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Genetic Advances in Glioma: Susceptibility Genes and Networks

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Abstract

Recent advances in human genome studies have opened new avenues for the identification of susceptibility genes for many complex genetic disorders, especially in the field of rare cancers such as glioma. To date, eight glioma susceptibility loci have been identified by candidate gene-association studies: *PRKDC* G6721T, *XRCC1* W399R, *PARP1* A762V, *MGMT* F84L, *ERCC1* A8092C, *ERCC2* Q751K, *EGF* +61 A/G and *IL13* R110G. Five loci have been identified by genome-wide association studies: *TERT* rs2736100, *CCDC26* rs4295627, *CDKN2A-CDKN2B* rs4977756, *PHLDB1* rs498872, and *RTEL1* rs6010620. Using the Ingenuity Pathway Analysis tool, we investigated whether these 13 susceptibility genes are biologically related. Our data provide not only networks for understanding the biological properties of gliomagenesis but useful pathway maps for future understanding of disease.

Keywords

Glioma; Susceptibility; Pathway analysis

Introduction

While primary brain tumors (PBTs), are relatively rare (5%–9% of all cancers), approximately 22,070 individuals are diagnosed each year in the US [1]. Moreover, PBTs have very poor prognosis and are associated with considerable morbidity and mortality. They are a leading cause of cancer death in childhood, the second leading cause of cancer-related death in men aged 20–39, and the fifth leading cause of cancer-related death in women aged 20–39. Gliomas, the most common type of brain tumors, are derived from glial cells that surround and support neurons in the brain. Gliomas of astrocytic, oligodendroglial, and ependymal origin account for ~ 80% of malignant PBTs.

Diverse environmental factors have been implicated in epidemiological studies of glioma including radiation, occupational exposure and environmental carcinogens, Allergy and

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Competing interests statement

The authors declare no competing financial interests

immunological conditions, and viral infection [2]. However, to date only therapeutic ionizing or high-dose radiation is an established risk factor [3]. A number of rare inherited cancer syndromes, melanoma-brain tumor (P16/CDKN2A mutations) [4], neurofibromatosis (NF1 mutations), tuberous sclerosis (APC mutations), and Li-Fraumeni (TP53 mutations) are recognized to confer substantive risk of glioma [5], however collectively these only explain a small proportion of cases [6–10]. Current evidence suggests that a model of glioma susceptibility based solely on high-risk mutations seems unlikely. Thus, as with other cancers, much of the inherited risk is likely to be a consequence of the co-inheritance of multiple low-risk variants, some of which will be common and hence identifiable through association-based analyses.

Completion of the Human Genome Project in 2000 has allowed complete annotation of genetic variation across the genome. This coupled with the development of analytical platforms capable of parallel processing of genotyping is allowing performing genome-wide association studies a cost-effective manner. In this brief review we will critically discuss the candidate genes and SNPs which have been linked to glioma risk. We also review emerging data on whole genome-association searches to identify risk loci. Finally, we have implemented an Ingenuity Pathways Analysis tool to study the inter-relationship between risk loci in a biologically meaningful fashion.

Candidate gene-association studies

Candidate gene-association studies for glioma have mainly focused on four hypothesized pathways: DNA repair, cell cycle, metabolism, and inflammation (including allergies and infections). These studies are continuously updated at The Genetic Association Database online (<http://geneticassociationdb.nih.gov/>). Although some promising findings have been reported, very few have been confirmed in subsequent independent replication studies. Because glioma is a rare cancer, there are serious limitations of small sample sizes (very few studies have had >500 cases and controls) and the characteristic heterogeneity of gliomas. Furthermore, studies have been seriously underpowered to establish interactions.

