

Genome-wide association studies in glioma

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GBM, glioblastoma multiforme; GWAS, genome-wide association study; LD, linkage disequilibrium; SNP, single nucleotide polymorphism

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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 summarise 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 tumour formation. These ongoing studies will be important to maximise the impact of research into glioma susceptibility, both in terms of insight into tumour aetiology as well as opportunities for clinical translation.

Introduction

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

To date the only recognised environmental risk factor for glioma is exposure to ionising 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 two-fold elevated risk in relatives of glioma patients (4). Furthermore, an increased risk of glioma is recognised to be associated with a number of Mendelian cancer predisposition syndromes, notable neurofibromatosis (NF1 and NF2), Li-Fraumeni and Turcot's (5-16). Additionally, 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 recognised 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 *et al.* (30), comprising a discovery case-control series of UK and European-American individuals (totalling 1,878 cases and 3,670 controls) and replication series of French, German and Swedish individuals (totalling 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 *et al.* (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 *et al.* (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 ($r^2=0.028$, $D'=1.0$).

A further GWAS by Sanson *et al.* (31) was carried out in 2011, making use of data from the UK and European-American studies previously reported by Shete *et al.* (30) as well as two additional case-control series from France and Germany (totalling 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 *et al.* (29) comprising a UK and European-American discovery series of 1,013 high-grade

glioma cases and 6,595 controls (in part overlapping with the study of Wrensch *et al.* (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 pre-existing 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 *et al.* (25), making use of datasets from Sanson *et al.* (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 *et al.* (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 eight 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 (Figure 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 below.

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 tumour cells and stroma (36), and dysregulation of JAK-STAT signalling 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 tumours 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 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 phosphatidylinositol 3-kinase which 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 tumours.

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 CRC 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 *et al.* 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 (CRC) 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 which 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 ($P=4.4 \times 10^{-19}$) (29,53). 5p15.33 is a pleiotropic cancer risk locus harbouring associations with multiple cancers including breast cancer, prostate cancer, and testicular germ cell tumour (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 tumour development.

7p11.2

The two statistically independent glioma risk SNPs identified (rs11979158 and rs2252586) lie just outside *EGFR* (epidermal growth factor receptor), a receptor tyrosine kinase (RTK) commonly activated in glioma (61). Association between these SNPs and glioma have 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 *et al.* (28) and Enciso-Mora *et al.* (34) suggest that the association is 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 non-coding 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 which 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 sub-regions 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 non-coding 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 tumours, 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 tumour 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-codeleted oligodendrogliomas, with these tumours 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 which 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 *VT11A*. As well as participating in regulating insulin-stimulated trafficking of secretory vesicles (85), *VT11A* plays a key role in neuronal development and in selectively maintaining spontaneous neurotransmitter release (86). While the glioma risk signal appears to be within *VT11A*, 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 (89) cancer. 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 have been reported to function as co-activators of Notch signalling (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 re-differentiation in t(11;17)(q23;21) acute promyelocytic leukaemia (APL) (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 leukaemia (CLL) (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 which 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 signalling 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 (98) (rs4938573) and lung adenocarcinoma (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* which is also specific to non-GBM tumours (30). Although a role for *PHLDA1* in glioma has yet to be established down-regulation of *PHLDA1* in neuronal cells has been shown to enhance cell death without Fas induction (100), additionally *PHLDA1* expression may be involved in regulation of anti-apoptotic 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 tumours (105).

15q24.2

The non-GBM association signal at 15q24.2 resides within *ETFFA*, 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 *ETFFA* have been reported to be a cause of recessive Glutaric acidemia IIA (107,108) which features gliosis.

16p13.3

This locus appears to harbour 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* which 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 (110) (rs8046148) and esophageal (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). rs7837822 lies within the 3'-untranslated region (3'-UTR) of *TP53*, a tumour 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, $P=0.57$) (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 ($P=1.1 \times 10^{-3}$) (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 (40) (rs6062509), lung adenocarcinoma (99) (rs41309931) and colorectal cancer (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 (72) (rs2284063), breast cancer (116) (rs738321), bladder cancer (117) (rs1014971), and multiple myeloma (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 ($1.11<OR<1.63$). The loci implicate genes and pathways known to be important in glioma and cancer biology, for example *IDH1* at 2q33.3, EGFR-AKT signalling (*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. Additionally, 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 tumours 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) (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 characterisation.

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 *et al.* (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 non-genetic 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). Additionally there is limited evidence for variants implicated in Vitamin D metabolism being associated with glioma (125). While Kitahara *et al.* (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 Randomisation 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 non-coding 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 *et al.* (128) for colorectal cancer and Dryden *et al.* (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 tumours (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) which aim to investigate genetic influences on telomere length across different tissues (133). Additionally, 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 recognised that glioma tumours 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 aetiology of glioma and potentially have therapeutic applications.

