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Inherited variant on chromosome 11q23 increases susceptibility to *IDH*-mutated but not *IDH*-normal gliomas regardless of grade or histology

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Introduction. Recent discoveries of inherited glioma risk loci and acquired *IDH* mutations are providing new insights into glioma etiology. *IDH* mutations are common in lower grade gliomas and secondary glioblastomas and uncommon in primary glioblastomas. Because the inherited variant in 11q23 has been associated with risk of lower grade glioma and not with glioblastomas, we hypothesized that this variant increases susceptibility to *IDH*-mutated gliomas, but not to *IDH*-wild-type gliomas.
Methods. We tested this hypothesis in patients with glioma and controls from the San Francisco Adult Glioma Study, the Mayo Clinic, and Illumina controls (1102 total patients, 5299 total controls). Case-control additive associations of 11q23 risk alleles (rs498872, T allele) were calculated using logistic regression, stratified by tumor *IDH* status (mutated or wild-type) and by histology and grade. We also adjusted for the recently discovered 8q24 glioma risk locus rs55705857 G allele.
Results. The 11q23 glioma risk locus was associated with increased risk of *IDH*-mutated gliomas of all histologies and grades (odds ratio [OR] = 1.50; 95% confidence interval [CI] = 1.29–1.74; $P = 1.3X10^{-7}$) but not with *IDH*-wild-type gliomas of any histology or grade (OR = 0.91; 95% CI = 0.81–1.03; $P = 0.14$). The associations were independent of the rs55705857 G allele.
Conclusion. A variant at the 11q23 locus increases risk for *IDH*-mutated but not *IDH*-wild-type gliomas, regardless of grade or histology.

Keywords: adult glioma, *IDH1* and *IDH2* mutation, rs498872, rs55705857, single-nucleotide polymorphism.

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We and others first reported several inherited variants that increase glioma risk in 2009.[1,2] Additional confirmation and new risk loci have been identified since then.[3–8] We[9] and Simon et al.[10] showed that the glioma risk loci in 8q24 and 11q23 first identified by Shete et al.[1] were associated with risk of lower grade infiltrating gliomas but not with glioblastomas.

It is now well established that mutation in the isocitrate dehydrogenase (*IDH*) 1 and 2 genes leads to genome-wide histone and DNA methylation changes that result in abnormal gene expression and gliomagenesis, defining a distinct subclass of gliomas.[11,12] *IDH* mutations occur in ~50%–80% of grade II-III gliomas and secondary glioblastomas but in fewer than 10% of primary glioblastomas.[13–17] Tumor *IDH* mutations are associated with younger age of onset and better overall survival among patients with gliomas of all grades and histologies[18,19] and are also associated with other somatic, genetic, and epigenetic alterations.[17,20]

Given these observations, we hypothesized that the 8q24 and 11q23 glioma risk loci might be specific to *IDH*-mutated, but not to *IDH*-wild-type gliomas. In a separate recent publication,[21] we showed that the 8q24 locus is specifically associated with risk for oligodendroglial tumors and *IDH*-mutated astrocytomas of all grades. Here, we report that the 11q23 glioma risk variant rs498872 T allele is associated with risk of *IDH*-mutated gliomas but not with risk of *IDH*-wild-type gliomas, regardless of grade or histology.

Materials and Methods

Subjects

The Institutional Review Boards at University of California San Francisco (UCSF) and Mayo Clinic approved the methods for this study, and informed consent was obtained from each study subject. For this study, only patients with no previous diagnosis of glioma were included.

Subjects from UCSF included case and control participants in the San Francisco Bay Area Adult Glioma Study (AGS) and additional controls obtained from Illumina, as previously described.[2] In brief, patients aged ≥20 years with newly diagnosed and histologically confirmed incident glioma (International Classification of Diseases for Oncology, morphology codes 9380–9481) were recruited from the local population-based registry, the Northern California Rapid Case Ascertainment program, and the UCSF Neuro-Oncology Clinic. All patients were diagnosed from 1991 through 2010. UCSF AGS controls were ascertained through random-digit dialing, had no history of brain tumor at time of recruitment, and were frequency matched to population-based patients on age, sex, and ethnicity; 74% of patients and 83% of controls who were contacted consented to participate. We obtained tumor tissue samples from 72% of participants who received a diagnosis from 1991 through 2005, and acquisition is ongoing for more recent series.