We recently published an overview of candidate genes associated with glioma susceptibility [11]. Based on those results, we identified eight susceptibility loci that each had been reliably associated with glioma in at least two populations from case-control studies. Table 1 presents a list of eight literature-defined putative functional polymorphisms. Additional criteria for inclusion included replication in at least one other population and replication with the same SNP. These eight genes and SNPs were: DNA repair genes *PRKDC* (also known as *XRCC7*) G6721T [12,13], *XRCC1* W399R [13–15], *PARP1* A762V [13,15], *MGMT* F84L [15,16], *ERCC1* A8092C [17,18], and *ERCC2* Q751K [13,18]; cell cycle gene *EGF* +61 A/G [19,20]; and inflammation gene *IL-13* R110G [21,22]. Studies that examined the correlations between metabolism genes and glioma risk did not generate a clear pattern of association. The effect estimates (odds ratios [ORs]) associated with variants is modest, typical between 0.5 and 1.5.

It has been reported that there is an inverse association between self-reported allergies and glioma risk [23]. The observation that *IL13* R110G showed a protective effect with glioma lends further biological plausibility for such a relationship as variation in *IL13* has been linked to atopy risk. Of these the eight susceptibility genes, six were from DNA repair pathway, which supports the importance of DNA repair genes in the pathogenesis of glioma. These observations suggest that evaluation of further polymorphisms mapping to these loci is likely to lead to the identification of additional novel risk variants.

Genome wide association studies

Two glioma genome wide association (GWA) studies have so far been reported. In our GWAS [24], we conducted a meta-analysis of two GWA studies which involved the genotyping of 454,576 tagging SNPs in a total of 1,878 glioma cases and 3670 controls (1,434 from the 1958 Birth Cohort controls, 2,236 from Cancer Genetic Markers of Susceptibility [CGEMS] breast controls), with validation in three additional independent series totaling 2545 cases and 2953 controls. We identified five risk loci for glioma at 5p15.33 (*TERT* rs2736100), 8q24.21 (*CCDC26* rs4295627), 9p21.3 (*CDKN2A–CDKN2B* rs4977756), 11q23.3 (*PHLDB1* rs498872), and 20q13.33 (*RTEL1* rs6010620). The second independent GWA study of glioma [25] reported was based on an analysis of 275,895 SNPs in 692 adult patients with high-grade glioma and 3992 controls (602 from University of California – San Francisco and 3390 from Illumina iControlDB) with a replication series of 176 high-grade glioma cases and 174 controls. That analysis provided further evidence to implicate the 9p21 (*CDKN2B* rs1412829) and 20q13.3 (*RTEL1* rs6010620) in glioma risk. Although the replication set of Wrensch et al. [25] did not reach formal statistical significance for 5p15.33 (*TERT* rs2736100), this SNP had the lowest p-value in their discovery set. Both GWA used publicly available controls in the discovery phase. While this reduces the cost of studies, it limits the ability to identify gene-environment interactions.

RTEL1 (regulator of telomere elongation helicase 1) is a DNA helicase critical for regulation of telomere length in mice, and its loss has been associated with shortened telomere length, chromosome breaks, and translocations [26]. Moreover, *RTEL1* is important member of the DNA double-strand break-repair pathway, and it maintains genomic stability directly by suppressing homologous recombination [27]. Coincidentally, *TERT* (telomerase reverse transcriptase) is also a telomerase-related gene that is essential for telomerase activity in maintaining telomeres and cell immortalization. *TERT* has an established role in glioma grade and prognosis [28,29]. *CCDC26* is a retinoic acid modulator of differentiation and death that induces caspase 8 transcription and increases apoptosis in response to death stimuli in neuroblastoma cells and in glioblastoma cells by down-regulating telomerase activity [30,31]. *CDKN2A* is a well-known tumor suppressor gene. *CDKN2A* encoding p16(INK4A) a negative regulator of cyclin-dependent kinases and p14(ARF1), an activator of p53. Regulation of p16/p14ARF is important for sensitivity to ionizing radiation, the only environmental factor strongly linked to gliomagenesis [32–34]. *CDKN2B* also is a cyclin-dependent kinase inhibitor that regulates cell growth and cell cycle G1 progression. In glioblastoma cells, overexpression of *CDKN2B* in a *CDKN2A*-deficient background has been shown to inhibit cell growth, induce replicative senescence, and inhibit telomerase activity [35]. Although there is no direct evidence for a role of *PHLDB1* in glioma, intriguingly, 11q23.3 is commonly deleted in neuroblastoma [36].

