European ancestry) (19). A final set of 127 tags was chosen by using rs10486567 as an obligate-include and by tagging the preliminary list of tags at an  $r^2 > 0.8$  in CEU (European), YRI (African) and CHB/JPT (Asian) HapMap samples (Supplementary Table 2A for list of all SNPs). All 7,034 SNPs selected for stage 3, were genotyped using a custom Illumina iSelect™ assay chip in 9,135 controls and 10,286 prostate cancer cases. Of 7,034 selected SNPs 6,313 SNPs passed manufacture and QC and provided > 90% genotype calls. Of 115 *JAZF1* SNPs, 9 SNPs failed to provide genotype data or resulted in low genotype call rates (<90%) and were excluded from the analysis. Genotype quality control, assessment of call rates, assessment of unique subjects, analysis of duplicate DNA samples, fitness for Hardy–Weinberg proportion in control DNA and subject exclusions are described in detail in Supplementary Methods from Yeager et al., 2009 (10).

### Admixture estimation

Of 7,034 SNPs on the stage 3 iSelect™ assay chip, 1,399 SNPs were selected and used for the detection of population structure as previously described (6). The population stratification analysis was done using the STRUCTURE program by merging the genotypes from all studies with those of the reference HapMap populations. The number of clusters (the “k” parameter) was set to three and the CEU, YRI and JPT+CHB samples were each specified to a different

cluster schematically representing populations of European, African and Asian origin, respectively. The origin of the study samples was left unspecified. A total of 372 subjects (1.8%) were estimated to have less than 80% European ancestry and were excluded from analysis. All individuals that had at greater than 80% European ancestry were retained for the study, regardless of their self-reported origin.

### Principal components analyses

Principal components analysis (PCA) was performed using the same 1,399 SNPs included for population stratification. These results were based on the remaining subjects after removal of individuals with admixed ancestry as described above. A Wilcoxon rank test was performed to check correlations with the case/control status for the top 5 eigenvectors. PC1 in JHU and top 3 PCs in CAPS studies showed significant differences between cases and controls. These principal components were used as covariates for association studies in JHU and CAPS sample sets.

### Statistical software

Tag SNP selection was performed using the GLU software package (20) using the HapMap CEU, JPT+CHB and YRI data. Models were adjusted for study and significant principal components per study. Population stratification analysis was performed with STRUCTURE software (21), Principal Component Analysis was performed with EIGENSTRAT software (22).  $\chi^2$  tests, Student T-tests, and logistic regression were used to compare the basic characteristics between cases and controls using SAS/STAT® system (SAS Institute Inc.). For single-marker case-control analyses, logistic regression under an additive genetic model was performed for each SNP adjusting for study site, and significant principle components using PLINK (23). A conditional analysis was also performed under additive model to account for the effect of SNP rs10486567 (0, 1 or 2 risk alleles). The association and LD plots were generated with snp.plotter, version 0.2 (24).

## RESULTS

We performed the third stage of CGEMS in 10,286 PrCa patients and 9,135 controls of European ancestry drawn from ten studies conducted in Europe and the United States (10) (also described in Methods and Supplementary Table 1). As part of this effort, we genotyped 106 tag *JAZF1* SNPs chosen on the basis of a tiered tagging strategy, the details of which have been published separately (10). First, the target region was bounded by the 0.2 cM HapMap recombination map (chr7: 27290918–27826082). A preliminary set of 7 tags was selected using rs10486567 as an obligate-include and tagging the region at a  $D^2 > 0.6$  based on genotypes from HapMap CEU (European ancestry) (19). A final set of 127 tags was chosen by using rs10486567 as an obligate-include and by tagging the preliminary selected 7 tags at an  $r^2 > 0.8$  in CEU (European), YRI (African) and CHB/JPT (Asian) HapMap samples (Supplementary Table 2A for list of all SNPs). 21 of these selected SNPs failed design, or showed poor performance. The successfully genotyped 106 SNPs covered a region of 275 Kb, starting from 25 Kb upstream of *JAZF1* and well into intron 2 (Figure 1).