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REFERENCES

1. Crocetti E, Trama A, Stiller C, Caldarella A, Soffiotti R, Jaal J, *et al.* Epidemiology of glial and non-glial brain tumours in Europe. *Eur J Cancer* **2012**;48(10):1532-42 doi 10.1016/j.ejca.2011.12.013.
2. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, *et al.* Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. *Cancer* **2008**;113(7 Suppl):1953-68 doi 10.1002/cncr.23741.
3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* **2016**;131(6):803-20 doi 10.1007/s00401-016-1545-1.
4. Hemminki K, Tretli S, Sundquist J, Johannesen TB, Granstrom C. Familial risks in nervous-system tumours: a histology-specific analysis from Sweden and Norway. *The Lancet Oncology* **2009**;10(5):481-8 doi 10.1016/S1470-2045(09)70076-2.
5. Li FP, Fraumeni JF, Jr., Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, *et al.* A cancer family syndrome in twenty-four kindreds. *Cancer research* **1988**;48(18):5358-62.
6. Srivastava S, Tong YA, Devadas K, Zou ZQ, Sykes VW, Chen Y, *et al.* Detection of both mutant and wild-type p53 protein in normal skin fibroblasts and demonstration of a shared 'second hit' on p53 in diverse tumors from a cancer-prone family with Li-Fraumeni syndrome. *Oncogene* **1992**;7(5):987-91.
7. Iavarone A, Matthey KK, Steinkirchner TM, Israel MA. Germ-line and somatic p53 gene mutations in multifocal osteogenic sarcoma. *Proceedings of the National Academy of Sciences of the United States of America* **1992**;89(9):4207-9 doi 10.1073/pnas.89.9.4207.
8. Malkin D, Li FP, Strong LC, Fraumeni JF, Jr., Nelson CE, Kim DH, *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* **1990**;250(4985):1233-8 doi 10.1126/science.1978757.
9. Malkin D, Jolly KW, Barbier N, Look AT, Friend SH, Gebhardt MC, *et al.* Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. *The New England journal of medicine* **1992**;326(20):1309-15 doi 10.1056/NEJM199205143262002.
10. Sidransky D, Tokino T, Helzlsouer K, Zehnbaue B, Rausch G, Shelton B, *et al.* Inherited p53 gene mutations in breast cancer. *Cancer research* **1992**;52(10):2984-6.
11. Kyritsis AP, Bondy ML, Xiao M, Berman EL, Cunningham JE, Lee PS, *et al.* Germline p53 gene mutations in subsets of glioma patients. *J Natl Cancer Inst* **1994**;86(5):344-9 doi 10.1093/jnci/86.5.344.
12. Chen P, Iavarone A, Fick J, Edwards M, Prados M, Israel MA. Constitutional p53 mutations associated with brain tumors in young adults. *Cancer genetics and cytogenetics* **1995**;82(2):106-15 doi [http://dx.doi.org/10.1016/0165-4608\(94\)00213-U](http://dx.doi.org/10.1016/0165-4608(94)00213-U).
13. Evans DG, Sainio M, Baser ME. Neurofibromatosis type 2. *J Med Genet* **2000**;37(12):897-904.
14. Gutmann DH, James CD, Poyhonen M, Louis DN, Ferner R, Guha A, *et al.* Molecular analysis of astrocytomas presenting after age 10 in individuals with NF1. *Neurology* **2003**;61(10):1397-400.
15. Poley JW, Wagner A, Hoogmans MM, Menko FH, Tops C, Kros JM, *et al.* Biallelic germline mutations of mismatch-repair genes: a possible cause for multiple pediatric malignancies. *Cancer* **2007**;109(11):2349-56 doi 10.1002/cncr.22697.
16. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, *et al.* The molecular basis of Turcot's syndrome. *The New England journal of medicine* **1995**;332(13):839-47 doi 10.1056/NEJM199503303321302.
17. Randerson-Moor JA, Harland M, Williams S, Cuthbert-Heavens D, Sheridan E, Aveyard J, *et al.* A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. *Human molecular genetics* **2001**;10(1):55-62.

18. Tachibana I, Smith JS, Sato K, Hosek SM, Kimmel DW, Jenkins RB. Investigation of germline PTEN, p53, p16INK4A/p14ARF, and CDK4 alterations in familial glioma. *American Journal of Medical Genetics* **2000**;92(2):136-41 doi 10.1002/(sici)1096-8628(20000515)92:2<136::aid-ajmg11>3.0.co;2-s.
19. Bainbridge MN, Armstrong GN, Gramatges MM, Bertuch AA, Jhangiani SN, Doddapaneni H, *et al.* Germline mutations in shelterin complex genes are associated with familial glioma. *J Natl Cancer Inst* **2015**;107(1):384 doi 10.1093/jnci/dju384.
20. Walsh KM, Anderson E, Hansen HM, Decker PA, Kosel ML, Kollmeyer T, *et al.* Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. *Genetic epidemiology* **2013**;37(2):222-8 doi 10.1002/gepi.21707.
21. Kinnersley B, Kamatani Y, Labussiere M, Wang Y, Galan P, Mokhtari K, *et al.* Search for new loci and low-frequency variants influencing glioma risk by exome-array analysis. *Eur J Hum Genet* **2016**;24(5):717-24 doi 10.1038/ejhg.2015.170.
22. Amirian ES, Armstrong GN, Zhou R, Lau CC, Claus EB, Barnholtz-Sloan JS, *et al.* The Glioma International Case-Control Study: A Report From the Genetic Epidemiology of Glioma International Consortium. *Am J Epidemiol* **2016**;183(2):85-91 doi 10.1093/aje/kwv235.
23. Kinnersley B, Mitchell JS, Gousias K, Schramm J, Idbaih A, Labussiere M, *et al.* Quantifying the heritability of glioma using genome-wide complex trait analysis. *Scientific reports* **2015**;5:17267 doi 10.1038/srep17267.
24. Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il'yasova D, Kinnersley B, *et al.* Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. *Nature genetics* **2017**;49(5):789-94 doi 10.1038/ng.3823.
25. Kinnersley B, Labussiere M, Holroyd A, Di Stefano AL, Broderick P, Vijayakrishnan J, *et al.* Genome-wide association study identifies multiple susceptibility loci for glioma. *Nat Commun* **2015**;6:8559 doi 10.1038/ncomms9559.
26. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, *et al.* Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nature genetics* **2009**;41(8):905-8 doi 10.1038/ng.408.
27. Stacey SN, Sulem P, Jonasdottir A, Masson G, Gudmundsson J, Gudbjartsson DF, *et al.* A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. *Nature genetics* **2011**;43(11):1098-103 doi 10.1038/ng.926.
28. Jenkins RB, Xiao Y, Sicotte H, Decker PA, Kollmeyer TM, Hansen HM, *et al.* A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with IDH1 or IDH2 mutation. *Nature genetics* **2012**;44(10):1122-5 doi 10.1038/ng.2388.
29. Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, *et al.* Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. *Nature genetics* **2014**;46(7):731-5 doi 10.1038/ng.3004.
30. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, *et al.* Genome-wide association study identifies five susceptibility loci for glioma. *Nature genetics* **2009**;41(8):899-904 doi 10.1038/ng.407.
31. Sanson M, Hosking FJ, Shete S, Zelenika D, Dobbins SE, Ma Y, *et al.* Chromosome 7p11.2 (EGFR) variation influences glioma risk. *Human molecular genetics* **2011**;20(14):2897-904 doi 10.1093/hmg/ddr192.
32. Enciso-Mora V, Hosking FJ, Di Stefano AL, Zelenika D, Shete S, Broderick P, *et al.* Low penetrance susceptibility to glioma is caused by the TP53 variant rs78378222. *Br J Cancer* **2013**;108(10):2178-85 doi 10.1038/bjc.2013.155.

