

Genome-Wide Association Studies in Glioma Ben Kinnersley<sup>1</sup>, Richard S. Houlston<sup>1</sup>, and Melissa L. Bondy<sup>2</sup>

## Abstract

Since the first reports in 2009, genome-wide association studies (GWAS) have been successful in identifying germline variants associated with glioma susceptibility. In this review, we describe a chronological history of glioma GWAS, culminating in the most recent study comprising 12,496 cases and 18,190 controls. We additionally summarize associations at the 27 glioma-risk SNPs that have been reported so far. Future efforts are likely to be principally focused on assessing association of germline-risk SNPs

with particular molecular subgroups of glioma, as well as investigating the functional basis of the risk loci in tumor formation. These ongoing studies will be important to maximize the impact of research into glioma susceptibility, both in terms of insight into tumor etiology as well as opportunities for clinical translation. *Cancer Epidemiol Biomarkers Prev*; 27(4): 418–28. ©2018 AACR.

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## Introduction

Gliomas account for approximately 80% of all malignant primary brain tumors with approximately 26,000 individuals diagnosed in Europe each year (1, 2). Diffuse gliomas have traditionally been classified into oligodendroglial and astrocytic tumors and graded II to IV, with the revised 2016 World Health Organization classification additionally incorporating the tumor molecular features of *IDH1/IDH2* (IDH) mutation and 1p/19q codeletion (3). The most common tumor type, glioblastoma multiforme (GBM), typically has a median survival of only 15 months (2).

To date the only recognized environmental risk factor for glioma is exposure to ionizing radiation, which is responsible for only a very small number of cases (2). Evidence for a genetic component to glioma risk is provided by observations of an approximately 2-fold elevated risk in relatives of glioma patients (4). Furthermore, an increased risk of glioma is recognized to be associated with a number of Mendelian cancer predisposition syndromes, notable neurofibromatosis (NF1 and NF2), Li-Fraumeni, and Turcot (5–16). In addition, germline mutation of *CDKN2A* has been reported to be a cause of the astrocytoma-melanoma syndrome (17, 18). More recently, germline *POT1* variants have been implicated in development of oligodendroglioma (19); however, their penetrance is yet to be established. Collectively, these syndromes are very rare and explain little of the risk of glioma.

Attempts to study the contribution of low-frequency variants of moderate effect have generally been through sequencing of candidate genes in glioma cases and controls; however, they have failed to identify any genes associated with glioma. Indeed, a recent study of 1,662 cases and 1,301 controls failed to replicate

52 variants previously implicated by candidate gene studies (20). In combination with more systematic approaches such as those making use of the exome array (21), these studies do not currently provide support for this class of susceptibility allele playing a major role in glioma predisposition.

More fruitful have been efforts over the past decade to investigate the contribution of small-effect variants that are common in the general population to many traits including glioma through the genome-wide association study (GWAS). The combination of technological advancements and collaborative efforts in establishment of consortia such as the Glioma International Case-Control (GICC) study (22) has enabled genotyping of hundreds of thousands of variants in thousands of glioma cases and controls. It is now recognized that a substantial component of glioma genetic risk is explained by combinations of common polymorphisms of modest effect (23), with 27 loci in total identified so far from glioma GWAS (24–33).

This review provides a brief overview of discoveries from glioma GWAS, as well as a short discussion of future perspectives.

## Chronological History of Glioma Risk Loci Discovery

The first glioma GWAS was carried out in 2009 by Shete and colleagues (30), comprising a discovery case-control series of UK and European-American individuals (totaling 1,878 cases and 3,670 controls) and replication series of French, German, and Swedish individuals (totaling 2,545 cases and 2,953 controls). This study identified five susceptibility loci at 5p15.33, 8q24.21, 9p21.3, 11q23.3, and 20q13.33 (30). The loci at 9p21.3 and 20q13.33 were independently confirmed by Wrensch and colleagues (26) in a contemporaneous study of European-American individuals comprising a discovery phase of 692 high-grade glioma cases and 3,992 controls as well as a replication phase of 176 high-grade glioma cases and 174 controls (26). In this study, the top SNP rs1412829 at 9p21.3 is in linkage disequilibrium (LD) with the SNP rs4977756 reported by Shete and colleagues (ref. 30;  $r^2 = 0.75$ ,  $D' = 0.89$ ). At 20q13.33, the two reported SNPs rs6010620 and rs4809324 were reported to represent independent association signals ( $r^2 = 0.028$ ,  $D' = 1.0$ ).

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A further GWAS by Sanson and colleagues (31) was carried out in 2011, making use of data from the United Kingdom and European-American studies previously reported by Shete and colleagues (30) as well as two additional case-control series from France and Germany (totaling 4,147 cases and 7,435 controls). This study led to the identification of 7p11.2 as a susceptibility locus for glioma, which contained two statistically independent SNP associations with glioma risk (31). More recently, a GWAS was carried out in 2014 by Walsh and colleagues (29) comprising a United Kingdom and European-American discovery series of 1,013 high-grade glioma cases and 6,595 controls (in part overlapping with the study of Wrensch and colleagues; ref. 26), as well as a European-American replication series of 631 GBM cases and 1,141 controls. This study reported a novel glioma risk locus at 3q26.2 (near *TERC*) (29).

