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Genetics in glioma- lessons learned from genome wide association studies

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Abstract

Purpose of review—The purpose of this review is to describe the recent knowledge gathered from the identification of seven genomic regions that have been linked to the risk of developing malignant glioma.

Recent findings—The recent novel discoveries in fine mapping and genotype-phenotype studies will be highlighted. Through imputation and next generation sequencing a novel genetic variant, rs55705857 with a strong association at 8q24 has been discovered and validated in two studies. This locus is specifically associated with IDH1 and IDH2 mutated tumors and oligodendroglial tumors, albeit the specific mechanism of tumor development is not understood. The genetic variants associated with risk of glioma in the EGFR gene have also been associated with specific somatic aberrations, including loss at the CDKN2A/B locus and allele specific loss of EGFR in the tumors. A specific TP53 low frequency variant has also been associated with glioma risk and validated in a separate data set. The genetic risk in the telomere regulating genes TERT and RTEL appear to be associated with higher grade tumors without IDH mutations.

Summary—The link of genetic loci to specific tumor subtypes may have relevance for understanding glioma biology, for developing new diagnostic tools and targeted therapy for glioma.

Keywords

glioma etiology; genotype; phenotype; glioblastoma; oligodendroglioma

Introduction

Understanding the etiology of a disease is very important to identify strategies for prevention, surveillance and potential targets for treatments. The etiology of glioma has for many years not been very well understood. Rare genetic syndromes with germline mutations are well known to be causal for gliomas, such as the Li-Fraumeni syndrome caused by TP53 mutations, neurofibromatosis type 1 and 2. Common environmental exposures such as smoking, alcohol and diet have not been consistently associated with malignant brain

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tumors. The only consistent associations of external exposure is higher doses of ionizing radiation, described in cohort studies from the tinea capitis cohort in Israel and atomic bomb survivors in Japan. In addition there is an inverse association of asthma and allergies observed in many case- control studies. However, if the underlying causes of this is due to the host immune system, external agents or medication against asthma and allergies has not been entangled [1]. During the last years a new genetic era has emerged with the technology of screening the whole genome. This review gives an overview in the recent discoveries of low penetrant genetic variants that contribute to our understanding of the iniation and development of gliomas.

Established genetic risk loci

Since the first published genome wide association studies in 2009 [2, 3], several loci associated with glioma risk have been discovered. This includes loci mapped in or near genes such as CCDC26 in 8q24, PHLDB1 at chromosome 11q23.3 , the TP53 polyadenylation site by rs78378222 at 17p13.1 [4], rs11979158 and rs2252586 in EGFR at chromosome 7,[5, 6]and rs4977756 in CDKN2A/B [2, 3]. In addition, there are two genetic variants associated with telomere regulation also associated with glioma risk, rs2736100 in the TERT gene and rs6010620 in RTEL [2, 3]. A recent additional GWAS of 1850 glioma cases confirmed the previously identified loci but did not identify any novel genomic areas [7]. Separating the analyses on cases with family history found support for an association with the RTEL gene in cases with a family history of brain tumors [8]. The lack of identification of additional loci implies that most of the common high risk glioma loci have been discovered and that larger and more pathologically homogeneous data sets will be necessary to delineate additional rare loci. Interestingly, several of the genetic variants are in or near genes that often are found to acquire somatic mutation s in glioma: for example, TP53, CDKN2A/B, EGFR and TERT [9, 10]. One should remember that tagging SNPs identified through GWAS should be seen only as a marker of a genomic area and that there are likely one or more functional genetic variants in linkage disequilibrium with tagging SNP. Therefore additional fine mapping studies have been performed for some of the regions to discover true functional variants and to understand the relationship between the germline variants and the acquired somatic events.

Fine mapping and tagging studies

Several efforts have been made after the initial genome wide association studies to explore the genomic area by resequencing and fine mapping.