33. Rajaraman P, Melin BS, Wang Z, McKean-Cowdin R, Michaud DS, Wang SS, *et al.* Genome-wide association study of glioma and meta-analysis. *Human genetics* **2012**;131(12):1877-88 doi 10.1007/s00439-012-1212-0.
34. Enciso-Mora V, Hosking FJ, Kinnersley B, Wang Y, Shete S, Zelenika D, *et al.* Deciphering the 8q24.21 association for glioma. *Human molecular genetics* **2013**;22(11):2293-302 doi 10.1093/hmg/ddt063.
35. Amos CI, Dennis J, Wang Z, Byun J, Schumacher FR, Gayther SA, *et al.* The OncoArray Consortium: A Network for Understanding the Genetic Architecture of Common Cancers. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **2017**;26(1):126-35 doi 10.1158/1055-9965.EPI-16-0106.
36. Sanz-Moreno V, Gaggioli C, Yeo M, Albrengues J, Wallberg F, Viros A, *et al.* ROCK and JAK1 signaling cooperate to control actomyosin contractility in tumor cells and stroma. *Cancer Cell* **2011**;20(2):229-45 doi 10.1016/j.ccr.2011.06.018.
37. Nicolas CS, Amici M, Bortolotto ZA, Doherty A, Csaba Z, Fafouri A, *et al.* The role of JAK-STAT signaling within the CNS. *JAKSTAT* **2013**;2(1):e22925 doi 10.4161/jkst.22925.
38. Riemenschneider MJ, Buschges R, Wolter M, Reifenberger J, Bostrom J, Kraus JA, *et al.* Amplification and overexpression of the MDM4 (MDMX) gene from 1q32 in a subset of malignant gliomas without TP53 mutation or MDM2 amplification. *Cancer research* **1999**;59(24):6091-6.
39. Garcia-Closas M, Couch FJ, Lindstrom S, Michailidou K, Schmidt MK, Brook MN, *et al.* Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nature genetics* **2013**;45(4):392-8, 8e1-2 doi 10.1038/ng.2561.
40. Eeles RA, Al Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, *et al.* Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nature genetics* **2013**;45(4):385-91 doi 10.1038/Ng.2560.
41. Boland E, Clayton-Smith J, Woo VG, McKee S, Manson FD, Medne L, *et al.* Mapping of deletion and translocation breakpoints in 1q44 implicates the serine/threonine kinase AKT3 in postnatal microcephaly and agenesis of the corpus callosum. *American journal of human genetics* **2007**;81(2):292-303 doi 10.1086/519999.
42. Turner KM, Sun Y, Ji P, Granberg KJ, Bernard B, Hu L, *et al.* Genomically amplified Akt3 activates DNA repair pathway and promotes glioma progression. *Proceedings of the National Academy of Sciences of the United States of America* **2015**;112(11):3421-6 doi 10.1073/pnas.1414573112.
43. Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol* **2009**;174(4):1149-53 doi 10.2353/ajpath.2009.080958.
44. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, *et al.* IDH1 and IDH2 mutations in gliomas. *The New England journal of medicine* **2009**;360(8):765-73 doi 10.1056/NEJMoa0808710.
45. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, *et al.* Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell* **2010**;17(5):510-22 doi 10.1016/j.ccr.2010.03.017.
46. Christensen BC, Smith AA, Zheng S, Koestler DC, Houseman EA, Marsit CJ, *et al.* DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma. *J Natl Cancer Inst* **2011**;103(2):143-53 doi 10.1093/jnci/djq497.
47. Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, *et al.* Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2009**;27(25):4150-4 doi 10.1200/JCO.2009.21.9832.

48. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, *et al.* Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. *The New England journal of medicine* **2015**;372(26):2499-508 doi 10.1056/NEJMoa1407279.
49. Gur G, Rubin C, Katz M, Amit I, Citri A, Nilsson J, *et al.* LRIG1 restricts growth factor signaling by enhancing receptor ubiquitylation and degradation. *EMBO J* **2004**;23(16):3270-81 doi 10.1038/sj.emboj.7600342.
50. Yang JA, Liu BH, Shao LM, Guo ZT, Yang Q, Wu LQ, *et al.* LRIG1 enhances the radiosensitivity of radioresistant human glioblastoma U251 cells via attenuation of the EGFR/Akt signaling pathway. *Int J Clin Exp Pathol* **2015**;8(4):3580-90.
51. Wei J, Qi X, Zhan Q, Zhou D, Yan Q, Wang Y, *et al.* miR-20a mediates temozolomide-resistance in glioblastoma cells via negatively regulating LRIG1 expression. *Biomed Pharmacother* **2015**;71:112-8 doi 10.1016/j.biopha.2015.01.026.
52. Schumacher FR, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, *et al.* Genome-wide association study of colorectal cancer identifies six new susceptibility loci. *Nat Commun* **2015**;6:7138 doi 10.1038/ncomms8138.
53. Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL, *et al.* Identification of seven loci affecting mean telomere length and their association with disease. *Nature genetics* **2013**;45(4):422-7, 7e1-2 doi 10.1038/ng.2528.
54. Houlston RS, Cheadle J, Dobbins SE, Tenesa A, Jones AM, Howarth K, *et al.* Meta-analysis of three genome-wide association studies identifies susceptibility loci for colorectal cancer at 1q41, 3q26.2, 12q13.13 and 20q13.33. *Nature genetics* **2010**;42(11):973-7 doi 10.1038/ng.670.
55. Weinrich SL, Pruzan R, Ma L, Ouellette M, Tesmer VM, Holt SE, *et al.* Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTERT. *Nature genetics* **1997**;17(4):498-502 doi 10.1038/ng1297-498.
56. Haiman CA, Chen GK, Vachon CM, Canzian F, Dunning A, Millikan RC, *et al.* A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nature genetics* **2011**;43(12):1210-4 doi 10.1038/ng.985.
57. Wang Y, Broderick P, Webb E, Wu X, Vijaykrishnan J, Matakidou A, *et al.* Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nature genetics* **2008**;40(12):1407-9 doi 10.1038/ng.273.
58. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, *et al.* Lung cancer susceptibility locus at 5p15.33. *Nature genetics* **2008**;40(12):1404-6 doi 10.1038/ng.254.
59. Turnbull C, Rapley EA, Seal S, Pernet D, Renwick A, Hughes D, *et al.* Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. *Nature genetics* **2010**;42(7):604-7 doi 10.1038/ng.607.
60. Killedar A, Stutz MD, Sobinoff AP, Tomlinson CG, Bryan TM, Beesley J, *et al.* A Common Cancer Risk-Associated Allele in the hTERT Locus Encodes a Dominant Negative Inhibitor of Telomerase. *PLoS genetics* **2015**;11(6):e1005286 doi 10.1371/journal.pgen.1005286.
61. Huang PH, Xu AM, White FM. Oncogenic EGFR Signaling Networks in Glioma. 2009. re6-re p.
62. Yin W, Rossin A, Clifford JL, Gronemeyer H. Co-resistance to retinoic acid and TRAIL by insertion mutagenesis into RAM. *Oncogene* **2006**;25(26):3735-44 doi 10.1038/sj.onc.1209410.
63. Sparrmann A, van Lohuizen M. Polycomb silencers control cell fate, development and cancer. *Nature reviews Cancer* **2006**;6(11):846-56 doi 10.1038/nrc1991.
64. Lynch MD, Smith AJ, De Gobbi M, Flenley M, Hughes JR, Vernimmen D, *et al.* An interspecies analysis reveals a key role for unmethylated CpG dinucleotides in vertebrate Polycomb complex recruitment. *EMBO J* **2012**;31(2):317-29 doi 10.1038/emboj.2011.399.
65. Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, *et al.* Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect

- gene expression. Proceedings of the National Academy of Sciences of the United States of America **2009**;106(28):11667-72 doi 10.1073/pnas.0904715106.
66. Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, *et al.* A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nature genetics **2007**;39(8):984-8 doi 10.1038/ng2085.
 67. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, *et al.* Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nature genetics **2007**;39(5):645-9 doi http://www.nature.com/ng/journal/v39/n5/supinfo/ng2022_S1.html.
 68. Crowther-Swanepoel D, Broderick P, Di Bernardo MC, Dobbins SE, Torres M, Mansouri M, *et al.* Common variants at 2q37.3, 8q24.21, 15q21.3 and 16q24.1 influence chronic lymphocytic leukemia risk. Nature genetics **2010**;42(2):132-6 doi 10.1038/ng.510.
 69. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, *et al.* Genome-wide association study identifies novel breast cancer susceptibility loci. Nature **2007**;447(7148):1087-93 doi 10.1038/nature05887.
 70. Yap KL, Li S, Munoz-Cabello AM, Raguz S, Zeng L, Mujtaba S, *et al.* Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. Mol Cell **2010**;38(5):662-74 doi 10.1016/j.molcel.2010.03.021.
 71. Kotake Y, Nakagawa T, Kitagawa K, Suzuki S, Liu N, Kitagawa M, *et al.* Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15INK4B tumor suppressor gene. Oncogene **2011**;30(16):1956-62 doi <http://www.nature.com/ncj/v30/n16/supinfo/ncj2010568s1.html>.
 72. Bishop DT, Demenais F, Iles MM, Harland M, Taylor JC, Corda E, *et al.* Genome-wide association study identifies three loci associated with melanoma risk. Nature genetics **2009**;41(8):920-5 doi 10.1038/ng.411.
 73. Kyritsis AP, Zhang B, Zhang W, Xiao M, Takeshima H, Bondy ML, *et al.* Mutations of the p16 gene in gliomas. Oncogene **1996**;12(1):63-7.
 74. Foulkes WD, Flanders TY, Pollock PM, Hayward NK. The CDKN2A (p16) gene and human cancer. Molecular medicine **1997**;3(1):5-20.
 75. Alentorn A, Dehais C, Ducray F, Carpentier C, Mokhtari K, Figarella-Branger D, *et al.* Allelic loss of 9p21.3 is a prognostic factor in 1p/19q codeleted anaplastic gliomas. Neurology **2015**;85(15):1325-31 doi 10.1212/WNL.0000000000002014.
 76. Miyake Y, Nakamura M, Nabetani A, Shimamura S, Tamura M, Yonehara S, *et al.* RPA-like mammalian Ctc1-Stn1-Ten1 complex binds to single-stranded DNA and protects telomeres independently of the Pot1 pathway. Mol Cell **2009**;36(2):193-206 doi 10.1016/j.molcel.2009.08.009.
 77. Chen LY, Redon S, Lingner J. The human CST complex is a terminator of telomerase activity. Nature **2012**;488(7412):540-4 doi 10.1038/nature11269.
 78. Zhang C, Doherty JA, Burgess S, Hung RJ, Lindstrom S, Kraft P, *et al.* Genetic determinants of telomere length and risk of common cancers: a Mendelian randomization study. Human molecular genetics **2015**;24(18):5356-66 doi 10.1093/hmg/ddv252.
 79. Walsh KM, Wiencke JK, Lachance DH, Wiemels JL, Molinaro AM, Eckel-Passow JE, *et al.* Telomere maintenance and the etiology of adult glioma. Neuro Oncol **2015**;17(11):1445-52 doi 10.1093/neuonc/nov082.
 80. Walsh KM, Codd V, Rice T, Nelson CP, Smirnov IV, McCoy LS, *et al.* Longer genotypically-estimated leukocyte telomere length is associated with increased adult glioma risk. Oncotarget **2015**;6(40):42468-77 doi 10.18632/oncotarget.6468.
 81. Law MH, Bishop DT, Lee JE, Brossard M, Martin NG, Moses EK, *et al.* Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma. Nature genetics **2015**;47(9):987-95 doi 10.1038/ng.3373.