In addition to this, a sequence-based association study in the Icelandic population led to the discovery of rs78378222 at 17p13.1 (*TP53*) as a risk variant for several cancers including glioma (27). The association with glioma was confirmed in an independent European study (32). To refine the association signal at 8q24.21 in glioma, the region was fine-mapped by sequencing as well as statistical imputation of preexisting GWAS datasets. This led to the identification of rs55705857 as being responsible for the 8q24.21 glioma association, with the SNP exhibiting a much larger effect size than the initial GWAS tagSNPs and being highly restricted to low-grade IDH-mutated glioma (28, 34). Following on from this, in 2015, a GWAS was carried out by Kinnersley and colleagues (25), making use of datasets from Sanson and colleagues (31) as well as an independent replication series, in total comprising 5,637 cases and 9,158 controls. This study identified five new glioma risk loci, one for GBM at 12q23.33 (*POLR3B*), and four for non-GBM gliomas at 10q25.2 (*VTI1A*), 11q23.2 (*ZBTB16*), 12q21.2, and 15q24.2 (*ETFA*).

The largest and most recent glioma GWAS was carried out in 2017 by Melin and colleagues (24). This featured a meta-analysis of six existing GWAS and two new GWAS making use of the Illumina OncoArray (35), in total comprising 12,496 cases and 18,190 controls. The study identified 13 new glioma risk loci, five for GBM at 1p31.3 (*JAK1*), 11q14.1, 16p13.3 (near *MPG*), 16q12.1 (*HEATR3*) and 22q13.1 (*SLC16A8*), and 8 for non-GBM glioma at 1q32.1 (*MDM4*), 1q44 (*AKT3*), 2q33.3 (near *IDH1*), 3p14.1 (*LRIG1*), 10q24.33 (*OBFC1*), 11q21 (*MAML2*), 14q12 (*AKAP6*), and 16p13.3 (*LMF1*). At previously identified loci, with the exception of associations at 3q26.2 and 12q23.33 all associations retained genome-wide significance. Many of the loci demonstrated specificity for GBM or non-GBM glioma (Fig. 1).

A brief overview of the glioma susceptibility loci identified by GWAS as well as the datasets used is provided in Table 1.

Details of each glioma risk locus so far identified are presented in the following sections.

### 1p31.3

At the GBM locus 1p31.3, the risk allele of rs12752552 (*T*) is associated with increased expression of *JAK1* in brain cortex and cerebellar hemisphere (24). *JAK1* is involved in actomyosin contractility in tumor cells and stroma (36), and dysregulation of JAK-STAT signaling is thought to play an important role in development of high-grade glioma (37), providing an attractive mechanistic basis for the 1p31.3 association.

### 1q32.1

The non-GBM risk SNP rs4252707 is within the eighth intron of *MDM4*, with the risk allele (*A*) associated with increased expression of this gene (24). *MDM4* is amplified in glioma tumors lacking *TP53* mutation, consistent with its role in inactivation of p53-dependent growth control (38). Another SNP in the region, rs4245739, has been reported to be associated with ER-negative

**Figure 1.** Relative impact of SNP associations at glioma-risk loci for GBM and non-GBM tumors. Glioma risk estimates are from Melin and colleagues, 2017 (24). ORs were derived with respect to the risk allele.