It is very interesting to note that the function of the five glioma susceptibility genes identified by GWA studies (*RTEL1*, *TERT*, *CCDC26*, *CDKN2A–CDKN2B*, and *PHLDB1*), four (*TERT*, *RTEL1*, *CCDC26*, and *CDKN2B*) have very close links to telomerase. *TERT* is the telomerase catalytic subunit, and *RTEL1* is directly involved in telomerase length, whereas the other two are related to telomerase activity. Taken together, these data provide strong evidence that common variation in telomerase-related genes contributes to glioma predisposition.

While the effect estimates of glioma associated with each of these five risk genes and variants are modest (ORs 1.18–1.36) in GWA the risk variants are common in the population and hence they play a significant role in the development of glioma in general. Because there is substantial genetic heterogeneity exists within glioma tumors of the same histological subtype, it is generally believed that there are multiple pathways and genes of genetic alterations leading to the pathogenesis of gliomas. Thus, it remains to be discovered how these genes (and SNPs)

work in networks, and the susceptibility genes must be examined together to determine the true meaning of how these genes form functional biological networks and pathways that confer risk for glioma.

Network analysis

Ingenuity Pathway Analysis software (Ingenuity® Systems, www.ingenuity.com) were utilized to investigate the functional epistatic relationships among the genes identified by the candidate gene and GWAS approaches. Figure 1 shows how these genes relate to one or another and form pathways. Of these 14 genes, 12 (all except *RTEL1* and *CCDC26*) have established direct or indirect interactions, with 21 network-eligible genes involved. These networks were identified around several major genes, including cell cycle genes *CDKN2A*, *ERBB2*, and *EGF*; telomerase maintenance gene *TERT*; and inflammation gene *NFKB*. Filtering the interaction data to focus on these genes revealed 3 pairs of direct two-way interactions: (1) *PARP1* and *XRCC1*, (2) *PARP1* and *PRKDC*, (3) *PARP1* and *TERT*; and 6 pairs of indirect two-way interactions: (1) *TERT* and *CDKN2A*, (2) *TERT* and *IL13*, (3) *TERT* and *EGF*, (4) *EGF* and *ERCC1*, (5) *EGF* and *PRKDC*, and (6) *PARP1* and *CDKN2A*. The key bio-functions of these genes are related to (1) DNA replication, recombination, and repair; (2) the cell cycle; and (3) cell death (Fig.2). Glioma signaling was the most significant disease specific canonical pathway.

It should be noted that there are certain limitations to our in silico analysis: it is exploratory and hypothesis generating. Since there are many different gene-gene interactions resulting from various cellular/experimental conditions, the gene relationships denoted in our network may not represent the actual causal relationship between genes. It does, however, provide exploration of the connectivity between genes and disease development. Hence despite its limitations, this preliminary analysis suggests interconnectedness of several currently well known gene-gene interactions, base excision repair pathway genes *XRCC1* interacts with *PARP1* [37,38]; and *TERT* interacts with *PARP1*[39]. It also uncovered new information for direct interactions between *PARP1* and *PRKDC*.

Conclusions and future directions

While the candidate gene-association studies have thus far identified variation in DNA repair pathway genes as most promising basis of inherited susceptibility this may in part be a consequence of a self fulfilling prophecy as such genes have been the major subject of evaluation. Adopting an agnostic approach GWA studies have implicated cell cycle- and telomerase-related genes as important risk determinants. The development and progression of gliomas are likely due to a multistep process that involves functional inactivation of tumor suppressor genes (i.e., *CDKN2A* and *CDKN2B*) and DNA repair genes (i.e., *PARP1*, *PRKDC*, and *ERCC2*) as well as activation of oncogenes and proto-oncogenes (i.e., *EGF* and *ERBB2*). It is possible that a profile of genetic alterations including the cell cycle control, DNA repair pathway, and telomerase change-related genes will provide the most informative approach for molecular epidemiological studies aimed at understanding variations in glioma risk.

