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Polymorphisms in genes in the androgen pathway and risk of Barrett' s esophagus and esophageal adenocarcinoma

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Abstract

The strong male predominance in Barrett' s esophagus (BE) and esophageal adenocarcinoma (EAC) remains inadequately explained, but sex hormones might be involved. We hypothesized that single nucleotide polymorphisms (SNPs) in the androgen pathway influence risk of developing BE and EAC. This genetic-epidemiological analysis included 14 studies from Australia, Europe and North America. Polymorphisms in 16 genes coding for the androgen pathway were analyzed using a gene-based approach: versatile gene-based test association study (VEGAS). This method evaluates associations between a trait and all SNPs within a specific gene rather than each SNP marker individually as in a conventional GWAS. The data were stratified for sex, body-mass index, waist-to-hip ratio, tobacco smoking and gastroesophageal reflux status. Included were data from 1,508 EAC patients, 2,383 BE patients, and 2,170 control participants. SNPs within the gene *CYP17A1* were associated with risk of BE in the sexes combined (p=0.002) and in males (p=0.003), but not in females separately (p=0.3). This association was found in tobacco smokers (p=0.003), and in BE patients without reflux (p=0.004), but not in non-smokers (p=0.2) or those with reflux (p=0.036). SNPs within *JMJD1C* were associated with risk of EAC in females (p=0.001). However, none of these associations replicated in a subsequent sample. Fourteen other genes studied did not reach statistically significant levels of association with BE, EAC, or the combination of BE and EAC, after correcting for the number of genes included in the analysis. In conclusion, genetic variants in the androgen-related genes *CYP17A1* and *JMJD1C* might be associated with risk of BE and EAC, respectively, but replication data with larger sample sizes are needed.

Keywords

Genome-Wide Association Study; Barrett esophagus; Esophageal Neoplasms; Neoplasm; Hormones; Gonadal Steroid Hormone

Introduction

The reasons for the strong male predominance in the incidence of esophageal adenocarcinoma (EAC) and its precursor condition Barrett' s esophagus (BE) remain inadequately known.[1,2] Understanding the basis for the male predominance in these conditions could bring new etiologic insights.[1] Gastroesophageal reflux disease, obesity, and tobacco smoking are the main known risk factors,[3,4] but they do not entirely explain the current male predominance in EAC or BE in western countries.[5,6] Emerging evidence suggests that genetic factors may contribute to the etiology of BE and EAC,[7–11] but these factors have not been investigated with respect to sex-specific differences. It has been hypothesized that sex hormones are involved in the male predominance.[12] Most research addressing the influence of sex hormones has examined the female sex hormone estrogen, which has failed to provide robust evidence of strong associations.[1] Another potentially relevant sex hormonal exposure is androgens, but the literature addressing the role of the male sex hormone androgen in the etiology of BE and EAC is limited. However, a recent case-control study found an increased risk of BE among participants with high levels of free testosterone and low levels of estrone sulfate.[13] Androgen receptors are known to be expressed in EAC,[14] and the risk of EAC seems to be decreased in prostate-cancer patients using anti-androgen therapy.[15,16] However, to the best of our knowledge no study has evaluated single nucleotide polymorphisms (SNPs) in genes coding for the androgen pathway in relation to risk of BE or EAC. We conducted a large genetic-epidemiologic study to test whether SNPs in 16 genes encoding components of the androgen pathway are associated with the risk of developing BE or EAC.

Material and Methods

Study Design

We used summary data from a genome-wide association study (GWAS) conducted by the Barrett' s and Esophageal Adenocarcinoma Consortium (BEACON). The study was based on data from 14 cohort and case-control studies from Australia, Europe (England, Ireland and Sweden), and North America (Canada and the United States). Most of these studies had a population-based design. The data were used to study the associations between BE and EAC in relation to SNPs in 16 genes known to be involved in the androgen pathway: 1) Sex hormone-binding globulin *(SHBG)*; 2) Steroid-5-Alpha-Reductase Alpha Polypeptide 1 (3-Oxo-5 Alpha-Steroid) *(SRD5A1)*; 3) Steroid 5 Alpha-Reductase 3 *(SRD5A3)*; 4) Cytochrome P450, Family 17, Subfamily A, Polypeptide 1 *(CYP17A1)*; 5) Cytochrome P450, Family 7, Subfamily A, Polypeptide 1 *(CYP7A1)*; 6) Cytochrome P450, Family 1, Subfamily A, Polypeptide 1 *(CYP1A1)*; 7) Cytochrome P450, Family 11, Subfamily B, Polypeptide 1 *(CYP11B1)*; 8) Cytochrome P450, Family 11, Subfamily B, Polypeptide 2 *(CYP11B2)*; 9) Hydroxysteroid (11-Beta) Dehydrogenase 1 *(HSD11B1)*; 10) Aldo-Keto