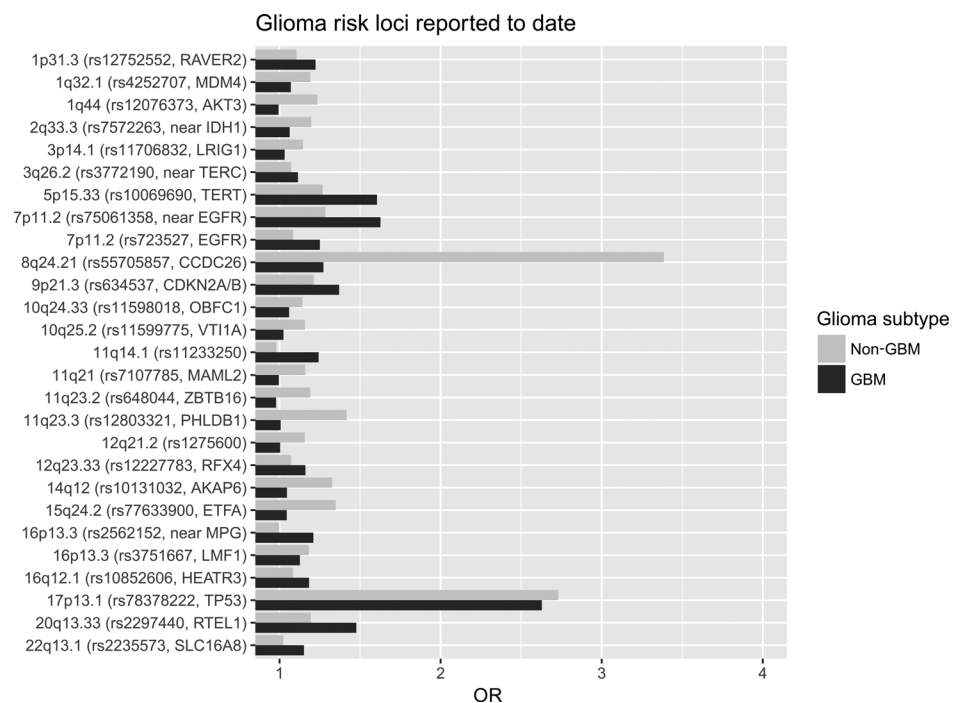


Table 1. Glioma susceptibility loci identified by GWAS in European populations

Glioma association study			Reported glioma-risk variants						
Reference	Study	Sample size (cases/controls)	Glioma subtype	Locus	Gene	SNP	Alleles	P	OR (95% CI)
Shete et al., 2009 (30)	UK-GWAS	631/1,434	All	5p15.33	TERT	rs2736100	T/G	$1.50 \times 10^{-17}$	1.27 (1.19-1.37)
	MDA-GWAS	1,247/2,236	All	8q24.21	CCDC26	rs4295627	G/T	$2.34 \times 10^{-18}$	1.36 (1.29-1.43)
	French-replication	1,392/1,602	All	8q24.21	CCDC26	rs891835	G/T	$7.54 \times 10^{-11}$	1.24 (1.17-1.30)
	German-replication	504/573	All	9p21.3	CDKN2A/B	rs4977756	A/G	$7.24 \times 10^{-15}$	1.24 (1.19-1.30)
	Swedish-replication	649/778	All	11q23.3	PHLDB1	rs498872	C/T	$1.07 \times 10^{-8}$	1.18 (1.13-1.24)
	Total	4,423/6,623	All	20q13.33	RTEL1	rs6010620	G/A	$2.52 \times 10^{-12}$	1.28 (1.21-1.35)
	SFAGS	692/3,992	High-grade	9p21.3	CDKN2A/B	rs1412829	C/T	$1.85 \times 10^{-10}$	1.42 (1.27-1.58)
	Mayo-replication	176/174	High-grade	20q13.33	RTEL1	rs6010620	G/A	$3.40 \times 10^{-9}$	1.52 (1.32-1.75)
	Total	868/4,166	High-grade	20q13.33	RTEL1	rs4809324	C/T	$1.70 \times 10^{-9}$	1.60 (1.37-1.87)
	Sanson et al., 2011 (31)	UK-GWAS	631/2,699	All	7p11.2	EGFR	rs11979158	A/G	$7.72 \times 10^{-8}$
French-GWAS	German-GWAS	1,423/1,190	All	7p11.2	EGFR	rs2252586	T/C	$2.09 \times 10^{-8}$	1.18 (1.11-1.25)
	MDA-GWAS	846/1,310	All	7p11.2	EGFR	rs2252586	T/C	$2.09 \times 10^{-8}$	1.18 (1.11-1.25)
Stacey et al., 2011 (27)	Total	1,247/2,236	All	17p13.1	TP53	rs78378222	T/G	$1.0 \times 10^{-5}$	2.35 (1.61-3.44)
	Iceland imputation	4,147/7,435	All	17p13.1	TP53	rs78378222	T/G	$1.0 \times 10^{-5}$	2.35 (1.61-3.44)
	Iceland genotyped	135/57,881	All	17p13.1	TP53	rs78378222	T/G	$1.0 \times 10^{-5}$	2.35 (1.61-3.44)
Rajaraman et al., 2012 (33)	USA UCSF	72/7,200	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	Total	658/573	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	USA Mayo Clinic	530/283	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	Total	1,395/45,937	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	GliomaScan	1,856/4,955	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	Mayo Clinic	860/795	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	UCSF AGS	953/1,079	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	Total	1,813/1,874	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	SFAGS	692/3,992	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
	TCGA cases, WTCCC controls	323/2,603	Oligodendroglioma	8q24.21	CCDC26	rs55705857	A/G	$2.2 \times 10^{-28}$	6.3 (4.6-8.8)
Walsh et al., 2014 (29)	Mayo-UCSF replication	631/1,141	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	Total	1,646/7,736	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	UK-GWAS	631/2,699	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	French-GWAS	1,423/1,190	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	German-GWAS	846/1,310	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	MDA-GWAS	1,175/2,236	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	SFAGS	677/3,940	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	Total	1,653/2,725	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	UK Replication	1,490/1,723	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
	Total	5,637/9,158	High-grade	3q26.2	Near TERC	rs1920116	G/A	$8.3 \times 10^{-9}$	1.30 (1.19-1.42)
Kinnersley et al., 2015 (25)	UK-GWAS	631/2,699	Non-GBM	10q25.2	VTG1A	rs11196067	A/T	$4.32 \times 10^{-8}$	1.19 (1.12-1.27)
	French-GWAS	1,423/1,190	Non-GBM	11q23.2	ZBTB16	rs648044	C/T	$6.26 \times 10^{-11}$	1.25 (1.17-1.34)
	German-GWAS	846/1,310	Non-GBM	12q21.2	Intergenic	rs12230172	G/A	$7.53 \times 10^{-11}$	1.23 (1.16-1.32)
	MDA-GWAS	1,247/2,236	GBM	12q23.3	POLR3B	rs3851634	T/C	$3.02 \times 10^{-9}$	1.23 (1.15-1.32)
	UK Replication	1,490/1,723	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
	Total	5,637/9,158	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
	SFAGS	692/3,992	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
	TCGA cases, WTCCC controls	323/2,603	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
	Mayo-UCSF replication	631/1,141	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
	Total	1,646/7,736	Non-GBM	15q24.2	ETFA	rs1801591	G/A	$5.71 \times 10^{-9}$	1.36 (1.23-1.51)
Melin et al., 2017 (24)	UK-GWAS	631/2,699	New loci	1p31.3	JAK1	rs12752552	T/C	$2.04 \times 10^{-9}$	1.22 (1.15-1.31)
	French-GWAS	1,423/1,190	GBM	1q32.1	MDM4	rs4252707	G/A	$3.34 \times 10^{-9}$	1.19 (1.12-1.26)
	German-GWAS	846/1,310	Non-GBM	1q44	AKT3	rs12076373	G/C	$2.63 \times 10^{-10}$	1.23 (1.16-1.32)
	MDA-GWAS	1,175/2,236	Non-GBM	2q33.3	Near IDH1	rs7572263	A/G	$2.18 \times 10^{-10}$	1.20 (1.13-1.26)
	SFAGS	677/3,940	Non-GBM	3p14.1	LRI/G1	rs11706832	A/C	$7.66 \times 10^{-9}$	1.15 (1.09-1.20)
	Total	1,653/2,725	Non-GBM	10q24.33	OBFC1	rs11598018	C/A	$3.39 \times 10^{-8}$	1.14 (1.09-1.20)
	UK Replication	1,490/1,723	Non-GBM	11q14.1	Intergenic	rs11233250	C/T	$9.95 \times 10^{-10}$	1.24 (1.16-1.33)
	Total	1,519/804	Non-GBM	11q14.1	Intergenic	rs11233250	C/T	$9.95 \times 10^{-10}$	1.24 (1.16-1.33)
	UCSF/Mayo	1,519/804	Non-GBM	11q14.1	Intergenic	rs11233250	C/T	$9.95 \times 10^{-10}$	1.24 (1.16-1.33)
	Total	12,496/18,190	Non-GBM	11q21	MAML2	rs7107785	T/C	$3.87 \times 10^{-10}$	1.16 (1.11-1.21)

