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Polymorphism in the *GALNT1* Gene and Epithelial Ovarian Cancer in Non-Hispanic White Women: The Ovarian Cancer Association Consortium

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Abstract

Aberrant glycosylation is a well-described hallmark of cancer. In a previous ovarian cancer case control study that examined polymorphisms in 26 glycosylation-associated genes, we found strong statistical evidence ($P = 0.00017$) that women who inherited two copies of a single-nucleotide polymorphism in the UDP-*N*-acetylgalactosamine:polypeptide *N*-acetylgalactosaminyltransferase, *GALNT1*, had decreased ovarian cancer risk. The current study attempted to replicate this observation. The *GALNT1* single-nucleotide polymorphism rs17647532 was genotyped in 6,965 cases and 8,377 controls from 14 studies forming the Ovarian Cancer Association Consortium. The fixed effects estimate per rs17647532 allele was null (odds ratio, 0.99; 95% confidence interval, 0.92–1.07). When a recessive model was fit, the results were unchanged. Test for hetero geneity of the odds ratios revealed consistency across the 14 replication sites but significant differences compared with the original study population ($P = 0.03$). This study underscores the need for replication of putative findings in genetic association studies.

Introduction

Glycosylation is a common posttranslational modification of proteins important for stability, solubility, secretion of signal, regulation of interactions, extracellular recognition, and folding (1). O-linked glycosylation involves the transfer of monosaccharide *N*-acetylgalactosamine (GalNAc) from UDP-GalNAc to the hydroxyl group of a serine or threonine residue on proteins and is catalyzed by GalNAc-transferases (ppGalNac-T or GALNT; ref. 2). In ovarian cancer cells, alterations in the O-glycosylation machinery result in aberrantly glycosylated proteins, which expose previously masked peptide motifs and new antigenic targets, thereby altering host immunogenic response (3).

We previously investigated associations between polymorphisms in 26 glycosylation-associated genes and epithelial ovarian cancer risk (4). Results based on 829 cases and 939 controls suggested that a polymorphism in the *GALNT1* gene (rs17647532) was statistically significantly ($P = 0.00017$) inversely associated with epithelial ovarian cancer under a recessive model (4). To replicate this finding (5), we genotyped this *GALNT1* variant in 14 independent study populations from the Ovarian Cancer Association Consortium (OCAC; ref. 6) and performed a pooled analysis.

Materials and Methods

Approval and Consent

All study participants provided written informed consent before the collection of biological samples or interview/clinical data. Each group involved in the OCAC has Institutional Review Board approval for this analysis and the Universities of Southern California and Duke have Institutional Review Board approval to serve as data coordinating centers for the OCAC.

Study Populations

The original study included the Mayo Clinic Ovarian Cancer Case Control Study (MAY) and the North Carolina Ovarian Cancer Study NCO-1 (Duke; ref. 4). The replication included non-Hispanic White subjects from 14 studies: the Australian cancer study and Australian ovarian cancer study (AUS); the Washington Ovarian Cancer case-control study (DOV); the German Ovarian Cancer case-control study (GER); the Hawaiian Ovarian Cancer study (HAW); the Hormones and Ovarian Cancer Prediction Study (HOP); the Danish Cancer Society MALOVA ovarian cancer case-control study (MAL); the North Carolina Ovarian Cancer Study (NCO-2); the New England-based Case-Control Study (NEC); the Polish Ovarian Cancer Study (POL); the SEARCH Ovarian Cancer Case-Control Study, Cambridge, United Kingdom (SEA); the Genetic Epidemiology of Ovarian Cancer Study, Stanford University (STA); the UC Irvine Ovarian Cancer Study (UCI); the UK Ovarian Cancer Population Study (UKO); and the USC/Los Angeles County Case-Control Studies of Ovarian Cancer (USC). Details of these studies are provided on the OCAC web portal[26] and prior publications (7–16). Subjects (444 cases and 468 controls) from the NCO-1 that were included in the previous publication on *GALNT1* were excluded from the replication analysis.