Reductase Family 1, Member D1 *(AKR1D1)*; 11) Aldo-Keto Reductase Family 1, Member C4 *(AKR1C4)*; 12) Cytochrome P450, Family 19, Subfamily A, Polypeptide 1 *(CYP19A1)*; 13) Jumonji Domain Containing 1C *(JMJD1C)*; 14) Hydroxysteroid (11-Beta) Dehydrogenase 2 *(HSD11B2)*; 15) UDP Glucuronosyltransferase 2 Family, Polypeptide B4 *(UGT2B4)*, and 16) 3-oxo-5-alpha-steroid 4-dehydrogenase 2 (*SRD5A2)*.[17] We could not include the Androgen Receptor *(AR)* and the Family With Sequence Similarity 9, Member B *(FAM9B)* genes, because no SNPs were genotyped within these genes, which are both on chromosome X. Thus, the final number of genes was 16.

Replication analyses of significant associations were performed in an independent set of data from the 1958 British Birth Cohort.[18] More information about these participants can be found in the supplementary text.

Genotyping

Discovery Set—Genotyping of DNA from buffy coat samples was performed using the Illumina HumanOmni1-Quad platform. Annotations were based on version H of the Illumina product files and corresponded to the Genome Reference Consortium GRCh37 release. The quality control (QC) has been published previously[10]. In brief, samples with call rates <95% that were an admixture of DNA from more than one patient (n=18) or had low DNA input and a weak signal (n=14) were removed from further analysis. The remaining 6,448 samples, including HapMap controls (n=68) and duplicate samples (n=67), underwent quality assurance (QA) and quality control (QC) as follows. Batch and plate effects were evaluated using intensity data and allelic frequency and checked for case-control associations. No important batch or plate effects or case-control associations with experimental factors were found. We used heterozygosity, sex chromosome intensity data, identity by descent (IBD) analysis, visualization of B allele frequency (BAF), and log R ratio (LRR) plots to identify samples that had one or more of misannotated sex, unexpected relatedness, or were sample mixtures. Two mixed samples were discovered and removed from further analysis. In the case of misannotated sex or unexpected relatedness, if the source of the discrepancy could be identified, the samples were kept; otherwise they were removed (n=47) from further analysis. Finally, 6,061 samples, all with European ancestry, remained for analysis: 1,508 from EAC patients, 2,383 from BE patients, and 2,170 from control participants.

SNPs were excluded if they had missing call rates >5%, Hardy Weinberg equilibrium p-values among controls $\leq 10e^{-4}$, discordances among any of the duplicate pairs, Mendelian errors, or minor allele frequencies <1%. After QA/QC, 802,272 SNPs remained and were used for the initial GWAS analysis from which we chose 389 SNPs located within the 16 selected genes for use in the versatile gene-based test association study (VEGAS) analysis described below.

Replication Set—The DNA samples were genotyped using the Fluidigm TM high-throughput platforms and Fluidigm 96.96 Dynamic Arrays according to the manufacturer' s instructions and were read using the Fluidigm EP1 commercial system. Each array had a capacity for genotyping 96 samples against sets of 96 SNPs. DNA samples were plated in

sets of 96 samples and combined into 384-well arrays for genotyping, with the case and control samples mixed on each 384-well plate. Genotypes were automatically called using BioMark Genotyping Analysis software, but all cluster plots were also checked manually and adjusted as needed. The Barrett's cases were identified at endoscopy with a confirmed histopathological diagnosis of intestinal metaplasia from the UK Barrett's Oesophagus Gene Study as previously described.[10] Control paricipants were ascertained from the Wellcome Trust Case Control Consortium 2 (WTCCC2) by frequency matching on age (five-year age bands) and sex to Barrett's esophagus cases excluding individuals with a past history of cancer (excluding non-melanoma skin cancer). All recruited participants gave informed consent and the studies have been approved by the relevant institutional ethics review board.

