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Telomere maintenance and the etiology of adult glioma

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A growing body of epidemiologic and tumor genomic research has identified an important role for telomere maintenance in glioma susceptibility, initiation, and prognosis. Telomere length has long been investigated in relation to cancer, but whether longer or shorter telomere length might be associated with glioma risk has remained elusive. Recent data address this question and are reviewed here. Common inherited variants near the telomerase-component genes *TERC* and *TERT* are associated both with longer telomere length and increased risk of glioma. Exome sequencing of glioma patients from families with multiple affected members has identified rare inherited mutations in *POT1* (protection of telomeres protein 1) as high-penetrance glioma risk factors. These heritable *POT1* mutations are also associated with increased telomere length in leukocytes. Tumor sequencing studies further indicate that acquired somatic mutations of *TERT* and *ATRX* are among the most frequent alterations found in adult gliomas. These mutations facilitate telomere lengthening, thus bypassing a critical mechanism of apoptosis. Although future research is needed, mounting evidence suggests that glioma is, at least in part, a disease of telomere dysregulation. Specifically, several inherited and acquired variants underlying gliomagenesis affect telomere pathways and are also associated with increased telomere length.

Keywords: genome-wide association, glioma, shelterin, telomerase, telomere.

Adult glioma development involves the progressive accumulation of genetic and epigenetic alterations that permit cells to evade apoptotic mechanisms and invade surrounding tissue. Even with improved surgical techniques and the addition of temozolomide to neuro-oncology practice, only modest increases in patient survival have been observed in the last decade.[1] This is especially true for patients with glioblastoma, the most aggressive form of the disease. Recent genome-wide studies of inherited glioma risk factors are revealing biologic pathways underlying gliomagenesis.[2–6] Additionally, genomic studies of glial tumors are identifying mutations that may become preventive or therapeutic targets.[7–10] These studies increasingly implicate genes related to telomere structure and function. As a consequence, telomere biology has become a major focus of glioma research.

Prior to 2009, few factors had been unequivocally associated with glioma risk. These risk factors were: prior therapeutic radiation, rare Mendelian cancer syndromes, male versus female sex, European versus African American ethnicity, and older age.[11] More recently, a history of atopic disease has been consistently associated with decreased glioma risk, suggesting a role for tumor immunosurveillance in inhibiting gliomagenesis.[11] Additionally, genome-wide association studies (GWAS) have added common genetic polymorphisms in 8 genomic regions to the list of confirmed glioma risk factors (*TERC*, *TERT*, *EGFR*, *CCDC26*, *CDKN2B*, *PHLDB1*, *TP53*, *RTEL1*).[2–6] Three of these glioma risk loci contain genes involved in telomere maintenance (*TERC*, *TERT*, *RTEL1*).[2–4] Moreover, recent publications demonstrate that acquired somatic mutations in *TERT* and *ATRX* can impact telomere maintenance in tumor cells and are important in glioma development and prognosis.[8–10,12–15] Thus, recent epidemiologic and tumor genomic studies have converged on telomere maintenance as a core biologic pathway in the etiology of adult glioma.

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Telomere Biology and Heritability of Telomere Length

Human telomeres, located at the ends of chromatids, are composed of tandem hexanucleotide DNA repeats (TTAGGG) and several associated telomere-binding proteins, including the shelterin complex.[16] The primary function of telomeres is to compensate for incomplete DNA replication at chromosome ends, caused by the eukaryotic "end replication problem."[17] Human telomeres are initially several kilobases in length but shorten with each mitotic division. When the telomere is depleted, further cellular division leads to loss of integral genomic content and genomic instability, initiating apoptosis.[18] Thus, telomere depletion ultimately induces replicative senescence and limits the proliferative capacity of cells. Leukocyte telomere length (LTL) is inversely associated with age, declining an average of 20–40 base pairs annually.[19,20]