Based on the genotype association test adjusted for study and significant principal components per study to account for subtle differences in population substructure (described in Method section), the strongest association was observed for the originally reported SNP, rs10486567 (6), with the compelling level of association below genome-wide significance ( $p = 7.79 \times 10^{-11}$ ,  $OR_{HET} 1.19$ ; 95%CI = 1.12 – 1.27 and  $OR_{HOM} 1.37$ ; 95%CI = 1.20 – 1.56) (Table 1 and Supplementary Tables 3, and 2A). The second strongest association was observed for SNP rs10807843, also located within intron 2, approximately 16 Kb from rs10486567 ( $D' =$

1.0,  $r^2 = 0.893$  in 9,135 controls from CGEMS) (Table 1). The results for all SNPs are presented in Supplementary Table 2A.

We also explored several outcomes with respect to rs10486567 and found no association with age of diagnosis ( $p = 0.365$ ), family history ( $p = 0.640$ ) or aggressiveness of PrCa ( $p = 0.324$ , Table 2). The association for rs10486567 was stronger for non-aggressive PrCa (Gleason score  $<7$  or stage  $<III$ ),  $p = 1.60 \times 10^{-4}$  for aggressive cancer,  $n = 4,597$  and  $p = 3.25 \times 10^{-8}$  for non-aggressive cancer,  $n = 4,514$  (Table 2 and Supplementary Tables 2B and 2C). Our sample set was enriched for individuals older than 60 years and without family history of PrCa, but the odds ratios (ORs) for association of rs1086567 with PrCa were comparable in each of the subgroups (Table 3).

To test for presence of additional independent association signals within *JAZF1*, we performed a genotype association test adjusting for rs10486567. Only a weak association was observed for SNP rs3919460 ( $p = 0.0053$ , Supplementary Table 2A). We also examined whether the variants of *JAZF1* associated with other traits would affect the genetic susceptibility to PrCa. In our samples, rs849140, previously associated with height ( $p = 5.3 \times 10^{-8}$ ) (25), was not associated with PrCa ( $p = 0.587$ ); rs849141, previously reported to be associated with height and body stature ( $p = 3.26 \times 10^{-11}$ ) (26), was well tagged by rs849136 ( $r^2 = 1.0$  with rs849141 in CEU HapMap) but was not associated with PrCa ( $p = 0.171$ ); the T2D-associated SNP rs864745 ( $p = 5.0 \times 10^{-14}$ ) (27) was tagged by rs849142 ( $r^2 = 1.0$  with rs864745 in CEU HapMap), which was also associated with SLE ( $p = 1.54 \times 10^{-10}$ ) (28) but showed no association with PrCa ( $p = 0.657$ , Table 4).

## DISCUSSION

Our study clearly confirms common SNPs in *JAZF1* are associated with risk for PrCa overall and establishes this candidate gene for PrCa susceptibility in individuals of European ancestry. We show that rs10486567, previously reported as a promising association ( $p = 2.14 \times 10^{-6}$ ) (6), is now conclusively associated with risk of PrCa ( $p = 7.79 \times 10^{-11}$ ). The association was for risk of PrCa overall and was not specific for cases with aggressive cancer, as was previously suggested (6), or cases with family history or early/late age of disease diagnosis. Association analysis for 106 *JAZF1* SNPs with adjustment for rs10486567 failed to reveal any independent signal, indicating that rs10486567 is a marker representing a single common allele associated with PrCa risk within *JAZF1*.

Located in intron 2 of *JAZF1*, rs10486567 is not predicted to affect mRNA expression, splicing, or transcription factor or miRNA-binding sites. Further deep resequencing efforts in PrCa patients together with information provided by the 1000 Genomes project (29) will help to catalog all common and rare variants in strong LD with rs10486567 in order to determine the optimal markers for investigation of their possible functional effects for PrCa.