The WTCCC2 study participants (control) were of European ancestry, as determined by projection onto the first two principal components of PCA of HapMap individuals, and were genotyped on a custom version of the Illumina Human1.2M-Duo array.[19]

Individuals with missing call rates >2% were removed from the analysis. SNPs were excluded based upon the same criteria as in the discovery set. After QC, 490,845 SNPs remained, from which we selected SNPs potentially associated with BE or EAC in the discovery set for use in the versatile gene-based test association study (VEGAS) analysis described below. The final replication set included 4613 participants: 851 BE patients, 977 EAC patients), and 2785 control participants.

Association Analysis

BE and EAC were analyzed as separate outcomes and then were combined. The combination was considered appropriate since our previous study found a shared genetic background for BE and EAC.[20] Case-control analyses were conducted with a log-additive logistic regression model where case status was regressed on each SNP genotype. The included covariates were sex, age and the first four principal component eigenvectors from principal component analysis (PCA). Eigenvectors were included as covariates to account for population stratification arising from ancestry. P-values for each SNP were calculated for each case type (EAC, BE and EAC+BE) and used as input for the VEGAS.

Stratified Analysis

To investigate potential gender differences, we stratified the analysis by sex. Previous studies have shown that gastroesophagael reflux disease, high body mass index (BMI) and tobacco smoking are risk factors for both BE and EAC.[21–24] We therefore stratified participant data for gastroesophageal reflux disease (weekly reflux symptoms and no reflux symptoms), BMI (lean/normal BMI ≤25 kg/m^2, overweight BMI >25 and ≤30 kg/m^2, and obese BMI > 30 kg/m^2), waist-to-hip ratio (WHR) (lean WHR ≤0.9 and obese WHR >0.9), and smoking status (non-smokers and ever smokers). Participants with missing data on any of these variables were excluded from the analysis. The stratified analyses were not further stratified on sex due to power issues.

Versatile Gene-Based Test Association Study (VEGAS)

VEGAS is a gene-based approach that considers an association between a trait and all SNPs within a specific gene rather than each SNP marker individually as in a conventional GWAS.[25] Even if the individual effect sizes at any given SNP are small, collectively all SNPs within a gene could still account for a substantial proportion of variation in risk. Therefore, studies of combined risk alleles might identify candidate genes influencing disease occurrence. By combining the effects of all SNPs in a gene into a statistic and correcting for linkage disequilibrium (LD), the gene-based procedure can assess combined effects between SNPs that would be missed in a standard GWAS. In this study, VEGAS was used to examine associations between androgen-pathway gene variants and risk of BE or EA.[20] In brief, VEGAS explores associations on a per-gene basis using the p-values from all SNPs within a defined gene. An extended range of 10kb (upstream and downstream of the gene) for each gene was used. VEGAS corrects for LD as well as the number of SNPs within each gene. VEGAS takes account of LD between markers in a gene by using simulation based on the LD structure of a set of reference individuals, or, as in this study, using a custom set of individuals whose genotype information was available, i.e. the same individuals as analysed.[25] A Bonferroni corrected p-value of 0.003 was considered statistically significant since the gene-based test included 16 genes (0.05/16=0.003). We also investigated if any single SNPs within each of the studied genes showed any independent effect on risk of BE, EAC or BE+EAC. For this approach, we used a Bonferroni corrected p-value by dividing 0.05 by the number of SNPs within each gene.

Results

Study Participants

The age and sex distributions of the study participants in the discovery set (1508 EAC case patients, 2383 BE case patients, and 2170 control participants) were similar in the case groups and the control groups (Table 1). However, for the replication set (977 EAC case patients, 851 BE case patients, and 2785 control participants) the age and sex distribution differed between the case and control groups as detailed in Table 1.