82. Chahal HS, Wu W, Ransohoff KJ, Yang L, Hedlin H, Desai M, *et al.* Genome-wide association study identifies 14 novel risk alleles associated with basal cell carcinoma. *Nat Commun* **2016**;7:12510 doi 10.1038/ncomms12510.
83. Gudmundsson J, Thorleifsson G, Sigurdsson JK, Stefansdottir L, Jonasson JG, Gudjonsson SA, *et al.* A genome-wide association study yields five novel thyroid cancer risk loci. *Nat Commun* **2017**;8:14517 doi 10.1038/ncomms14517.
84. Cao Y, Saygili Y, Ummadisingu A, Teuscher J, Luo J, Pellet N, *et al.* 11% efficiency solid-state dye-sensitized solar cells with copper(II/I) hole transport materials. *Nat Commun* **2017**;8:15390 doi 10.1038/ncomms15390.
85. Bose A, Guilherme A, Huang S, Hubbard AC, Lane CR, Soriano NA, *et al.* The v-SNARE Vti1a regulates insulin-stimulated glucose transport and Acrp30 secretion in 3T3-L1 adipocytes. *The Journal of biological chemistry* **2005**;280(44):36946-51 doi 10.1074/jbc.M508317200.
86. Ramirez DM, Khvotchev M, Trauterman B, Kavalali ET. Vti1a identifies a vesicle pool that preferentially recycles at rest and maintains spontaneous neurotransmission. *Neuron* **2012**;73(1):121-34 doi 10.1016/j.neuron.2011.10.034.
87. Zhang B, Jia WH, Matsuda K, Kweon SS, Matsuo K, Xiang YB, *et al.* Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk. *Nature genetics* **2014**;46(6):533-42 doi 10.1038/ng.2985.
88. Lan Q, Hsiung CA, Matsuo K, Hong YC, Seow A, Wang Z, *et al.* Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nature genetics* **2012**;44(12):1330-5 doi 10.1038/ng.2456.
89. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, *et al.* Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nature genetics* **2013**;45(4):353-61, 61e1-2 doi 10.1038/ng.2563.
90. Wu L, Sun T, Kobayashi K, Gao P, Griffin JD. Identification of a family of mastermind-like transcriptional coactivators for mammalian notch receptors. *Molecular and cellular biology* **2002**;22(21):7688-700.
91. Chen SJ, Zelent A, Tong JH, Yu HQ, Wang ZY, Derre J, *et al.* Rearrangements of the retinoic acid receptor alpha and promyelocytic leukemia zinc finger genes resulting from t(11;17)(q23;q21) in a patient with acute promyelocytic leukemia. *The Journal of clinical investigation* **1993**;91(5):2260-7 doi 10.1172/JCI116453.
92. Ahmad KF, Engel CK, Prive GG. Crystal structure of the BTB domain from PLZF. *Proceedings of the National Academy of Sciences of the United States of America* **1998**;95(21):12123-8 doi 10.1073/pnas.95.21.12123.
93. Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, *et al.* A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nature genetics* **2014**;46(10):1103-9 doi 10.1038/ng.3094.
94. Law PJ, Berndt SI, Speedy HE, Camp NJ, Sava GP, Skibola CF, *et al.* Genome-wide association analysis implicates dysregulation of immunity genes in chronic lymphocytic leukaemia. *Nat Commun* **2017**;8:14175 doi 10.1038/ncomms14175.
95. Rice T, Zheng S, Decker PA, Walsh KM, Bracci P, Xiao Y, *et al.* Inherited variant on chromosome 11q23 increases susceptibility to IDH-mutated but not IDH-normal gliomas regardless of grade or histology. *Neuro Oncol* **2013**;15(5):535-41 doi 10.1093/neuonc/nos324.
96. Zhou QL, Jiang ZY, Mabardy AS, Del Campo CM, Lambright DG, Holik J, *et al.* A novel pleckstrin homology domain-containing protein enhances insulin-stimulated Akt phosphorylation and GLUT4 translocation in adipocytes. *The Journal of biological chemistry* **2010**;285(36):27581-9 doi 10.1074/jbc.M110.146886.
97. Denduluri SK, Idowu O, Wang Z, Liao Z, Yan Z, Mohammed MK, *et al.* Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance. *Genes Dis* **2015**;2(1):13-25 doi 10.1016/j.gendis.2014.10.004.

98. Skibola CF, Berndt SI, Vijai J, Conde L, Wang Z, Yeager M, *et al.* Genome-wide association study identifies five susceptibility loci for follicular lymphoma outside the HLA region. *American journal of human genetics* **2014**;95(4):462-71 doi 10.1016/j.ajhg.2014.09.004.
99. McKay JD, Hung RJ, Han Y, Zong X, Carreras-Torres R, Christiani DC, *et al.* Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nature genetics* **2017**;49(7):1126-32 doi 10.1038/ng.3892.
100. Johnson EO, Chang KH, de Pablo Y, Ghosh S, Mehta R, Badve S, *et al.* PHLDA1 is a crucial negative regulator and effector of Aurora A kinase in breast cancer. *J Cell Sci* **2011**;124(Pt 16):2711-22 doi 10.1242/jcs.084970.
101. Sellheyer K, Nelson P, Kutzner H, Patel RM. The immunohistochemical differential diagnosis of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheiform basal cell carcinoma using BerEP4 and stem cell markers. *J Cutan Pathol* **2013**;40(4):363-70 doi 10.1111/cup.12085.
102. Dieci G, Fiorino G, Castelnuovo M, Teichmann M, Pagano A. The expanding RNA polymerase III transcriptome. *Trends in genetics : TIG* **2007**;23(12):614-22 doi 10.1016/j.tig.2007.09.001.
103. Saito H, Osaka H, Sasaki M, Takanashi J, Hamada K, Yamashita A, *et al.* Mutations in POLR3A and POLR3B encoding RNA Polymerase III subunits cause an autosomal-recessive hypomyelinating leukoencephalopathy. *American journal of human genetics* **2011**;89(5):644-51 doi 10.1016/j.ajhg.2011.10.003.
104. McCartney S, Little BM, Langeberg LK, Scott JD. Cloning and characterization of A-kinase anchor protein 100 (AKAP100). A protein that targets A-kinase to the sarcoplasmic reticulum. *The Journal of biological chemistry* **1995**;270(16):9327-33.
105. Leiserson MD, Blokh D, Sharan R, Raphael BJ. Simultaneous identification of multiple driver pathways in cancer. *PLoS Comput Biol* **2013**;9(5):e1003054 doi 10.1371/journal.pcbi.1003054.
106. Frerman FE. Acyl-CoA dehydrogenases, electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase. *Biochemical Society transactions* **1988**;16(3):416-8.
107. Indo Y, Glassberg R, Yokota I, Tanaka K. Molecular characterization of variant alpha-subunit of electron transfer flavoprotein in three patients with glutaric acidemia type II--and identification of glycine substitution for valine-157 in the sequence of the precursor, producing an unstable mature protein in a patient. *American journal of human genetics* **1991**;49(3):575-80.
108. Freneaux E, Sheffield VC, Molin L, Shires A, Rhead WJ. Glutaric acidemia type II. Heterogeneity in beta-oxidation flux, polypeptide synthesis, and complementary DNA mutations in the alpha subunit of electron transfer flavoprotein in eight patients. *The Journal of clinical investigation* **1992**;90(5):1679-86 doi 10.1172/JCI116040.
109. Xipell E, Aragon T, Martinez-Velez N, Vera B, Idoate MA, Martinez-Irujo JJ, *et al.* Endoplasmic reticulum stress-inducing drugs sensitize glioma cells to temozolomide through downregulation of MGMT, MPG, and Rad51. *Neuro Oncol* **2016** doi 10.1093/neuonc/now022.
110. Ruark E, Seal S, McDonald H, Zhang F, Elliot A, Lau K, *et al.* Identification of nine new susceptibility loci for testicular cancer, including variants near DAZL and PRDM14. *Nature genetics* **2013**;45(6):686-9 doi 10.1038/ng.2635.
111. Wu C, Kraft P, Zhai K, Chang J, Wang Z, Li Y, *et al.* Genome-wide association analyses of esophageal squamous cell carcinoma in Chinese identify multiple susceptibility loci and gene-environment interactions. *Nature genetics* **2012**;44(10):1090-7 doi 10.1038/ng.2411.
112. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene* **2007**;26(15):2157-65 doi 10.1038/sj.onc.1210302.