8q24

The chromosomal 8q24 region has been associated with risk of several common cancer sites (reviewed in Huppi K et al [11]). However, the loci for the other cancers are approximately 1-2 MB proximal to the 8q24.21glioma locus at. An imputation effort combined with next generation sequencing revealed a genetic variant rs55705857 at 8q24.21 with a strong association to IDH mutated tumors and the histopathological subtype oligodendroglioma with an odds ratio of approximately 6.0, a level of association rarely seen in low penetrant association studies [12]. The association was confirmed by a separate European study that

performed fine-mapping of the genomic area using 1000 genomes and a case control set of a total of 4147 glioma cases and 7435 controls. This study found an equally strong association with an odds ratio for low-grade glioma associated with rs55705857 was 4.3 (P = 2.31 × 10(-94) [13] The mechanism by which the 8q24 genetic variant confers an increased risk of glioma is unknown, The SNP is completely conserved throughout mammalian evolution and the surrounding sequence models as a miRNA [12]. The variant resides within the CCDC26 locus which has been implicated in several inflammatory pathways [13]. The association with IDH mutation suggests that the variant may also be involved in the generation of the promoter DNA hypermethylation phenotype. The mechanism of action cannot simply be mediated only through IDH1 or IDH2 mutations, as oligodendroglioma with wild type IDH also are linked to the risk locus. The PHLDB1 locus is likewise association primarily to IDH mutated tumors [14] – thus there is clearly an interaction between germline variants and the acquisition of specific somatic alterations.

Tp53

In 2005 Malmer et al. observed an association of a specific p53 haplotype and glioma [15].More recently, a GWAS –imputation based study was performed in the Icelandic population (with validation in two US populations) showing that a genetic variant in the polyadenylation site of TP53 (rs78378222) is associated with glioma [4]. The genetic variant has recently been validated by a fine mapping study showing association both for glioblastoma and other gliomas [16]. Studies of RNA transcripts suggest that the rs78378222[C] variant gives a impaired termination and polyadenylation of the *TP53*. Transcript [4], but no studies of correlation to protein expression has yet been published.

RTEL and TERT

Several loci within or near the TERT gene have been associated with multiple kinds of cancer [17].The association has also been observed in the Han Chinese population [18]. A genetic tagging study of the TERT locus analyzed the association between rs2736100 with telomere length and attrition rate at age 50 and 60 in 900 individuals and found an association between rs2736100 and telomere length especially at older age [15]. This result indicates that TERT genotypes might have higher impact of disease at older age [19]. This is supported by a study showing a stronger association with glioma at higher age irrespective of glioma subtype [20].

Genotype- phenotype correlations

Some of the risk variants for glioma have distinctly been correlated to specific acquired tumor alterations (Figure 1). Glioblastoma, the most aggressive types of glioma, are genetically heterogeneous tumors, but a study using micro dissection of several areas within the same tumor has shown that somatic events in the EGFR and CDKN2A/B locus are early events appearing in all areas of the tumors, while later mutations are a stochastic process (See Figure 2; redrawn with permission [21]). The germline EGFR variants have been associated with allele specific loss of EGFR and homozygous loss at the CDKN2A/B locus using SNP array data from a Swedish cohort and TCGA data as validation (See Table 1 from the publication [22]). The EGFR risk genotypes has not been associated with EGFR

amplification measured by fluorescence in situ hybridization (FISH) [23], but FISH has not the potential to detect allele specific loss as done by paired samples of blood and tumor with a SNP array using the recently developed ASCAT algorithm [22]. Overall the SNPs in EGFR and CDKN2A/B seem to be associated with all types of glioma and the SNPs in TERT with higher grade and chromosome 10 loss [23].

The PHLDB1 (11q23.3) and CCDC26 (8q24) genetic variants have been strongly associated with IDH1 and 2 mutation [24]. Thus it is likely that these SNPs are also associated with a hypermethylated phenotype [25]. The results of the US study showed that rs55705857 (8q24.21) is associated with risk of oligodendroglial tumors regardless of tumor 1p/19q and IDH mutation status but IDH mutated and not wild type astrocytoma showed association [12]. In the study by Jenkins et al, approximately 40% of patients of these glioma subtypes carry one or more of the risk alleles for rs55705857 (8q24.21) - compared to 8% of the controls - indicating that this marker could be used to support diagnosis in intracranial tumors when biopsy is difficult. While the sensitivity of such a single germline marker is still not sufficient for diagnosis, in the future such blood tests may be used in combination with other clinical, laboratory and radiologic information such as PET-CT methionine or PET-MR imaging. Somatic mutations have recently been observed in the promoter of TERT in a high frequency in glioblastoma and progressive astrocytoma and oligodendroglioma, giving a clear picture of TERT as an important mediator of glioma progression and malignancy grade [10]. The TERT and RTEL risk genotypes are also correlated with higher grade tumors indicating that there is a genotype- phenotype correlation [23].