Polymorphisms in the Androgen Pathway and risk of Barrett' s Esophagus and Esophageal Adenocarcinoma in the Discovery Set

In both genders combined, SNPs in *CYP17A1* were statistically significantly associated with risk of BE (p=0.002; Table 2). Table 3 shows the results for the SNP with the lowest p-value in each gene. Only one single SNP within *CYP17A1* was associated with BE after correction for multiple testing (rs4919686, p=0.001), which suggests that most of the association for this gene was due to this SNP. SNPs in *CYP17A1* were associated with BE risk in males only (p = 0.003; Table 4), and an analysis stratified for tobacco smoking revealed an association between SNPs in *CYP17A1* and risk of BE in smokers (p=0.003), but not in non-smokers (Supplementary Table 2a). We also revealed an association between SNPs in *CYP17A1* and BE risk in participants not suffering from reflux disease (p=0.004), but not in participants with reflux (Supplementary Table 2a). None of the other 15 genes reached statistically significant associations with BE, EAC or BE+EAC (Table 2). However, sex stratified analysis showed that *JMJD1C* was associated with risk of EAC in females

(p=0.001), but not in males (Table 4). None of the other stratified analyses revealed any significant associations with either of the phenotypes (Supplementary 2a–c).

Polymorphisms in JMJD1C and CYP17A1 and risk of Barrett' s Esophagus and Esophageal Adenocarcinoma in the Replication Set

We analyzed the replication set to examine the positive associations between SNPs in *CYP17A1* and risk of BE and SNPs in *JMJD1C* and risk of EAC in females found in the discovery set. No statistically significant association was found for SNPs in *CYP17A1* in males and females with BE (p=0.19) or for SNPs in *CYP17A1* and BE in males (p=0.27; Supplementary Table 3). The association found between SNPs in *JMJD1C* and risk of EAC in females was not significant in the replication set (p=0.53; Supplementary Table 3).

Discussion

This study found an association between SNPs in the androgen-related genes *CYP17A1* and risk of BE in males and both sex combined and *JMJD1C* and risk of EAC in females, but these associations were not found in the replication set. SNPs in the other 14 tested genes in the androgen pathway did not show any statistically significant influences on the risk of BE, EAC or BE+EAC.

Strengths of this study include the population-based design, the extensive data on genetic variants through the assessment of SNPs of relevant genes, and sample sizes that exceed those of most previous studies of BE and EAC. However, the limited number of female patients with BE or EAC makes it difficult to assess potential associations in females only or to ascertain potential differences in associations between the sexes. Additionally, statistical power decreased in sub-group analyses stratifying for covariates. Risk of type I errors is appreciable with large numbers of independent hypotheses, but Bonferroni correction is an established method to address such errors. Nevertheless, chance cannot be dismissed as a possible explanation for the potential associations found, particularly in light of the negative replication findings. Also, the lack of other associations might be due to type II errors. Moreover, no direct evidence is available to show that the gene variants addressed actually influence levels of androgen.

The lack of confirmation of the initial associations seen in the replication dataset should be interpreted cautiously. The statistical power was more limited in the replication set. Moreover, in each of the two genes, the set of genotyped SNPs between the datasets were not identical. Although both the discovery and replication set were of European ancestry, the discovery participants consisted mainly of individuals from the US and Australia (Supplementary Table 1), while the replication set was from only the UK. Also, the replication set had a higher proportion of females included as control participants compared to case patients, and the sex distribution was also different between case patients and control participants for the replication, which might influence the results.

To the best of our knowledge, no previous genetic study has addressed the specific hypothesis tested in the present study. However, some studies have found that anti-androgen therapy might decrease risk of EAC.[14,15] The possible associations found in the present

study in combination with available epidemiologic evidence should prompt further research addressing the role of androgens in the etiology of BE and EAC and whether the male predominance might be explained by differences in androgen exposure. The present study was unable to examine risk associations with SNPs in *AR*, which could also be informative. The potential associations with SNPs in *CYP17A1* might be interesting, since at least one functional SNP in this gene (rs743572) has been found to be of carcinogenic relevance in some tumors.[26, 27] Interestingly, this SNP was nominally significant in our data (p=0.009 for BE and p=0.040 for BE+EAC). Moreover, the SNP with the lowest p-value in this study (rs4919686) has been associated with androgen-related disease occurrence.[28] The *CYP17A1* association with BE, but not with EAC, might be explained by differences in effects of genes involved in the development or that *CYP17A1* only has an importance in the development of BE, or a smaller effect on EAC than what we were able to pick up in this study. Regarding SNPs in the gene *JMJD1C*, GWAS-studies have found associations with testosterone levels[29] and sex-hormone binding globulin levels,[30] and such SNPs might also be of relevance for carcinogenesis.