113. Egan KM, Nabors LB, Olson JJ, Monteiro AN, Browning JE, Madden MH, *et al.* Rare TP53 genetic variant associated with glioma risk and outcome. *J Med Genet* **2012**;49(7):420-1 doi 10.1136/jmedgenet-2012-100941.
114. Wang Z, Rajaraman P, Melin BS, Chung CC, Zhang W, McKean-Cowdin R, *et al.* Further Confirmation of Germline Glioma Risk Variant rs78378222 in TP53 and Its Implication in Tumor Tissues via Integrative Analysis of TCGA Data. *Hum Mutat* **2015**;36(7):684-8 doi 10.1002/humu.22799.
115. Vannier JB, Sandhu S, Petalcorin MI, Wu X, Nabi Z, Ding H, *et al.* RTEL1 is a replisome-associated helicase that promotes telomere and genome-wide replication. *Science* **2013**;342(6155):239-42 doi 10.1126/science.1241779.
116. Michailidou K, Lindstrom S, Dennis J, Beesley J, Hui S, Kar S, *et al.* Association analysis identifies 65 new breast cancer risk loci. *Nature* **2017**;551(7678):92-4 doi 10.1038/nature24284.
117. Rothman N, Garcia-Closas M, Chatterjee N, Malats N, Wu X, Figueroa JD, *et al.* A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. *Nature genetics* **2010**;42(11):978-84 doi 10.1038/ng.687.
118. Weinhold N, Johnson DC, Chubb D, Chen B, Forsti A, Hosking FJ, *et al.* The CCND1 c.870G>A polymorphism is a risk factor for t(11;14)(q13;q32) multiple myeloma. *Nature genetics* **2013**;45(5):522-5 doi 10.1038/ng.2583.
119. Cancer Genome Atlas Research N, Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, *et al.* Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. *The New England journal of medicine* **2015**;372(26):2481-98 doi 10.1056/NEJMoa1402121.
120. Di Stefano AL, Enciso-Mora V, Marie Y, Desestret V, Labussiere M, Boisselier B, *et al.* Association between glioma susceptibility loci and tumour pathology defines specific molecular etiologies. *Neuro Oncol* **2013**;15(5):542-7 doi 10.1093/neuonc/nos284.
121. Dubrow R, Darefsky AS. Demographic variation in incidence of adult glioma by subtype, United States, 1992-2007. *BMC Cancer* **2011**;11:325 doi 10.1186/1471-2407-11-325.
122. Chen H, Chen Y, Zhao Y, Fan W, Zhou K, Liu Y, *et al.* Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33) with glioma susceptibility in a Chinese population. *Am J Epidemiol* **2011**;173(8):915-22 doi 10.1093/aje/kwq457.
123. Wang D, Hu E, Wu P, Yuan W, Xu S, Sun Z, *et al.* Genetic variant near TERC influencing the risk of gliomas with older age at diagnosis in a Chinese population. *Journal of neuro-oncology* **2015**;124(1):57-64 doi 10.1007/s11060-015-1819-9.
124. Safaeian M, Rajaraman P, Hartge P, Yeager M, Linet M, Butler MA, *et al.* Joint effects between five identified risk variants, allergy, and autoimmune conditions on glioma risk. *Cancer causes & control : CCC* **2013**;24(10):1885-91 doi 10.1007/s10552-013-0244-7.
125. Anic GM, Thompson RC, Nabors LB, Olson JJ, Browning JE, Madden MH, *et al.* An exploratory analysis of common genetic variants in the vitamin D pathway including genome-wide associated variants in relation to glioma risk and outcome. *Cancer causes & control : CCC* **2012**;23(9):1443-9 doi 10.1007/s10552-012-0018-7.
126. Kitahara CM, Linet MS, Brenner AV, Wang SS, Melin BS, Wang Z, *et al.* Personal history of diabetes, genetic susceptibility to diabetes, and risk of brain glioma: a pooled analysis of observational studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **2014**;23(1):47-54 doi 10.1158/1055-9965.EPI-13-0913.
127. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol* **2011**;40(3):740-52 doi 10.1093/ije/dyq151.
128. Jager R, Migliorini G, Henrion M, Kandaswamy R, Speedy HE, Heindl A, *et al.* Capture Hi-C identifies the chromatin interactome of colorectal cancer risk loci. *Nat Commun* **2015**;6:6178 doi 10.1038/ncomms7178.

129. Dryden NH, Broome LR, Dudbridge F, Johnson N, Orr N, Schoenfelder S, *et al.* Unbiased analysis of potential targets of breast cancer susceptibility loci by Capture Hi-C. *Genome research* **2014**;24(11):1854-68 doi 10.1101/gr.175034.114.
130. Dixon JR, Jung I, Selvaraj S, Shen Y, Antosiewicz-Bourget JE, Lee AY, *et al.* Chromatin architecture reorganization during stem cell differentiation. *Nature* **2015**;518(7539):331-6 doi 10.1038/nature14222.
131. Flavahan WA, Drier Y, Liao BB, Gillespie SM, Venteicher AS, Stemmer-Rachamimov AO, *et al.* Insulator dysfunction and oncogene activation in IDH mutant gliomas. *Nature* **2016**;529(7584):110-4 doi 10.1038/nature16490.
132. Telomeres Mendelian Randomization C, Haycock PC, Burgess S, Nounu A, Zheng J, Okoli GN, *et al.* Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. *JAMA Oncol* **2017**;3(5):636-51 doi 10.1001/jamaoncol.2016.5945.
133. e GP. Enhancing GTEx by bridging the gaps between genotype, gene expression, and disease. *Nature genetics* **2017**;49(12):1664-70 doi 10.1038/ng.3969.

TABLES

Table 1: Glioma susceptibility loci identified by GWAS in european populations. Odds ratios are reported with respect to the risk allele, highlighted in bold.