Conclusions

Many of the genes that are associated with an increased risk of glioma also have been identified as genes often mutated in gliomas or highly correlated with specific acquired mutations. EGFR and CDKN2A/B are frequently mutated in gliomas and SNPs within or near these genes are associated with the development of gliomas. SNPs in 8q24 and 11q23.3 are associated with gliomas that acquire IDH mutation . Taken together these observations lead to the hypothesis that germline genetic risk variant s interact with acquired alterations to influence glioma development. Furthermore, it is likely that additional risk variant and acquired alteration interactions will be discovered in the future. The coming years will witness the performance and publication of functional studies that will further delineate the mechanisms behind the pathologic and molecular associations that have been discovered.

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Bullet points

1. Common genetic variants contribute to glioma risk
2. Fine mapping of the associated regions has discovered stronger associations in 8q24 and TP53
3. The genetic variants are correlated to specific histologic and molecular subtypes of gliomas

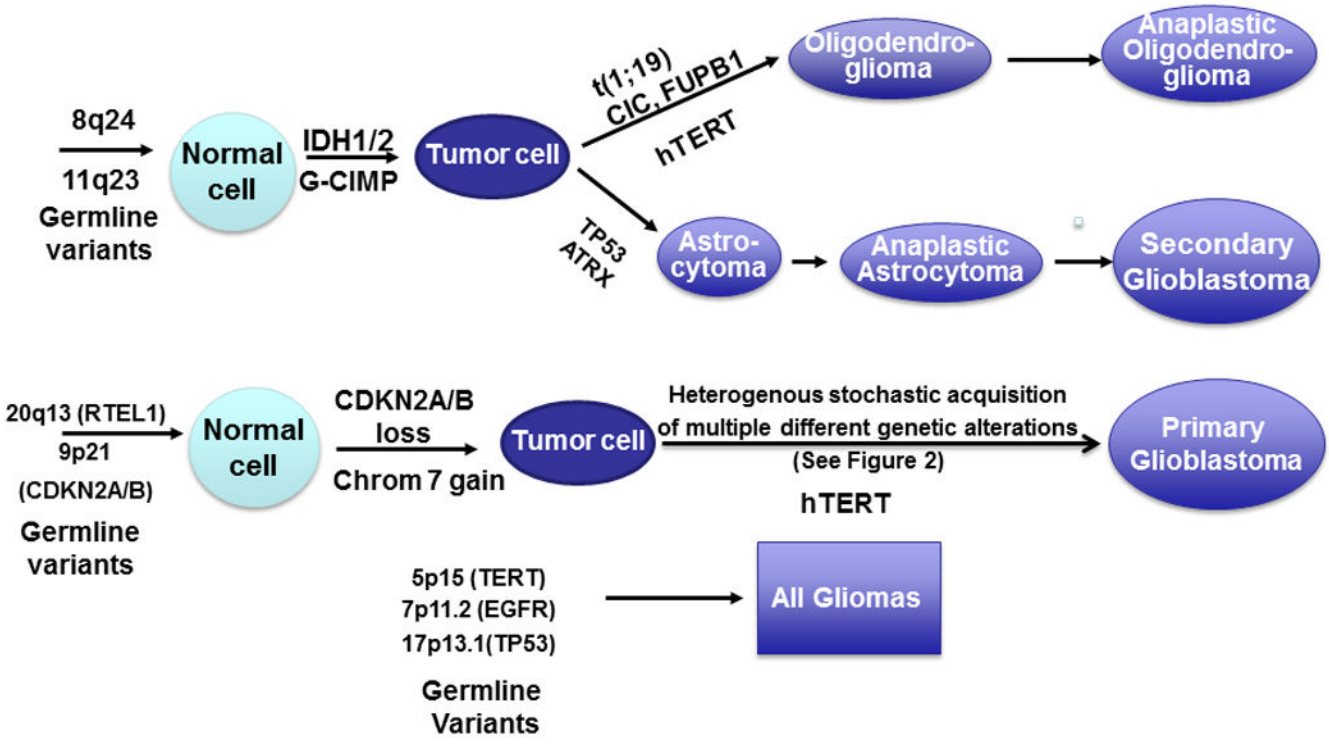

Figure 1. Pathways for glioma development

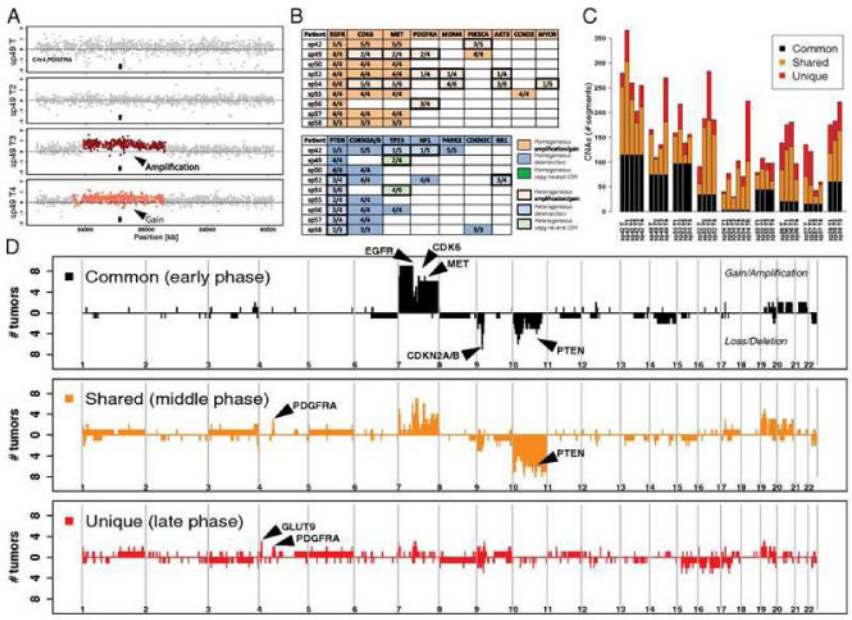

Figure 2.

Gliomas are not only many different subtypes but the intratumour heterogeneity on a molecular level is also evident. (From reference 21)

Table 1