The Mayo Clinic cases consisted of patients ≥18 years of age who had surgical resection or biopsy of a glioma from 2001 through 2009. Patients were identified at diagnosis for those initially cared for at the Mayo Clinic and at the time of pathologic confirmation for those who initially received a diagnosis elsewhere and were subsequently cared for at Mayo. Pathologic diagnosis was confirmed by review of the primary surgical material for all cases by 2 Mayo Clinic neuropathologists. The control group consisted of consenting individuals who underwent a general medical examination at the Mayo Clinic and have been previously described.[9] Individuals <18 years of age and those with a history of a brain tumor were not eligible to be controls. The participation rates were ~70% for patients and 50% for controls, and tumor tissue samples were available from ~67% of patients.

Analyses for this study were restricted to white participants, and histological glioma definitions were based on World Health Organization (WHO) criteria.[22] Histological categories included glioblastomas, grades 2 and 3 astrocytomas, oligodendrogliomas, and oligoastrocytomas.

Assays for IDH *Mutation*

UCSF AGS tumor specimens were sequenced to identify *IDH1* and *IDH2* mutations with use of previously described methods.[13] In brief, the region spanning the R132 codon of *IDH1* and the region spanning the R172 codon of *IDH2* were amplified by polymerase chain reaction with M13 tagged primers to facilitate amplification and sequencing. Products were run on a 1.5% agarose gel and subsequently sequenced in both directions at the UCSF Genomics Core Facility according to the manufacturer's protocol. Sequences were analyzed with Applied Biosystems Sequence Scanner Software, version 1.0. At the Mayo Clinic, *IDH1* mutation detection was performed using pyrosequencing. *IDH2* mutation detection was performed using both pyrosequencing and Sanger sequencing as previously described.[23] Primer sequences are available upon request.

Genotyping Germline Single-Nucleotide Polymorphisms (SNPs)

Genotype data for SNP rs498872 in the 11q23 region from UCSF AGS, Mayo Clinic, and Illumina controls came from Illumina genome-wide and custom panels with use of previously described genotyping methods and quality-control measures.[2,9,21] Genotype data for SNP rs55705857 in the 8q24 region subjects came from custom panels of previously described UCSF AGS and Mayo Clinic patients and controls.[22]

Statistical Analysis

Initial analyses included additive logistic regression models for 0, 1, or 2 copies of the T risk allele of rs498872 to obtain unadjusted single point associations. Models were run separately for (1) patients with tumor *IDH* mutation versus controls and (2) patients without tumor *IDH* mutation versus controls. Analyses were conducted for 7 nondiscrete grade and histology groupings: (1) all gliomas, (2) glioblastomas, (2) grade 2 gliomas, (4) grade 3 gliomas, (5) grade 2/3 oligodendrogliomas, (6) grade 2/3 oligoastrocytomas, and (7) grade 2/3 astrocytomas. Analyses were first performed separately for UCSF AGS and Mayo Clinic subjects and then pooled and analyzed using logistic regression models adjusted for study site. We also examined genetic heterogeneity between sites by including a site-by-SNP interaction term. To determine whether the association of glioma with rs498872 is independent of the association of glioma with rs55705857 G allele, we also conducted analyses in which both rs498872 and rs55705857 were included in the logistic model along with study site.