Genotyping and Quality Control

A single *GALNT1* single-nucleotide polymorphism (SNP; rs17647532) was genotyped using either the iPlex Sequenom MassArray system (Sequenom, Inc.; Australian Cancer Study and Australian Ovarian Cancer Study) or 5′-nuclease TaqMan allelic discrimination assay (TaqMan, Applied Biosystems; all other sites). Laboratory procedures and quality control measures were described previously (4,7–16). Call rates ranged from 96% to 99%, concordance across laboratories was 99%, and concordance between duplicate samples was 100%. No deviations from Hardy-Weinberg equilibrium (HWE) expectations were observed among the controls.

Statistical Analysis

The variables included study site, age at diagnosis for cases or interview for controls, tumor behavior, and histology (serous, mucinous, clear cell, and endometrioid). Unconditional logistic regression was used to model the association between the SNP and risk of ovarian cancer adjusted for age group, fitting both log-additive and recessive models. Goodness-of-fit *P* values were calculated to evaluate heterogeneity across the study populations. Statistical analyses were carried out using PLINK (17) and SAS version 9.1 (SAS, Inc.). All statistical significance levels (*P* values) presented are two-sided.

Results

A total of 6,965 non-Hispanic White invasive epithelial ovarian cancer cases and 8,377 non-Hispanic White controls were included in the replication analysis (Table 1). The mean ages were 55.6 and 55.9 years, respectively. More than 79% of the cases had an invasive tumor behavior and 53.5% had a serous histology.

Across the studies, the minor allele frequencies varied from 9% to 12% among controls (Table 2). There was no association of the variant with cancer risk on a log-additive scale for any of the individual studies or across all OCAC studies combined. When the previously published data were included, the association remained null [odds ratio (OR), 0.98; 95% confidence interval (95% CI), 0.91–1.05] in the additive model. Because the earlier report (4) found the strongest results under a recessive model of transmission, additional models were fit to the

[26] http://www.srl.cam.ac.uk/consortia/ocac/index.html

data. Although the estimated ORs at five of the 14 replication sites were in the same inverse direction as the earlier report, none of these were statistically significant and the combined results across sites suggest no association with risk (Fig. 1). A test for heterogeneity of the ORs by site suggests no significant differences ($P = 0.65$). However, when we tested for heterogeneity of the ORs again, with the earlier results from Mayo and Duke included, the results were statistically significant ($P = 0.03$).

The *GALNT1* SNP associations were not observed in histologic cell type–specific subgroup analyses or in borderline compared with invasive ovarian cancer cases (data not shown).

Discussion

We previously reported an association between a *GALNT1* SNP and ovarian cancer: Homozygous carriers of the variants were observed to have >90% lower risk than noncarriers (4), but the current study does not replicate this finding. Because the variant is rare, only 1.2% of the population would be expected to be homozygous carriers. Thus, the initial report was based on few cases and controls. In addition, there was deviation from HWE among controls in the original finding ($P = 0.002$ in combined data). In the current analysis with nearly 7,000 cases and more than 8,400 controls, there were only 98 cases and 104 controls homozygous for the variant. A logical conclusion is that the original observation represents a false-positive finding (18). This conclusion is underscored by the test for heterogeneity of the ORs across all study sites: No heterogeneity was observed among the 14 OCAC replication sites, but inclusion of the original findings yielded statistical evidence for heterogeneity. However, we cannot rule out the possibility that other as yet unidentified variants at the locus influence ovarian cancer risk.

In summary, the present analysis fails to replicate an earlier reported association of a *GALNT1* variant with risk of ovarian cancer. This study highlights the need to replicate putative findings in genetic association studies.