(Continued on the following page)

Table 1. Glioma susceptibility loci identified by GWAS in European populations (Cont'd)

Reference	Glioma association study		Reported glioma-risk variants		Locus	Gene	SNP	Alleles	P	OR (95% CI)
	Study	Sample size (cases/controls)	Glioma subtype	Gene						
			Non-GBM		14q12	AKAP6	rs10131032	G/A	$5.07 \times 10^{-11}$	1.33 (1.22–1.44)
			GBM		16p13.3	Near MPG	rs2562152	A/T	$1.93 \times 10^{-8}$	1.21 (1.13–1.29)
			Non-GBM		16p13.3	LMI1	rs3751667	C/T	$2.61 \times 10^{-9}$	1.18 (1.12–1.25)
			GBM		16q12.1	HEATR3	rs10852606	T/C	$1.29 \times 10^{-11}$	1.18 (1.13–1.24)
			GBM		22q13.1	SLC16A8	rs2235573	G/A	$1.76 \times 10^{-10}$	1.15 (1.10–1.20)
			<i>Existing loci</i>							
			All glioma		3q26.2	Near TERC	rs3772190	G/A	$2.25 \times 10^{-6}$	1.11 (1.06–1.15)
			GBM		5p15.33	TERT	rs10069690	C/T	$8.33 \times 10^{-74}$	1.61 (1.53–1.69)
			GBM		7p11.2	EGFR	rs75061358	T/G	$4.94 \times 10^{-34}$	1.63 (1.50–1.76)
			GBM		7p11.2	EGFR	rs723527	A/G	$4.79 \times 10^{-23}$	1.25 (1.20–1.31)
			Non-GBM		8q24.21	CCDC26	rs55705857	A/G	$7.28 \times 10^{-149}$	3.39 (3.09–3.71)
			GBM		9p21.3	CDKN2A/B	rs634537	T/G	$7.23 \times 10^{-45}$	1.37 (1.31–1.43)
			Non-GBM		10q25.2	VTTIA	rs11599775	G/A	$3.44 \times 10^{-9}$	1.16 (1.10–1.22)
			Non-GBM		11q23.2	ZBTB16	rs648044	A/G	$4.66 \times 10^{-12}$	1.19 (1.13–1.25)
			Non-GBM		11q23.3	PHLDB1	rs12803321	G/C	$6.33 \times 10^{-43}$	1.42 (1.35–1.49)
			Non-GBM		12q21.2	Intergenic	rs1275600	T/A	$3.72 \times 10^{-9}$	1.16 (1.10–1.21)
			GBM		12q23.33	RFX4	rs12227783	A/T	$1.60 \times 10^{-5}$	1.16 (1.08–1.24)
			Non-GBM		15q24.2	ETFA	rs77633900	G/C	$1.60 \times 10^{-13}$	1.35 (1.25–1.46)
			All glioma		17p13.1	TP53	rs78378222	T/G	$8.64 \times 10^{-38}$	2.53 (2.19–2.91)
			GBM		20q13.3	RTEL1	rs2297440	T/C	$3.66 \times 10^{-46}$	1.48 (1.40–1.56)

NOTE: ORs are reported with respect to the risk allele, highlighted in bold.

breast (39) and prostate cancer (40), and it is unclear if the association signals are fully independent ( $r^2 = 0.10$ ,  $D' = 1$ ).