Results and Discussion

Gliomas are a heterogeneous class of tumors. In each subgroup defined by grade and histology, there are distinct clinical and molecular profiles.[24] The discovery of *IDH* mutations has altered our understanding of gliomagenesis and may lead to the eventual inclusion of *IDH* status in the WHO glioma classification scheme.[18,25,26] Numerous reports have demonstrated that *IDH* mutation segregates gliomas into clinically relevant subgroups; patients with *IDH*-mutated tumors tend to have much better prognoses.[14,16,27]

We identified tumor *IDH* mutations in 379 (34%) of 1102 patients with glioma (874 from UCSF and 228 from the Mayo Clinic) for whom both *IDH* mutation and rs498872 genotype data were available. The *IDH* mutation rate was 8% in glioblastomas, 84% in grade 2 gliomas, 63% in grade 3 gliomas, 83% in grade 2/3 oligodendrogliomas, 90% in grade 2/3 oligoastrocytomas, and 61% in grade 2/3 astrocytomas (Table 1). Patient characteristics, including age, sex, and median survival, are also shown in Table 1. The prevalence of *IDH* mutations in our study patients by histology and grade was comparable to that found in other studies[16,17,28] and in the remaining UCSF and Mayo samples without constitutional SNP genotyping. The control group included 5299 controls (1116 from UCSF, 3389 Illumina controls, and 794 from the Mayo Clinic) (Table 2).

In a recent report,[21] we showed that a novel variant on 8q24 is strongly associated with risk of all oligodendroglial gliomas and with *IDH*-mutated astrocytic gliomas. In this report, we show that the T allele of rs498872 on 11q23 confers increased risk for *IDH*-mutated gliomas of all grades and histological groups but not for *IDH*-wild-type gliomas of any

Table 1. Demographic and survival characteristics of UCSF Adult Glioma Study and Mayo Clinic glioma patients stratified by IDH1/2 mutation status

Histology	Total		IDH1/2-wild-type					IDH1/2-mutated				
	Number	% IDH mutated	Number	% men	Median age at diagnosis	Number deceased	Median survival years	Number	% men	Median age at diagnosis	Number deceased	Median survival years
All gliomas	1102	34	723	63	58	631	1.3	379	62	40	133	11.5
Glioblastomas	663	8	607	64	58	551	1.2	56	66	44	43	2.1
Gr 2 Gliomas	224	84	36	56	51	21	6.4	188	63	39	53	13.6
Gr 3 Gliomas	215	63	80	53	54	59	1.7	135	59	41	37	14.5
Oliodendrogliomas Gr 2/3	134	83	23	39	51	12	12.6	111	57	43	21	NA
Oliogoastrocytomas Gr 2/3	87	90	9	33	33	7	2.3	78	63	39	22	13.1
Astrocytomas Gr 2/3	218	61	84	60	55	61	1.7	134	64	37	47	10.3

NA - The median survival has not yet been reached.

Table 2. Associations of 11q23 rs498872T allele with glioma risk stratified by tumor IDH1/2 mutation status in UCSF Adult Glioma and Mayo Clinic Studies

Histology		*IDH1/2*-wild-type gliomas				Test for heterogeneity by study site	*IDH1/2*-mutated gliomas				Test for heterogeneity by study site
			case-control association					case-control association			
	Number	RAF	OR (95% CI)	*P* value	*P* value	Number	RAF	OR (95% CI)	*P* value	*P* value
Controls	5299	0.31				5299	0.31			
All gliomas	723	0.29	0.91 (0.81–1.03)	0.14	0.32	379	0.41	1.50 (1.29–1.74)	**1.3E-07**	0.11
Glioblastomas	607	0.29	0.91 (0.80–1.04)	0.17	0.24	56	0.43	1.65 (1.14–2.40)	**0.008**	0.28
Gr 2 Gliomas	36	0.29	0.93 (0.56–1.53)	0.77	0.69	188	0.39	1.38 (1.12–1.71)	**0.002**	0.35
Gr 3 Gliomas	80	0.29	0.90 (0.64–1.27)	0.54	0.74	135	0.43	1.59 (1.25–2.03)	**1.8E-04**	0.27
Oliodendrogliomas Gr 2/3	23	0.24	0.72 (0.37–1.40)	0.33	0.95	111	0.41	1.52 (1.16–1.99)	**0.002**	0.31
Oligoastrocytomas Gr 2/3	9	0.28	0.86 (0.31–2.39)	0.78	NA*	78	0.38	1.29 (0.93–1.79)	0.134	0.17
Astrocytomas Gr 2/3	84	0.30	0.97 (0.70–1.34)	0.84	0.93	134	0.41	1.53 (1.20–1.96)	**5.5E-04**	0.80