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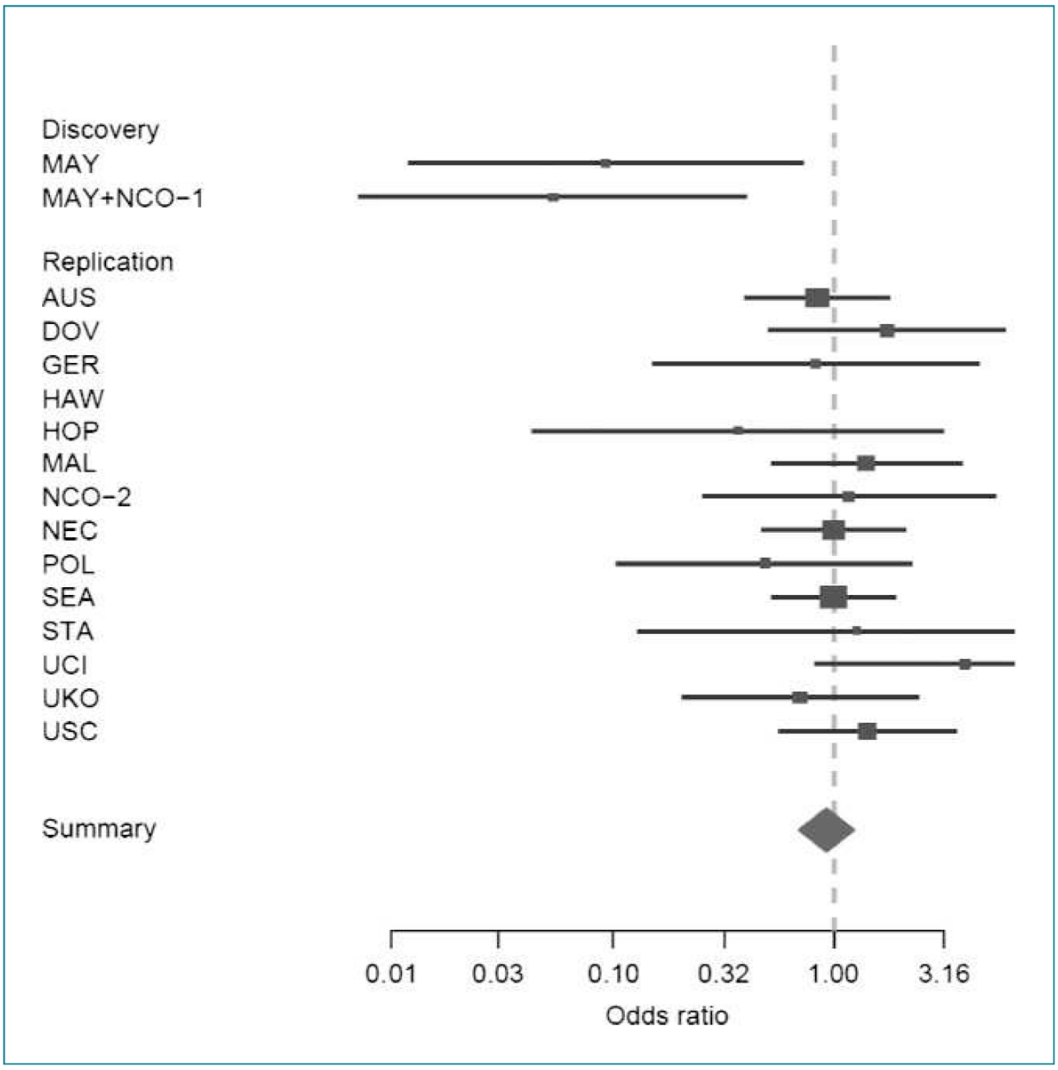

Figure 1.
Forest plot for study-specific risk and 95% CIs for the association between ovarian cancer risk and the *GALNT1* SNP (rs17647532) in the discovery set and the 14 studies in the replication set using a recessive model. The study site nomenclature is described in Materials and Methods.

Table 1

Distribution of demographic and clinicopathologic characteristics for 15,342 OCAC non-Hispanic Caucasian subjects

Variable	Cases (*n* = 6,965)	Controls (*n* = 8,377)
Age (y), mean (SD)	55.6 (11.8)	55.9 (11.1)
Age group (y), *n* (%)		
<40	642 (9.2)	586 (7.0)
40–49	1,422 (20.4)	1,969 (23.5)
50–59	2,182 (31.3)	2,459 (29.4)
60–69	1,872 (26.9)	2,284 (27.3)
>70	847 (12.2)	1,079 (12.8)
Site, *n* (%)		
AUS	930 (13.4)	1,064 (12.7)
DOV	620 (8.9)	617 (7.4)
GER	251 (3.6)	428 (5.1)
HAW	90 (1.3)	158 (1.9)
HOP	307 (4.4)	594 (7.1)
MAL	440 (6.3)	794 (9.5)
NCO	250 (3.6)	202 (2.4)
NEC	982 (14.1)	1,050 (12.5)
POL	275 (3.9)	597 (7.1)
SEA	1,092 (15.7)	1,213 (14.5)
STA	369 (5.3)	181 (2.2)
UCI	404 (5.8)	418 (5.0)
UKO	467 (6.7)	564 (6.7)
USC	488 (7.0)	497 (5.9)
Histology		
Serous	3,718 (53.5)	
Mucinous	919 (13.2)	
Endometroid	906 (13.1)	
Clear cell	489 (7.0)	
Mixed cell	158 (2.3)	
Other	755 (10.9)	
Behavior		
Borderline/LMP	1,237 (17.8)	
Invasive	5,520 (79.2)	
Unknown	208 (3.0)	