The risk allele G of rs10486567 is the major allele in Europeans (0.73) and Africans (0.68), while it is rare in East Asians (0.16) based on allele frequencies in HapMap (19). Of note, PrCa is less frequent in individuals of Asian ancestry (30). Despite differences in allele frequencies, an association between rs10486567 and PrCa has been noted in African-Americans, Latinos, Japanese Americans and Native Hawaiians, but due to the small sample sizes in non-Caucasian populations the results often did not reach conclusive statistical significance (31). In the first stage of GWAS for PrCa conducted by PRACTICAL consortium that included 1,854 cases and 1,894 controls of European ancestry, rs10486567 did not meet the criteria ( $p < 0.05$  or  $p\text{-trend} < 0.01$ ) to be followed up in larger sample sets (8). It is important to note that the first stage of the GWAS mentioned above is not sufficiently powered to detect most variants with modest effect size, nominally in the range of 1.1 to 1.25, as has been observed for rs10486567.

This SNP has also been associated with PrCa in an independent set of 1,725 cases and 35,392 controls of European ancestry with OR 1.13 and  $p = 4.4 \times 10^{-3}$  (32).

Currently, there is no biological explanation for the functional implications for *JAZF1* in prostate carcinogenesis. Intra-chromosomal fusions between *JAZF1* and *SUZ12* (33) or *JAZF1* and *PHF* (34) have been identified in endometrial cancer but there are no reports on these or other fusions of *JAZF1* in PrCa. It will be important to determine the molecular functions of *JAZF1* that can be important for several traits with which genetic variants within *JAZF1* have recently been associated. *JAZF1* is a large gene of approximately 350 kb. Rs10486567, associated with risk of PrCa, is located in intron 2. Several SNPs located close to each other in another LD block within intron 1 and ~210 Kb centromeric from rs10486567, have been associated with height (25), body stature (26) and increased risk of type 2 diabetes (T2D) (27) and systemic lupus erythematosus (SLE) (28). We agnostically tested all these SNPs in our set of samples but observed no association with PrCa. An inverse correlation between the risk of PrCa and T2D has been observed in epidemiological studies (35–37), a finding consistent with the results for genetic variants within the *HNF1B* (*TCF2*) gene (6,38, 39). Although the inverse correlation between PrCa and T2D has also been suggested for variants in *JAZF1* (40), our results did not show an effect of the T2D risk variant on susceptibility to PrCa.