Glioma association study			Reported glioma risk variants						
Reference	Study	Sample size (cases/controls)	Glioma Subtype	Locus	Gene	SNP	Alleles	P-value	OR (95% CI)
Shete et al., 2009 (30)	UK-GWAS	631/1,434	All	5p15.33	<i>TERT</i>	rs2736100	T/ G	1.50x10 ⁻¹⁷	1.27 (1.19-1.37)
	MDA-GWAS	1,247/2,236	All	8q24.21	<i>CCDC26</i>	rs4295627	G /T	2.34x10 ⁻¹⁸	1.36 (1.29-1.43)
	French-replication	1,392/1,602	All	8q24.21	<i>CCDC26</i>	rs891835	G /T	7.54x10 ⁻¹¹	1.24 (1.17-1.30)
	German-replication	504/573	All	9p21.3	<i>CDKN2A/B</i>	rs4977756	A/ G	7.24x10 ⁻¹⁵	1.24 (1.19-1.30)
	Swedish-replication	649/778	All	11q23.3	<i>PHLDB1</i>	rs498872	C/T	1.07x10 ⁻⁸	1.18 (1.13-1.24)
	Total	4,423/6,623	All	20q13.33	<i>RTEL1</i>	rs6010620	G /A	2.52x10 ⁻¹²	1.28 (1.21-1.35)
Wrensch et al., 2009 (26)	SFAGS	692/3,992	High-grade	9p21.3	<i>CDKN2A/B</i>	rs1412829	C /T	1.85x10 ⁻¹⁰	1.42 (1.27-1.58)
	Mayo-replication	176/174	High-grade	20q13.33	<i>RTEL1</i>	rs6010620	G /A	3.40x10 ⁻⁹	1.52 (1.32-1.75)
	Total	868/4,166	High-grade	20q13.33	<i>RTEL1</i>	rs4809324	C /T	1.70x10 ⁻⁹	1.60 (1.37-1.87)
Sanson et al., 2011 (31)	UK-GWAS	631/2,699	All	7p11.2	<i>EGFR</i>	rs11979158	A /G	7.72x10 ⁻⁸	1.23 (1.15-1.35)
	French-GWAS	1,423/1,190	All	7p11.2	<i>EGFR</i>	rs2252586	T/ C	2.09x10 ⁻⁸	1.18 (1.11-1.25)
	German-GWAS	846/1,310							
	MDA-GWAS	1,247/2,236							
	Total	4,147/7,435							
Stacey et	Iceland imputation	135/>37,881	All	17p13.1	<i>TP53</i>	rs78378222	T/ G	1.0x10 ⁻⁵	2.35 (1.61-3.44)

al., 2011 (27)									
	Iceland genotyped	72/7,200							
	USA UCSF	658/573							
	USA Mayo Clinic	530/283							
	Total	1,395/>45,937							
Rajaraman et al., 2012 (33)	GliomaScan	1,856/4,955							
Jenkins et al., 2012 (28)	Mayo Clinic	860/795	Oligodendrogl oma	8q24.21	<i>CCDC26</i>	rs55705857	A/G	2.2x10 ⁻²⁸	6.3 (4.6-8.8)
	UCSF AGS	953/1,079							
	Total	1,813/1,874							
Walsh et al., 2014 (29)	SFAGS	692/3,992	High-grade	3q26.2	Near <i>TERC</i>	rs1920116	G/A	8.3x10 ⁻⁹	1.30 (1.19-1.42)
	TCGA cases, WTCCC controls	323/2,603							
	Mayo-UCSF replication	631/1,141							
	Total	1,646/7,736							
Kinnersley et al., 2015 (25)	UK-GWAS	631/2,699	Non-GBM	10q25.2	<i>VTI1A</i>	rs11196067	A/T	4.32x10 ⁻⁸	1.19 (1.12-1.27)
	French-GWAS	1,423/1,190	Non-GBM	11q23.2	<i>ZBTB16</i>	rs648044	C/T	6.26x10 ⁻¹¹	1.25 (1.17-1.34)
	German-GWAS	846/1,310	Non-GBM	12q21.2	Intergenic	rs12230172	G/A	7.53x10 ⁻¹¹	1.23 (1.16-1.32)

	MDA-GWAS	1,247/2,236	GBM	12q23.3	<i>POLR3B</i>	rs3851634	T/C	3.02x10 ⁻⁹	1.23 (1.15-1.32)
	UK Replication	1,490/1,723	Non-GBM	15q24.2	<i>ETFA</i>	rs1801591	G/A	5.71x10 ⁻⁹	1.36 (1.23-1.51)
	Total	5,637/9,158							
Melin et al., 2017 (24)	UK-GWAS	631/2,699	<i>New loci</i>						
	French-GWAS	1,423/1,190	GBM	1p31.3	<i>JAK1</i>	rs12752552	T/C	2.04x10 ⁻⁹	1.22 (1.15-1.31)
	German-GWAS	846/1,310	Non-GBM	1q32.1	<i>MDM4</i>	rs4252707	G/A	3.34x10 ⁻⁹	1.19 (1.12-1.26)
	MDA-GWAS	1,175/2,236	Non-GBM	1q44	<i>AKT3</i>	rs12076373	G/C	2.63x10 ⁻¹⁰	1.23 (1.16-1.32)
	SFAGS	677/3,940	Non-GBM	2q33.3	Near <i>IDH1</i>	rs7572263	A/G	2.18x10 ⁻¹⁰	1.20 (1.13-1.26)
	GliomaScan	1,653/2,725	Non-GBM	3p14.1	<i>LRIG1</i>	rs11706832	A/C	7.66x10 ⁻⁹	1.15 (1.09-1.20)
	GICC	4,572/3,286	Non-GBM	10q24.33	<i>OBFC1</i>	rs11598018	C/A	3.39x10 ⁻⁸	1.14 (1.09-1.20)
	UCSF/Mayo	1,519/804	GBM	11q14.1	Intergenic	rs11233250	C/T	9.95x10 ⁻¹⁰	1.24 (1.16-1.33)
	Total	12,496/18,190	Non-GBM	11q21	<i>MAML2</i>	rs7107785	T/C	3.87x10 ⁻¹⁰	1.16 (1.11-1.21)
			Non-GBM	14q12	<i>AKAP6</i>	rs10131032	G/A	5.07x10 ⁻¹¹	1.33 (1.22-1.44)
			GBM	16p13.3	Near <i>MPG</i>	rs2562152	A/T	1.93x10 ⁻⁸	1.21 (1.13-1.29)
			Non-GBM	16p13.3	<i>LMF1</i>	rs3751667	C/T	2.61x10 ⁻⁹	1.18 (1.12-1.25)
			GBM	16q12.1	<i>HEATR3</i>	rs10852606	T/C	1.29x10 ⁻¹¹	1.18 (1.13-1.24)
			GBM	22q13.1	<i>SLC16A8</i>	rs2235573	G/A	1.76x10 ⁻¹⁰	1.15 (1.10-1.20)
			<i>Existing loci</i>						
			All glioma	3q26.2	Near <i>TERC</i>	rs3772190	G/A	2.25x10 ⁻⁶	1.11 (1.06-1.15)
			GBM	5p15.33	<i>TERT</i>	rs10069690	C/T	8.33x10 ⁻⁷⁴	1.61 (1.53-1.69)
		GBM	7p11.2	<i>EGFR</i>	rs75061358	T/G	4.94x10 ⁻³⁴	1.63 (1.50-1.76)	