Compared with many other cancers, little is known about the lifestyle or environment factors that influence the risk of developing brain tumors. Identifying these environment factors and investigations of not only gene-gene but also gene-environment interactions are important. Besides the GLIOGENE familial glioma study assembled in 2007, we are now launching another international consortium, the GLIOGENE case-control prospective study in the beginning of 2010, to examine the complex interplay of gene-gene and gene-environment interactions in 6000 glioma patients and 6000 healthy controls. With this, we will be able to

identify the potential risk and protective factors in a much larger study, and ultimately find improved ways to diagnose and treat the disease.

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Figure 1. Biological networks for selected glioma susceptibility genes

Interactions among the glioma susceptibility genes (green emblems) were analyzed using Ingenuity Pathway Analysis (<http://www.ingenuity.com>). This diagram shows the direct (solid lines) and indirect (dashed lines) interactions among the 21 genes. The red solid lines are the direct two-way interactions, and blue dashed lines are the indirect two-way interactions. For clarity, we do not show all of the interactions identified but focus primarily on direct interactions that link glioma.

Figure 2. Functional annotations of the glioma susceptibility genes

The annotations show that the key bio-function of these susceptibility genes is related to DNA replication, recombination and repair pathway. The 21 network genes associated with biological functions in the Ingenuity Pathways Knowledge Base were considered for the analysis. Fisher's exact test was used to calculate a p-value determining the probability that each biological function assigned to that network is due to chance alone. Threshold bar shows cut-off point of significance $P < 0.05$, $-\log(P\text{-value})$ of 1.3.

TABLE 1

Selected glioma susceptibility genes and SNPs observed in at least two studies

Main pathways, genes	Associated SNPs	Effect	OR (95%CI)	Reference
DNA repair				
(1) Double strand break repair: <i>PRKDC</i>	G6721T (rs7003908)	Risk	GG vs TT, 1.82 (1.13–2.93); GG vs TT, 1.44 (1.13–1.84)	[12] [13]
(2) Base excision repair				
<i>XRCC1</i>	W399R (rs25487)	Risk	AA vs GG, 1.23 (0.96–1.57); AA vs GG, 1.32 (0.97–1.81); GA/AA VS GG, 1.44 (1.05–1.92)	[13] [14] [15]
<i>PARP1</i>	A762V (rs1136410)	Protective	CT/CC vs TT, 0.80 (0.67–0.95); CT/CC vs TT, 0.71 (0.52–0.97)	[13] [15]
(3) Nucleotide excision repair				
<i>ERCC1</i>	A8092C (rs3212981)	Risk	AA/AC vs CC, 4.41 (1.6–12.2); AA/AC vs CC, 1.67 (0.93–3.02)	[17] [18]
<i>ERCC2</i>	Q751K (rs13181)	Risk	CC vs AA, 1.19 (0.93–1.52); AA vs AC/CC, 1.66 (1.01–2.72)	[13] [18]
(4) Direct reversal of damage: <i>MGMT</i>	F84L (rs12917)	Protective or risk?	CT/TT vs CC, 0.66 (0.45–0.94); CT/TT vs CC, 1.26(0.90–1.75);	[15] [16]
Cell cycle: <i>EGF</i>	+61 A/G (rs4444903)	Risk	P=0.032; AG/GG vs AA, 1.52(1.03–2.23);	[19] [20]
Inflammation : <i>IL13</i>	R110G (rs20541)	Protective	AG vs GG, 0.75 (0.48–1.17); TT vs CC/CT, 0.39 (0.16–0.93)	[21] In press