### 1q44

At 1q44, rs12076373 maps to the eighth intron of *AKT3* (v-akt murine thymoma viral oncogene homolog 3) one of the major downstream effectors of PI3K that is highly expressed during active neurogenesis (41). *AKT3* is highly expressed in glioma and plays an important role in tumor viability by activating DNA repair (42).

### 2q33.3

The non-GBM risk SNP at 2q33.3 (rs7572263) is 50-kb telomeric to *IDH1* (isocitrate dehydrogenase 1). Mutation of *IDH1* is a driver for gliomagenesis (43, 44) and is responsible for the CpG island methylator (G-CIMP) phenotype (45, 46). IDH mutation predominates in non-GBM glioma (47, 48); therefore, dysregulation of *IDH1* is highly plausible as a basis for susceptibility of these tumors.

### 3p14.1

The 3p14.1 association marked by rs11706832 localizes to intron 2 of *LRIG1* (leucine-rich repeats- and immunoglobulin-like domains-containing protein 1). *LRIG1* is highly expressed in the brain and negatively regulates the *EGFR* signaling pathway (49). Reduced *LRIG1* expression correlates with tumor aggressiveness as well as resistance to temozolomide and radiotherapy (50, 51). An additional association at 3p14.1 is with rs812481 and colorectal cancer risk (52), as this SNP is correlated with rs11706832 the association signals appear to overlap ( $r^2 = 0.67$ ,  $D' = 0.83$ ).

### 3q26.2

The GWAS tagSNP rs1920116 is in strong LD with variants at the nearby gene *TERC* (telomerase RNA component), leading Walsh and colleagues to suggest that this could be a plausible basis for the high-grade glioma association (29). The risk allele of rs1920116 was found to be positively associated with leukocyte telomere length (LTL,  $P = 5.5 \times 10^{-20}$ ), consistent with the functional basis of the 3q26.2 association involving *TERC* (29, 53). The strongest association with telomere length at 3q26.2 was exhibited by rs10936599, which is also a known colorectal cancer risk locus (53, 54); there is moderate correlation between rs10936599 and rs1920116 ( $r^2 = 0.44$ ,  $D' = 0.72$ ) suggesting these are not independent signals. In the latest glioma GWAS, the 3q26.2 locus does not attain genome-wide significance (24).

### 5p15.33

The original glioma tagSNP rs2736100 is intronic within *TERT*, the gene coding for telomerase reverse transcriptase that is primarily involved in telomere length regulation (55). Consistent with a *TERT*-mediated role in telomere length maintenance, the risk allele of rs2736100 was found to be positively associated with LTL ( $P = 4.4 \times 10^{-19}$ ; refs. 29, 53). 5p15.33 is a pleiotropic cancer risk locus harboring associations with multiple cancers including breast cancer, prostate cancer, and testicular germ cell tumor (56–59). In the latest glioma meta-analysis, the strongest association at 5p15.33 is with rs10069690 and GBM. Intriguingly, the rs10069690 risk allele (T) has been shown to create a splice-



donor site leading to an alternate *TERT* splice isoform lacking telomerase activity (60), providing direct evidence for its functional effects on tumor development.

#### 7p11.2

The two statistically independent glioma-risk SNPs identified (rs11979158 and rs2252586) lie just outside *EGFR*, a receptor tyrosine kinase (RTK) commonly activated in glioma (61). Association between these SNPs and gliomas has been reported to be independent of *EGFR* amplification, *p16* deletion, and *IDH1* mutation status (31). The authors note that the absence of a particular subtype association is consistent with *EGFR* activation playing a role in both initiation of primary GBM and progression from lower-grade glioma to secondary GBM (61). While the latest glioma meta-analysis has identified more strongly associated SNPs (rs75061358 for rs2252586 and rs723527 for rs11979158), the fine-mapped locus is still consistent with two independent signals.

#### 8q24.21

After identification through fine-mapping rs55705857 represents the likely causal variant at the 8q24.21 glioma risk locus (28, 34). Jenkins and colleagues (28) and Enciso-Mora and colleagues (34) suggest that the association confined to IDH-mutated gliomas, in particular those with 1p/19q co-deletion (i.e., classical oligodendroglioma). rs55705857 is located within *CCDC26*, a long intergenic noncoding RNA (lincRNA), which has been shown to be a retinoic acid-dependent modulator of myeloid cell differentiation and death (62). The SNP additionally resides within a conserved unmethylated CpG cluster. These motifs are sufficient for recruitment of repressive polycomb complex components that are implicated in control of cell fate, development, and cancer through gene silencing (63–65). 8q24.21 is a pleiotropic cancer risk locus with different cancers mapping to distinct subregions within the locus (66–69). The locus contains the oncogene *Myc*, regulation of which provides a plausible basis of predisposition at 8q24.21.