*All IDH-wild-type oligoastrocytomas are from UCSF.
ORs from additive model for 0, 1, or 2T alleles in rs498872 are adjusted for study site. *P* values $\leq$ .05 are in bold. RAF = risk allele frequency.

grade or histology (Table 2 and Fig. 1). These associations were statistically significant for all histological groups of *IDH*-mutated gliomas, with the exception of grade 2/3 oligoastrocytomas. Associations did not display significant heterogeneity across study site (Table 2). Sanson et al.[5] reported a similar result in their analysis of all glioma grades and histologies. By stratifying analyses by histology and grade, we revealed that the association between rs498872 and glioma risk in *IDH*-mutated gliomas is independent of the known associations between low-grade glioma and both *IDH* mutation and the 11q23 variant.[9,27,28]

We further showed that the specific and significant association of the inherited T allele in rs498872 is independent of the association of the 8q24 variant, rs55705857 (Table 3), which we had recently found to be associated with *IDH*-mutated astrocytic gliomas and with both *IDH*-mutated and *IDH*-wild-type oligodendroglial tumors.[21] Thus, the 11q23 variant appears to be even more specifically associated with *IDH* mutation status than the 8q24 locus. We have now identified 2 independent risk loci that confer inherited susceptibility to *IDH*-mutated gliomas, which comprise a distinct glioma subclass.[11,12]

Because germline risk SNPs, by definition, precede tumor development, our results may help elucidate the mechanism behind the pathogenesis of these tumors after the causal variant in 11q23 is identified. At present, we can only speculate whether the 11q23 variant actively promotes development of *IDH* mutations, whether individuals without the risk alleles more readily suppress cells that develop these mutations, or whether some other mechanism explains the specific association of this SNP with risk of *IDH*-mutated gliomas. At this time, there are no known biologic functions associated with the 11q23 SNP to explain our observed associations, and further functional studies are needed.

Genome-wide association studies (GWAS) have greatly advanced our knowledge of the genetic mechanisms underlying carcinogenesis but typically have not focused on associations between inherited variants and acquired somatic mutations. As knowledge of cancer biology improves, the resolution at which tumors are meaningfully classified will continue to become finer. Although GWAS of cancer have long restricted cases to only those subjects whose tumor is of a particular histologic subtype, there is a growing trend to restrict cases to only those tumors that carry specific somatic mutations.[29,30] Both the present finding and our recently identified novel variant on 8q24, rs55705857, that was strongly associated with risk of *IDH*-mutated astrocytic gliomas[21] showed that *IDH* mutation stratifies gliomas into relevant etiologic subgroups. This demonstrates that acquired genetic alterations in the tumor can be used to restrict analyses to phenotypically homogeneous cases that are likely to share similar underlying genetic risk factors. The identification of 2 germline alterations that impact the development of *IDH*-mutated gliomas may bring us closer to understanding the causal mechanisms underlying the development of these tumors. In addition, our results may help to