The sex differences in associations are not likely to be explained by sex difference in the exposure to environmental risk factors, i.e. reflux, obesity and tobacco smoking, since the strengths of associations with EAC and BE are similar in men and women.[5,6] Regarding the association with BMI, it has been argued that abdominal adiposity, the typical male fat distribution, may contribute to the male predominance of EAC, since abdominal obesity is associated with an elevated risk of EAC independent of BMI.[22,31] However, a stratified analysis by BMI found no evidence of an increased male predominance among overweight individuals compared with lean, which argue against abdominal obesity as a factor contributing to the male predominance.[32] The slope of the increase curve in the incidence of EAC is similar in both sexes, but the increase starts at a much later age in women.[33] These factors taken together seem to argue in favor of sex hormonal influence.

In conclusion, although this large-scale genetic-epidemiological study does not provide strong overall support for polymorphisms in the androgen pathway being strongly associated with the risk of BE or EAC, it cannot dismiss the hypothesis that polymorphisms in *CYP17A1* and *JMJD1C* might be associated with these diseases. However, these results need to be confirmed in independent studies with large sample size.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Impact Statements

The reasons for the strong male predominance in Barrett' s esophagus and esophageal adenocarcinoma remain unknown, but sex hormonal influence has been suggested. This is the first genetic-epidemiologic study addressing genetic variants in the aetiology of Barrett' s esophagus and esophageal adenocarcinoma. The results show that genetic variants in the androgen-related genes CYP17A1 and JMJD1C might be associated with risk of BE and EAC, respectively.

Table 1

Characteristics of the study participants with Barrett's esophagus (BE), esophageal adenocarcinoma (EAC), or either of these (BE+EAC), as well as control participants.

	Discovery set				Replication set		
	BE *Number (%)*	**EAC** *Number (%)*	**EAC+BE** *Number (%)*	**Controls** *Number (%)*	**BE** *Number (%)*	**EAC** *Number (%)*	**Controls** *Number (%)*
Total	2383 (100)	1508 (100)	3891 (100)	2170 (100)	851 (100)	977 (100)	2785 (100)
Men	1808 (76)	1333 (88)	3141 (81)	1704 (79)	634 (76)	848 (87)	1426 (51)
Women	575 (24)	175 (12)	750 (19)	466 (21)	217 (24)	129 (13)	1359 (49)
Age (both sexes, years)							
<50	401 (17)	125 (8)	526 (14)	304 (14)	81 (10)	22 (2)	0 (0)
50–59	630 (26)	365 (24)	995 (25)	551 (26)	223 (26)	100 (10)	2785 (100)
60–69	618 (26)	496 (33)	1114 (29)	745 (34)	303 (36)	410 (42)	0 (0)
≥70	734 (31)	522 (35)	1256 (32)	570 (26)	244 (29)	445 (46)	0 (0)

Table 2

Gene-based analysis of genes known to regulate androgen levels and risk of Barrett' s esophagus (BE), esophageal adenocarcinoma (EAC), and BE and EAC combined (BE+EAC), presented as P-values. P-values in bold are statistically significant at Bonferroni-corrected p-value of 0.05/16.

GENE	CHR	N[a]	Start position (bp)	Stop position (bp)	BE	EAC	BE+EAC
					P	P	P
HSD11B2	16	7	67465035	67471455	0.194	0.412	0.185
SHBG	17	15	7517381	7536699	0.811	0.415	0.801
SRD5A1	5	26	6633499	6669674	0.483	0.734	0.596
SRD5A3	4	22	56232767	56251746	0.736	0.181	0.714
UGT2B4	4	29	70345882	70391731	0.675	0.636	0.939
SRD5A2	2	25	31749655	31806039	0.163	0.983	0.549
CYP17A1	10	15	104590287	104597289	**0.002**	0.454	0.016
AKR1C4	10	21	5238797	5260909	0.689	0.330	0.408
JMJD1C	10	20	64926982	65225879	0.240	0.093	0.227
CYP7A1	8	20	59402736	59412719	0.637	0.755	0.602
CYP11B1	8	21	143953772	143961235	0.564	0.770	0.621
CYP11B2	8	21	143991974	143999258	0.825	0.763	0.802
CYP1A1	15	9	75011882	75017950	0.944	0.250	0.740
CYP19A1	15	60	51500253	51630794	0.436	0.623	0.523
HSD11B1	1	28	209859524	209908294	0.344	0.964	0.842
AKR1D1	7	24	137761177	137803049	0.799	0.533	0.784

[a]Number of SNPs within each gene.