Abbreviation: LMP, low malignant potential.

Table 2

Summary OR and 95% CI for the *GALNT1* SNP rs17647532 and risk of invasive epithelial ovarian cancer among non-Hispanic Caucasians

Site	*N*	Case/control			MAF*	P_{HWE}†	Additive model,‡ OR (95% CI)	Recessive model,‡ OR (95% CI)
		CC	*CT*	*TT*				
Discovery								
MAY	846	1/12	70/71	314/378	0.10	0.0003	0.88 (0.64–1.21)	0.14 (0.02–1.14)
NCO-1 (Duke)	922	0/8	80/91	364/379	0.10	0.35	0.78 (0.57–1.06)	NA
Replication								
AUS	1,994	12/16	185/207	733/841	0.11	0.44	1.00 (0.82–1.21)	0.84 (0.4–1.8)
DOV	1,237	7/4	109/133	504/480	0.11	0.16	0.85 (0.66–1.11)	1.75 (0.51–6.03)
GER	679	2/4	43/75	206/349	0.10	1.00	0.96 (0.66–1.39)	0.83 (0.15–4.58)
HAW	248	2/0	18/39	70/119	0.12	0.13	0.97 (0.54–1.74)	NA
HOP	901	1/5	69/124	237/465	0.11	0.41	1.05 (0.76–1.46)	0.37 (0.04–3.19)
MAL	1,234	7/9	77/152	356/633	0.11	1.00	0.96 (0.73–1.25)	1.4 (0.51–3.83)
NCO-2	452	4/3	46/41	200/158	0.12	0.74	0.92 (0.61–1.38)	1.17 (0.26–5.36)
NEC	2,032	11/8	97/92	380/397	0.10	0.09	1.11 (0.91–1.35)	1.00 (0.48–2.08)
POL	872	2/9	47/95	226/493	0.09	0.35	0.98 (0.70–1.38)	0.49 (0.1–2.27)
SEA	2,305	19/20	196/245	877/948	0.12	0.33	0.93 (0.77–1.12)	1.00 (0.52–1.92)
STA	550	3/1	76/37	290/143	0.11	0.70	1.01 (0.66–1.53)	1.27 (0.13–12.43)
UCI	822	8/2	79/83	317/333	0.10	0.29	1.13 (0.83–1.54)	3.92 (0.82–18.65)
UKO	1,031	6/8	81/100	380/456	0.10	0.36	0.96 (0.71–1.31)	0.71 (0.21–2.43)
USC	985	14/15	192/184	776/851	0.11	0.18	1.12 (0.86–1.47)	1.41 (0.56–3.55)
Overall§	15,342	98/104	1,315/1,607	5,552/6,666	0.11	0.76	0.99 (0.92–1.07)	1.12 (0.85–1.49)
Cumulative summary‖	17,108	99/124	1,465/1,768	6,230/7,422	0.11	0.11	0.98 (0.91–1.05)	0.94 (0.72–1.23)

NOTE: The discovery set includes two sites (MAY and NCO-1) and the replication set includes 14 OCAC sites (AUS, DOV, GER, HAW, HOP, MAL, NCO-2, NEC, POL, SEA, STA, UCI, UKO, and USC). The study site nomenclature is described in Materials and Methods.

Abbreviation: MAF, minor allele frequency.

*MAF estimated among controls.

†*P* value for testing departure from HWE among controls.

‡ORs and 95% CIs in models adjusted for age groups.

[§] Summary results across all 14 OCAC replication sites.

[||] Cumulative summary including previously published data from Mayo and Duke (NCO-1).