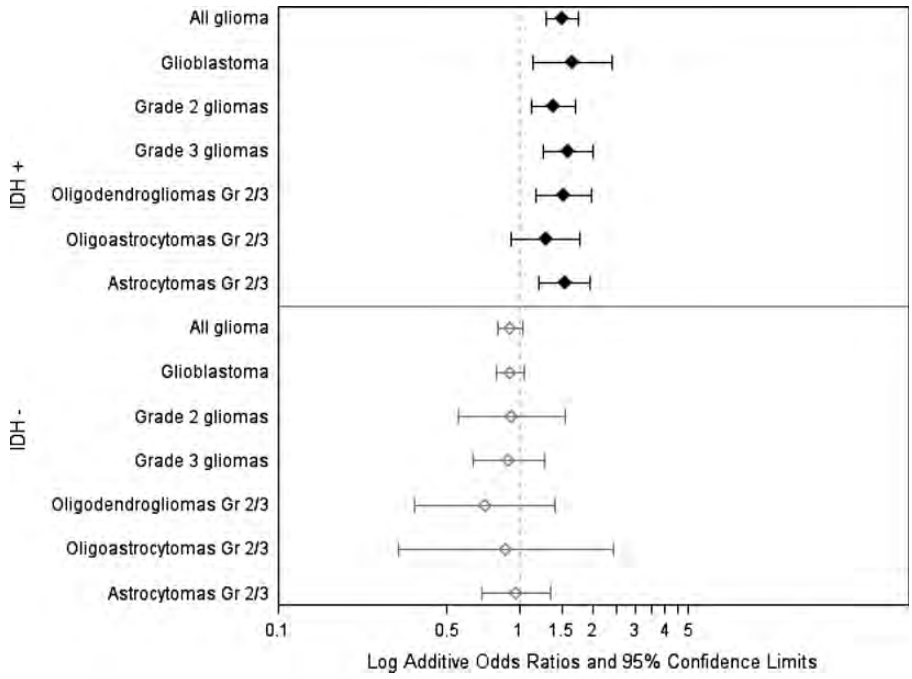

Fig. 1. Association of 11q23 variant with glioma risk, stratified by histology, grade, and *IDH* mutation status. Case-control ORs and 95% CIs for each category are from additive logistic models of 0, 1, or 2 rs498872 T alleles and adjusted for study site.

Table 3. Case-control ORs of IDH1/2–mutated gliomas with rs498872 T allele and rs55705857 G allele in UCSF Adult Glioma and Mayo Clinic Studies

Variable	Number	rs498872 (T allele)			rs55705857 (G allele)		
		RAF	OR (95% CI)	*P* value	RAF	OR (95% CI)	*P* value
Controls	1300	0.32			0.05		
IDH mutated tumors							
All gliomas	359	0.42	1.52 (1.27–1.83)	**5.1E-06**	0.19	5.21 (3.90–6.96)	**6.8E-29**
Glioblastomas	48	0.46	1.84 (1.19–2.85)	**6.2E-03**	0.22	7.55 (4.12–13.9)	**6.5E-11**
Gr 2 Gliomas	180	0.39	1.42 (1.12–1.80)	**4.3E-03**	0.21	5.56 (3.93–7.88)	**4.5E-22**
Gr 3 Gliomas	131	0.44	1.60 (1.23–2.07)	**4.4E-04**	0.16	4.25 (2.83–6.38)	**2.8E-12**
Oliodendrogliomas Gr 2/3	107	0.42	1.60 (1.18–2.16)	**2.3E-03**	0.20	5.89 (3.83–9.07)	**7.6E-16**
Oliogoastrocytomas Gr 2/3	74	0.39	1.33 (0.95–1.88)	0.10	0.16	3.73 (2.30–6.04)	**9.0E-08**
Astrocytomas Gr 2/3	130	0.42	1.54 (1.18–2.02)	**1.7E-03**	0.19	5.37 (3.59–8.04)	**3.4E-16**

Note: Fewer subjects had data available for rs55705857 than for rs498872 because only a recently completed custom genotyping panel[22] contained rs55705857.
ORs for each glioma subtype are from an additive model that includes both 0, 1, or 2 T alleles in rs498872 and 0, 1, or 2 G alleles in rs55705857 and is adjusted for study site. *P* values $\leq$ .05 are in bold.
RAF = risk allele frequency.

improve disease classification and prognostic accuracy in future studies.

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Conflict of interest statement. M. B. has consulted with Ivivi health sciences and Pharmacokinesis. All other authors: no conflicts.

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