			GBM	7p11.2	<i>EGFR</i>	rs723527	A/G	4.79x10 ⁻²³	1.25 (1.20-1.31)
			Non-GBM	8q24.21	<i>CCDC26</i>	rs55705857	A/G	7.28x10 ⁻¹⁴⁹	3.39 (3.09-3.71)
			GBM	9p21.3	<i>CDKN2A/B</i>	rs634537	T/G	7.23x10 ⁻⁴⁵	1.37 (1.31-1.43)
			Non-GBM	10q25.2	<i>VTI1A</i>	rs11599775	G/A	3.44x10 ⁻⁹	1.16 (1.10-1.22)
			Non-GBM	11q23.2	<i>ZBTB16</i>	rs648044	A/G	4.66x10 ⁻¹²	1.19 (1.13-1.25)
			Non-GBM	11q23.3	<i>PHLDB1</i>	rs12803321	G/C	6.33x10 ⁻⁴³	1.42 (1.35-1.49)
			Non-GBM	12q21.2	Intergenic	rs1275600	T/A	3.72x10 ⁻⁹	1.16 (1.10-1.21)
			GBM	12q23.33	<i>RFX4</i>	rs12227783	A/T	1.60x10 ⁻⁵	1.16 (1.08-1.24)
			Non-GBM	15q24.2	<i>ETFA</i>	rs77633900	G/C	1.60x10 ⁻¹³	1.35 (1.25-1.46)
			All glioma	17p13.1	<i>TP53</i>	rs78378222	T/G	8.64x10 ⁻³⁸	2.53 (2.19-2.91)
			GBM	20q13.3	<i>RTEL1</i>	rs2297440	T/C	3.66x10 ⁻⁴⁶	1.48 (1.40-1.56)

FIGURE LEGENDS

Figure 1: Relative impact of SNP associations at glioma risk loci for GBM and non-GBM tumours.

Glioma risk estimates are from Melin *et al.*, 2017 (24). Odds ratios (ORs) were derived with respect to the risk allele.

FIGURES

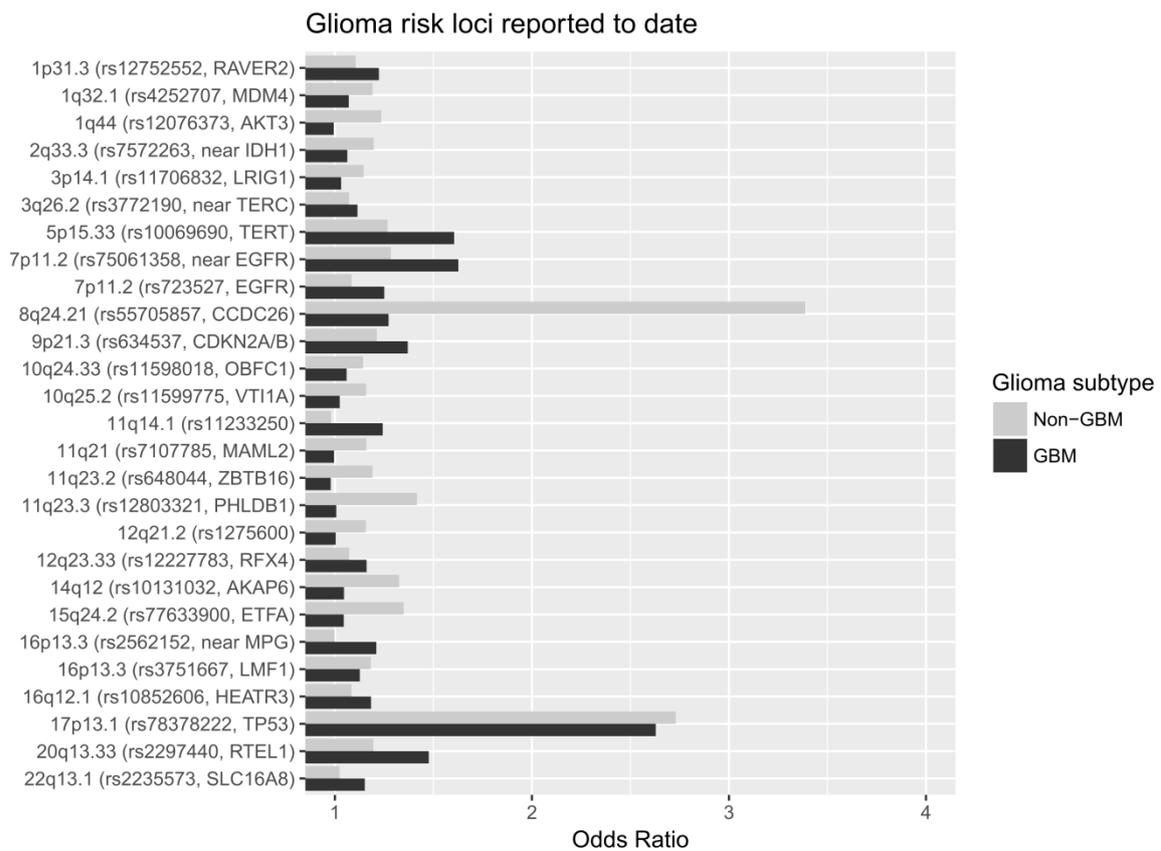


Figure 1: Relative impact of SNP associations at glioma risk loci for GBM and non-GBM tumours. Glioma risk estimates are from Melin *et al.*, 2017 (24). Odds ratios (ORs) were derived with respect to the risk allele.