#### 9p21.3

rs497756 lies within the intron of *CDKN2B-AS1* (*ANRIL*), a long noncoding RNA involved in transcriptional silencing of *CDKN2A* (70, 71), providing an attractive functional basis for the 9p21.3 glioma association. Consistent with the known importance of mutations at this locus in melanoma tumors, rs7023329 at 9p21.3 has been identified as a susceptibility locus for malignant melanoma (72). rs7023329 and rs497756 are not at all correlated, suggesting these associations represent distinct risk loci within 9p21.3. *p16/CDKN2A* is a tumor suppressor gene commonly deleted in a number of cancer types including glioma (73, 74). Interestingly, allelic loss of 9p21.3 has been recently shown to be present in 41.7% of anaplastic 1p/19q co-deleted oligodendrogliomas, with these tumors being associated with shorter overall survival (75).

#### 10q24.33

The 10q24.33 association marked by rs11598018 lies intronic to *OBFC1* (oligonucleotide/oligosaccharide-binding fold-containing protein 1), which functions in a telomere-associated CST complex that competes with shelterin to regulate telomere length (76, 77). The risk allele of rs11598018 (C) is associated with

increased leukocyte telomere length thereby supporting a relationship between genotype and biology (78–80). Variation at 10q24.33 is additionally associated with risk of melanoma (81), basal cell carcinoma (82), thyroid cancer (83), and renal cell carcinoma (84). The SNPs defined by these associations do not appear to be correlated with rs11598018 ( $r^2 = 0.11$ – $0.12$ ,  $D' = 0.72$ – $1.0$ ).

#### 10q25.2

At 10q25.2, the originally reported SNP rs1196067 as well as the most associated SNP in the latest GWAS are intronic within *VTT1A*. As well as participating in regulating insulin-stimulated trafficking of secretory vesicles (85), *VTT1A* plays a key role in neuronal development and in selectively maintaining spontaneous neurotransmitter release (86). While the glioma-risk signal appears to be within *VTT1A*, the possibility of other nearby genes such as *TCF7L2* playing a role cannot be excluded. At 10q25.2, there are additional associations with colorectal (87), lung (88), and breast cancer (89). These appear to be uncorrelated, perhaps indicative of tissue-specific effects.

#### 11q14.1

The GBM SNP rs11233250 was discovered in the latest glioma GWAS and lies in an intergenic region, with no obvious mechanistic candidates nearby.

#### 11q21

At 11q21, the non-GBM SNP rs7107785 lies within *MAML2*, encoding Mastermind-like protein 2. The mastermind-like protein family has been reported to function as coactivators of Notch signaling (90).

#### 11q23.2

The risk SNP rs648044 is specific to non-GBM glioma and is intronic within *ZBTB16*. *ZBTB16* is highly expressed in undifferentiated, multipotential progenitor cells and its expression has been shown to influence resistance to retinoid-mediated redifferentiation in t(11;17)(q23;21) acute promyelocytic leukaemia (APL; ref. 91). The BTB domain of *ZBTB16* has transcriptional repression activity and interacts with components of the histone deacetylase complex thereby linking the transcription factor with regulation of chromatin conformation (92). Additional associations have been reported at 11q23.2 with risk of prostate cancer (93) and chronic lymphocytic leukemia (CLL; ref. 94); however, they appear to represent distinctive association signals.

#### 11q23.3

Both the original tag-SNP rs498872 and most associated SNP from the latest glioma GWAS rs12803321 are intronic within *PHLDB1*. rs498872 has been shown to exhibit an association with IDH-mutated glioma but not IDH-wild-type glioma that is independent of histology or grade (95). Pleckstrin homology-like domain family B member 1 (*PHLDB1*) is an insulin-responsive protein that enhances Akt activation (96). Insulin signaling and the Akt pathway often play an important role in cancer progression (97) providing a rationale for the functional basis of the 11q23.3 association; however, the explanation for the specificity of association with IDH-mutated glioma remains to be established. Additional signals at 11q23.3 with other cancers include

follicular lymphoma (ref. 98; rs4938573) and lung adenocarcinoma (ref. 99; rs1056562), which appear to represent distinct signals (LD metrics with respect to rs12803321:  $r^2 = 0.04/0.03$ ,  $D' = 0.55/0.24$ , respectively).

#### 12q21.2

The non-GBM glioma association signal at 12q21.2 appears to map within *RP11-114H23.1*, a lincRNA of currently unknown function. Although only lying adjacent to *PHLDA1*, the known 11q23.3 association maps to the related gene *PHLDB1* that is also specific to non-GBM tumors (30). Although a role for *PHLDA1* in glioma has yet to be established downregulation of *PHLDA1* in neuronal cells has been shown to enhance cell death without Fas induction (100). In addition, *PHLDA1* expression may be involved in regulation of antiapoptotic effects of *IGF1* (101).

#### 12q23.3

The original published GBM SNP at 12q23.3 was rs3851634, which is intronic within *POLR3B* (25). RNA polymerase III (*POLR3B*) is involved in the transcription of small noncoding RNAs and short interspersed nuclear elements, as well as all transfer RNAs (102). Although mutations in *POLR3B* have been shown to cause recessive hypomyelinating leukoencephalopathy (103) thus far there is no evidence implicating the gene in the development of glioma. No variant at 12q23.3 exhibited genome-wide significance in the latest glioma GWAS, and therefore its status as a glioma-risk locus is uncertain.