In conclusion, our study has established rs10486567 within *JAZF1* on chromosome 7p15.2 as a bona-fide marker for association with susceptibility to PrCa in individuals of European ancestry. Here, we intentionally studied only tag SNPs from the region to test for presence of independent association signals. Future studies should be conducted to identify all common and uncommon variants by deep sequence analysis that are in strong LD with rs10486567 in order to nominate the optimal variants for evaluation of functional significance for susceptibility to PrCa.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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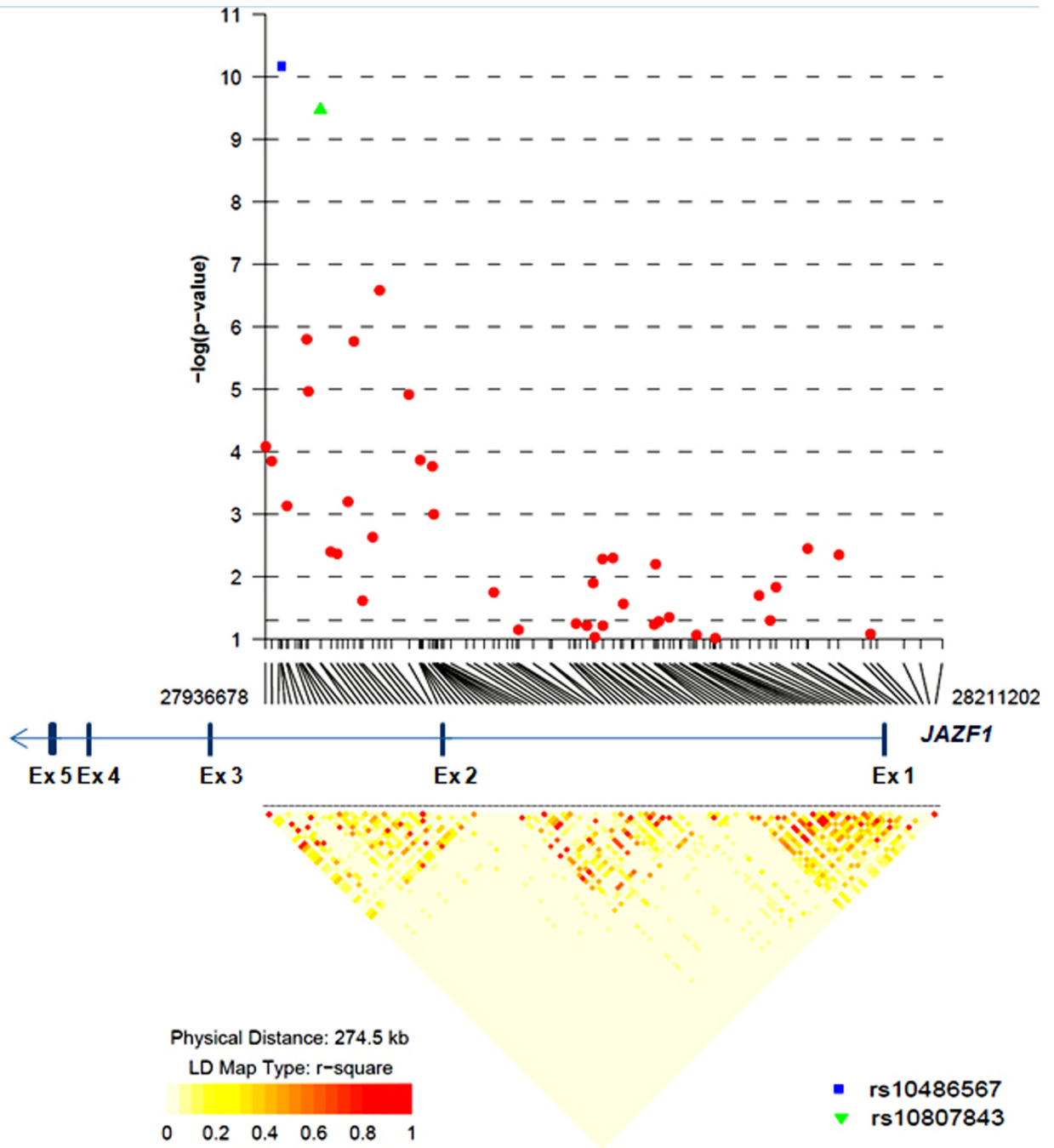
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**Figure 1.** LD structure and association results for 106 SNPs distributed over 275 Kb covering 25 Kb of promoter region through part of intron 2 of *JAZF1* gene. LD plot is based on all samples (10,286 prostate cancer patients and 9,135 controls) of European ancestry.

Table 1

Prostate cancer risk association results for top 3 *JAZF1* SNPs in 10,286 patients and 9,135 controls

SNP (Risk allele)	Location	$r^2$ with rs104865 67	Risk allele freq.		$\chi^2$ statistics	$I$ p-value	Heterozygous		Homozygous	
			Controls	Cases			OR	95% CI	OR	95% CI
rs10486567 (G)	27,943,088	--	0.759	0.788	46.55	$7.79 \times 10^{-11}$	1.19	1.12–1.27	1.37	1.20–1.56
rs10807843 (T)	27,958,915	0.893	0.777	0.805	43.88	$2.96 \times 10^{-10}$	1.2	1.12–1.27	1.35	1.17–1.56
rs38504 (C)	27,982,859	0.463	0.79	0.812	26.54	$1.73 \times 10^{-6}$	1.17	1.10–1.24	1.18	1.02–1.36

Results for top 3 *JAZF1* SNPs of 106 tested.