Table 3

Most significant single nucleotide polymorphisms (SNPs) within each gene and risk of Barrett' s esophagus (BE), esophageal adenocarcinoma (EAC), and BE and EAC combined. P-values in bold are statistically significant when Bonferroni adjusting each p-value for the number of SNPs within each gene.

GENE	N[a]	BE		EAC		BE+EAC	
		SNP	P	SNP	P	SNP	P
HSD11B2	7	rs5479	0.076	rs6499129	0.213	rs5479	0.065
SHBG	15	rs1641544	0.245	rs2543553	0.035	rs2543553	0.146
SRD5A1	26	rs39847	0.129	rs30434	0.107	rs1651071	0.157
SRD5A3	22	rs483978	0.397	rs9993675	0.121	rs4864984	0.382
UGT2B4	29	rs2736520	0.128	rs903446	0.111	rs2736520	0.142
SRD5A2	25	rs2300697	0.041	rs9282858	0.416	rs12470143	0.213
CYP17A1	15	rs4919686	**0.001**	rs284847	0.092	rs4919683	0.008
AKR1C4	21	rs11253045	0.086	rs2050308	0.011	rs2050308	0.03
JMJD1C	20	rs3816685	0.093	rs7100693	0.061	rs3816685	0.142
CYP7A1	20	rs6997473	0.177	rs10504255	0.212	rs11786580	0.198
CYP11B1	21	rs4736346	0.298	rs4464947	0.289	rs4736346	0.270
CYP11B2	21	rs4736318	0.400	rs7844961	0.141	rs7844961	0.239
CYP1A1	9	rs1048943	0.238	rs2470893	0.040	rs1048943	0.249
CYP19A1	60	rs28757128	0.014	rs28757128	0.005	rs28757128	0.003
HSD11B1	28	GA019904	0.068	GA019904	0.231	rs4393158	0.213
AKR1D1	24	rs3805362	0.233	rs17169522	0.099	rs3805362	0.212

[a]Number of SNPs within each gene

Table 4

Sex-specific gene-based analysis for androgen-pathway genes and risk of Barrett' s esophagus (BE), esophageal adenocarcinoma (EAC), and BE and EAC combined (BE+EAC), presented as p-values for each sex separately. P-values in bold are statistically significant when Bonferroni adjusting each p-value for the number of SNPs within each gene.

	BE		EAC		BE+EAC	
GENE	**Men[a]**	**Women[b]**	**Men[c]**	**Women[d]**	**Men[e]**	**Women[f]**
	P	**P**	**P**	**P**	**P**	**P**
HSD11B2	0.367	0.298	0.694	0.477	0.421	0.241
SHBG	0.866	0.542	0.247	0.418	0.623	0.452
SRD5A1	0.204	0.800	0.465	0.659	0.334	0.892
SRD5A3	0.685	0.019	0.556	0.044	0.527	0.247
UGT2B4	0.428	0.564	0.637	0.272	0.582	0.431
SRD5A2	0.037	0.510	0.945	0.265	0.188	0.305
CYP17A1	**0.003**	0.329	0.580	0.632	0.028	0.309
AKR1C4	0.777	0.832	0.732	0.230	0.639	0.588
JMJD1C	0.114	0.288	0.503	**0.001**	0.356	0.032
CYP7A1	0.875	0.212	0.927	0.156	0.906	0.103
CYP11B1	0.216	0.412	0.975	0.359	0.461	0.678
CYP11B2	0.391	0.384	0.948	0.311	0.741	0.589
CYP1A1	0.525	0.124	0.077	0.676	0.191	0.214
CYP19A1	0.186	0.163	0.841	0.198	0.463	0.258
HSD11B1	0.552	0.286	0.782	0.386	0.833	0.266
AKR1D1	0.528	0.182	0.299	0.987	0.325	0.293

[a] 1808 cases and 1703 controls,

[b] 575 cases and 466 controls,

[c] 1333 cases and 1704 controls,

[d] 175 cases and 466 controls,

[e] 3141 cases and 1702 controls and

f_{751} cases and 466 controls.