#### 14q12

At 14q12, the non-GBM glioma risk SNP rs10131032 resides within *AKAP6*. Protein Kinase A–Anchoring Protein 6 targets protein kinase A to the sarcoplasmic reticulum (104) and is commonly deleted in GBM tumors (105).

#### 15q24.2

The non-GBM association signal at 15q24.2 resides within *ETFA*, which participates in mitochondrial fatty acid beta oxidation; shuttling electrons between flavoprotein dehydrogenases and the membrane-bound electron transfer flavoprotein ubiquinone oxidoreductase (106). Mutations of *ETFA* have been reported to be a cause of recessive Glutaric acidemia IIA (107, 108) that features gliosis.

#### 16p13.3

This locus appears to harbor two independent association signals: one for GBM defined by rs2562152 and one for non-GBM defined by rs3751667. In contrast with 7p11.2, where both signals appear to be involved in *EGFR* regulation, the signals at 16p13.3 may have distinct molecular mechanisms. The non-GBM SNP rs3751667 is intronic within *LMF1*, whereas the GBM SNP rs2562152 maps 3-kb telomeric to *MPG* that encodes a N-methylpurine DNA glycosylase whose expression is linked to temozolomide resistance in glioma (109).

#### 16q12.1

At 16q12.1, the C-risk allele of rs10852606 is associated with reduced *HEATR3* expression in brain tissues, consistent with differential expression of *HEATR3* being the functional basis of

the 16q12.1 association. Variation at 16q12.1 is associated with risk of testicular (ref. 110; rs8046148) and esophageal (ref. 111; rs4785204) cancer (pairwise  $r^2$  and  $D'$  with rs10852606, 0.67, 1.0, and 0.16, 1.0, respectively) suggestive of pleiotropic effects on tumor risk.

#### 17p13.1

A GWAS for cutaneous basal cell carcinoma in Icelandic individuals identified rs78378222 ( $P = 5.2 \times 10^{-17}$ , OR = 2.36) as being associated with disease risk (27). rs78378222 lies within the 3'-untranslated region (3'-UTR) of *TP53*, a tumor suppressor gene highly mutated in many cancer types including glioma (112). The authors additionally showed that the variant affected the polyadenylation signal of *TP53*, impairing processing of *TP53* mRNA (27). This is highly suggestive of rs78378222 representing the functional variant at 17p13.1 through disrupting the normal functioning of *TP53*. The study additionally demonstrated a relationship between rs78378222 and risk of prostate cancer (OR = 1.44,  $P = 2.4 \times 10^{-6}$ ), glioma (OR = 2.35,  $P = 1.0 \times 10^{-5}$ ), colorectal adenoma (OR = 1.39,  $P = 1.6 \times 10^{-4}$ ), but not breast cancer (OR = 1.06,  $P = 0.57$ ; ref. 27). A number of additional studies have replicated the association between rs78378222 and glioma risk (20, 32, 113, 114).

#### 20q13.33

Both the original tag-SNP rs6010620 and top SNP in the most recent GWAS rs2297440 are intronic within *RTEL1* (regulator of telomere elongation helicase 1), encoding a DNA helicase involved in telomere and genome-wide replication, with mutations leading to genetic instability (115). A negative, albeit modest association has been demonstrated between the risk allele of rs6010620 and LTL ( $P = 1.1 \times 10^{-3}$ ; refs. 29, 53). However, the glioma risk and telomere length association signals at 20q13.33 do not fully overlap, raising the possibility of extra-telomeric functions at this glioma locus. Variation at 20q13.33 has additionally been implicated in prostate cancer (ref. 40; rs6062509), lung adenocarcinoma (ref. 99; rs41309931), and colorectal cancer (ref. 54; rs4925386). The prostate cancer SNP rs6062509 appears correlated with rs2297440 ( $r^2 = 0.466$ ,  $D' = 0.838$ ), indicative of a shared association signal, whereas the other associations appear to be independent.

#### 22q13.1

The GBM association at 22q13.1 marked by rs2235573 is intronic within *SLC16A8*. Variation at 22q13.1 is additionally associated with melanoma (ref. 72; rs2284063), breast cancer (ref. 116; rs738321), bladder cancer (ref. 117; rs1014971), and multiple myeloma (ref. 118; rs139371), which appear to represent independent signals.

### Perspectives from Glioma GWAS

The glioma GWAS risk loci so far provide support for a polygenic model of disease susceptibility, with currently identified risk SNPs for glioma account for at best around 27% and 37% of the familial risk of GBM and non-GBM tumors, respectively (24). Aside from the fine-mapped associations at 8q24.21 and 17p13.1, the glioma GWAS SNPs identified are relatively common (European MAF > ~9%) and have modest effect sizes ( $1.11 < \text{OR} < 1.63$ ). The loci implicate genes and pathways known to be

important in glioma and cancer biology; for example, *IDH1* at 2q33.3, EGFR–AKT signaling (*EGFR* at 7p11.2, *LRIG1* at 3p14.1, *JAK1* at 1q32.1, *PHLDB1* at 11q23.3), *CDKN2A/B* at 9p21.3, *Myc* at 8q24.21, *TP53* at 17p13.1. In addition, through identification of risk loci at *TERC* (3q26.2), *TERT* (5p15.33), *OBFC1* (10q24.33), and *RTEL1* (20q13.33) GWAS associations reveal telomere maintenance as an important feature in glioma progression.