$I$  p-values are for genotype association test (additive model) adjusted for study and significant principal components (see Supplementary Methods).

**Table 2**

Association of rs10486567 with clinical traits in prostate cancer patients

Trait	rs10486567 genotypes (number of cases)			<sup>I</sup> p-value
	AA 451	AG 3423	GG 6338	
Age at diagnosis	66.56 ± 7.58	66.36 ± 7.50	66.23 ± 7.49	0.365
Positive family history, %	17.15	17.18	17.97	0.64
Aggressive disease, %	52.1	51.32	49.82	0.324

<sup>I</sup>p-values are for  $\chi^2$  test or analysis of variances

**Table 3**

Prostate cancer risk for rs10486567 of *JAZF1* stratified by potential risk factors

Stratified variable	Number Controls/		Risk allele freq.		<i>I</i> <sup>1</sup> p-value	Heterozygous			Homozygous		
	Cases	Controls	Cases	Controls		OR	95%CI	<sup>3</sup> p-value	OR	95%CI	<sup>3</sup> p-value
Age < 60	1853/1761	0.767	0.799	0.07	1.12	0.77–1.63	0.602	1.31	0.91–1.89	0.549	
Age ≥ 60	6539/7771	0.756	0.785	2.74 × 10 <sup>-8</sup>	1.14	0.98–1.34		1.37	1.17–1.59		
No family history	6480/7087	0.758	0.787	5.75 × 10 <sup>-8</sup>	1.11	0.95–1.31	0.335	1.34	1.14–1.57	0.384	
With family history	642/1521	0.759	0.794	0.041	1.39	0.91–2.14		1.62	1.07–2.45		
<sup>2</sup> Non-aggressive cancer	9109/4510	0.754	0.792	3.25 × 10 <sup>-8</sup>	1.21	1.12–1.31	0.528	1.41	1.19–1.68	0.25	
<sup>2</sup> Aggressive cancer	9109/4598	0.754	0.781	1.60 × 10 <sup>-4</sup>	1.14	1.05–1.23		1.29	1.10–1.53		

<sup>1</sup> p-values are for additive logistic regression model adjusted for study and significant principle component per study

<sup>2</sup> compared to all controls;

<sup>3</sup> Breslow-Day test for homogeneity

**Table 4**

Association results for SNPs of *JAZF1* previously associated with other traits

*SNP (Minor allele)	Location	MAF		$\chi^2$ statistics		$\chi^2$		Heterozygous		Homozygous		Adjusted for rs10486567 <i>I</i> p-value
		Controls	Cases	p-value	OR	95% CI	OR	95% CI	OR	95% CI		
rs849140 (T)	28,150,227	0.397	0.396	1.07	1.07	0.587	1.03	0.96-1.09	0.99	0.91-1.08	0.829	
rs849136 (A)	28,141,482	0.281	0.287	3.53	3.53	0.17	1.06	0.99-1.13	1.03	0.92-1.15	0.199	
rs849142 (G)	28,152,416	0.496	0.498	0.84	0.84	0.657	1.03	0.96-1.11	1.01	0.93-1.10	0.899	

\* rs849140 is associated with height; rs849136 is in  $r^2=1.0$  with rs849141 associated with body stature;

rs849142 is in  $r^2=1.0$  with rs864745 associated with type 2 diabetes and systemic lupus erythematosus (SLE).

*I* p-values are from logistic additive genetic model adjusted for study and significant principal component per study;

rs10486567 was included as a covariate with 0, 1 and 2 allele dosage coding.