Wibom et al, plos one table 5 redrawn with permission showing a correlation between risk genotypes in EGFR and somatic events in EGFR and CDKN2A/B

					UMU						TCGA						
Risk variant	**Region**	**Cytoband**	**Gene**	**Event**	**Variant**	**n (major)[a]**	**n (major) event[a]**	**n (rare+hz)[a]**	**n(rare+hz) event[a]**	**P**	**Variant**	**n (major)**	**n (major) event**	**n(rare+ hz)**	**n(rare+ hz) event**	**P**	**Approach**
rs17172430	chr7:55054218-55242525	7p11.2	EGFR	LOH	rs1015793	60 (41/19)	19 (15/4)	21 (14/7)	2 (2/0)	0.0385	rs17172430	236	57	49	6	0.0455	GOI
rs11979158	Chr9:21957750-21965132	9p21.3	CDKN2A	HD	rs10245472	57 (39/18)	33 (26/7)	24 (16/8)	8 (7/1)	0.0374	rs11979158	209	51	76	10	0.0267	GOI
rs11979158	Chr9:21992901-21999312	9p21.3	CDKN2B	HD	rs10245472	57 (39/18)	32 (25/7)	24 (16/8)	7 (6/1)	0.0233	rs11979158	209	122	76	32	0.0107	GOI
rs17172430	chr9:21992901-21999312	9p21.3	CDKN2B	HD	rs1015793	60 (41/19)	34 (27/7)	21 (14/7)	5 (4/1)	0.0088	rs17172430	236	134	49	20	0.0300	GOI
rs17172430	chr9:21961989-21978896	9p21.3	MTAP, CDKN2A	HD	rs1015793	60 (41/19)	35 (28/7)	21 (14/7)	5 (4/1)	0.0062	rs17172430	236	135	49	20	0.0264	global
rs17172430	chr9:22010493-22055620	9p21.3	MTAP, CDKN2BAS	HD	rs1015793	60 (41/19)	33 (27/6)	21 (14/7)	4 (3/1)	0.0040	rs17172430	236	132	49	19	0.0210	global

n number, *major* samples homozygous for the major allele, *rare+hz* samples homozygous for the rare allele plus heterozygous samples, *event* samples positive for given event, *GOI* genes of interest.

[a]total number of samples (glioblastoma samples/non-glioblastoma samples).

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