#### Subtype specificities

While pragmatically within large case–control consortia glioma cases were divided into GBM and non-GBM classifications, it is becoming increasingly clear that these tumors comprise a number of distinctive molecular subtypes, principally involving various combinations of IDH mutation, 1p/19q co-deletion, and *TERT* promoter mutation (48, 119). A number of loci have been assessed for association with molecular features. Notably, rs55705857 at 8q24.21 is highly associated with IDH-mutated gliomas, in particular, those with 1p/19q co-deletion (i.e., classical oligodendroglioma; refs. 28, 34). In contrast, the 5p15.33, 9p21.3, and 20q13.3 loci are associated with IDH wild-type gliomas (120), and rs7837822 at 17p13.1 is reported to be associated with gliomas with *TERT* promoter mutation and IDH mutation without 1p/19q co-deletion (48). The majority of loci, particularly those discovered more recently, await molecular characterization.

#### Glioma risk loci in non-European populations

Glioma incidence varies across population group (121). While the majority of susceptibility studies have been carried out in the northern European population, a number have been carried out in different population groups. In a study of 976 glioma cases and 1,057 controls, Chen and colleagues (122) investigated previously identified risk SNPs in the Chinese population, where generally incidence is lower than in Europe. They reported significant associations at 5p15.33 [rs2736100,  $P = 3.69 \times 10^{-4}$ , OR = 1.26 (1.11–1.43), 11q23.3 (rs498872,  $P = 3.80 \times 10^{-6}$ , OR = 1.38 (1.20–1.57) and 20q13.3 (rs6010620,  $P = 2.79 \times 10^{-6}$ , OR = 1.39 (1.20–1.59)], but not at 8q24.21 or 9p21.3. An additional study of 980 cases and 990 controls reported an association between rs1920116 at 3q26.2 and glioma in the Chinese population (123). Aside from these studies there is a paucity of data currently available for glioma genetic risk in non-European populations.

#### Future Directions

##### Investigating nongenetic glioma risk factors

Glioma GWAS data can additionally be used in investigation of proposed risk factors not necessarily thought to have a genetic component. For example, risk SNPs at 5p15.33, 8q24.21, 9p21.3, 11q23.3, and 20q13.3 were not shown to be associated with allergy (124). In addition, there is limited evidence for variants implicated in Vitamin D metabolism being associated with glioma (125). While Kitahara and colleagues (126) report association between diabetes and reduced risk of glioma, there was no association in glioma with diabetes-related SNPs. Investigating the relationship between risk factors such as these and glioma can be carried out in a relatively unbiased fashion using a Mendelian Randomization approach (127).

#### Functional investigation of mechanistic effect at glioma-risk loci

For the vast majority of glioma risk loci identified so far, the molecular mechanisms underlining the associations have not yet been deciphered. Notable exceptions are the 17p13.1 locus, where rs78378222 has been demonstrated to disrupt *TP53* polyadenylation (27) and 5p15.33, where the risk SNP rs10069690 is reported to create a splice-donor site leading to an alternate *TERT* splice isoform lacking telomerase activity (60). As many of the risk SNPs are noncoding an attractive mechanism of action is through regulating expression of nearby genes. Regulatory targets at risk loci can be explored through Hi-C methodologies as exemplified by Jaeger and colleagues (128) for colorectal cancer and Dryden and colleagues (129) for breast cancer. Of vital importance is the use of appropriate model systems to investigate potential tissue- and developmental stage-specific differences in chromatin architecture, from neuronal progenitor cells (130) through to IDH mutated and wild-type tumors (131).

#### Exploring the relationship between telomere length and glioma risk

Recent reports assessing associations with glioma at telomere-risk loci (53) suggest that increased telomere length is a risk factor for glioma (132). However, these telomere length estimates were based on data from blood cells, and it is unclear whether this correlates with telomere length in cells in the brain. This can be addressed in the near future by projects such as enhancing GTEx (eGTEx) that aim to investigate genetic influences on telomere length across different tissues (133). In addition, the majority of telomere length loci also exhibit strong associations with glioma (i.e., 3q26.2 – *TERC*, 5p15.33 – *TERT*, 10q24.33 – *OBFC1*, 20q13.33 – *RTEL1*). This raises the issue of to what extent risk of glioma is being driven by telomere length at these individual loci, or whether there are any extra-telomeric effects.

#### Conclusion

The past decade has overseen a transformation in our understanding of inherited predisposition to glioma, with the majority of the genetic component explained by a polygenic contribution from at least 25 risk polymorphisms identified through GWAS. It is increasingly recognized that glioma tumors comprise multiple distinctive molecular subtypes, with which germline predisposition variants show particular preferences. Understanding the molecular basis of glioma predisposition loci is still in its relative infancy but is ultimately likely to lead to insight into the etiology of glioma and potentially have therapeutic applications.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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