In cells requiring continuous renewal (eg, germ and stem cells), telomere length is maintained by telomerase. Telomerase is inactive in most adult cells but is often reactivated in cancer cells. The telomerase enzyme adds nucleotides to telomeres and is composed of a reverse transcriptase (encoded by *TERT*) and an RNA template (encoded by *TERC*).[21] Telomere length and telomerase activity are strongly influenced by age, and more subtly influenced by other factors, including oxidative stress, smoking, sex, diet, exercise, and both inherited and acquired genetic variation.[22,23] Mean LTL is a highly heritable trait, with heritability estimates as high as 80%.[24,25] Recent GWAS have identified 8 genomic regions that are independently associated with mean LTL, located in or near *ACYP2, TERC, NAF1, TERT, OBFC1, CTC1, ZNF208,* and *RTEL1*.[26,27]

Shorter telomere length is causally linked to increased risk of coronary artery disease and idiopathic pulmonary fibrosis.[26] Inherited loss-of-function mutations in *TERC, TERT,* and *RTEL1* cause autosomal dominant dyskeratosis congenita, a rare Mendelian disorder characterized by defective telomere maintenance, bone marrow failure, predisposition to malignancy, and pulmonary fibrosis.[28] Furthermore, risk of pulmonary fibrosis has been associated with common genetic variants in *TERC, TERT*, and *OBFC1* via GWAS.[29] Because the pulmonary fibrosis risk alleles are also associated with shorter mean LTL, pulmonary fibrosis is, like dyskeratosis congenita, increasingly being understood as a telomeropathy.[30,31]

Leukocyte Telomere Length as a Biomarker of Glioma Risk

Although telomere length displays substantial interindividual variability, intra-individual variability is low across different tissues.[32,33] As a result, mean LTL may be a promising epidemiologic risk factor for cancers, including glioma. Whether longer or shorter telomeres are associated with increased cancer risk is a long-standing question in cancer epidemiology,[34] as both possibilities are backed by observational data.[35–37] Shorter telomere length is generally considered a marker of aging and poor health. Additionally, short or unprotected telomeres can form telomeric fusions, leading to genomic instability—a hallmark of cancer.[38] Conversely, telomere depletion triggers apoptosis; therefore, a predisposition to long telomeres may permit cells to escape growth arrest and undergo malignant transformation. Meta-analyses have not resolved this debate and suggest that the direction of association may differ across cancer types.[35–37]

At least 2 case-control studies have attempted to directly measure LTL and determine its association with glioma risk.[39,40] The first of these studies, which included 101 patients with a glioma and 198 healthy controls, did not identify a significant association between glioma risk and LTL. A larger study measured mean LTL in 467 adult glioma patients and 467 age- and sex-matched controls.[40] Multivariable modeling revealed that glioma patients had significantly longer LTL than control subjects, and this association was consistent across strata of tumor grade. Individuals in the upper tertile of LTL had increased risk of glioma relative to individuals in the middle tertile (odds ratio = 3.5). Interestingly, individuals in the lowest tertile of telomere length also had increased risk of glioma compared with individuals in the middle tertile, though the magnitude of this association was smaller (odds ratio = 2.2). These data indicate that longer telomere length confers increased risk of glioma relative to both median LTL and short LTL but that this association may be nonlinear.

Genome-wide Association Studies Link Telomere Length and Glioma Risk

GWAS have had great success in revealing the genetic etiology of adult glioma.[41] In total, 6 glioma GWAS have been published to date, resulting in the identification of 10 independently significant single nucleotide polymorphism (SNP) associations located in 8 regions (Table 1).[2–6,42] While the first 2 glioma GWAS implicated SNPs near *TERT* and *RTEL1* in gliomagenesis,[3,4] the most recent GWAS also implicated rs1920116, near *TERC*.[2] The authors of this study extended their findings by examining the functional relationship between glioma risk alleles and telomere length using data from a recent GWAS of LTL ($N = 37\,684$ individuals).[26] Interestingly, the top glioma risk alleles near *TERC* and *TERT* were significantly associated with longer LTL ($P = 5.5 \times 10^{-20}$ and 4.4×10^{-19}, respectively). In a haplotype block of ~100 kb containing the *TERC* gene, every SNP that was associated with glioma at $P < .01$ ($N = 54$ SNPs) was also associated with longer telomeres at $P < 1.0 \times 10^{-5}$. Associations in *TERT* were similarly uniform. Although these findings do not rule out the possibility that other genes in these 2 regions may underlie the genetic association with glioma, they strongly support the idea that inherited risk for glioma is, to some degree, mediated through longer telomere length.

Recent research has revealed at least 3 biologic functions of the regulator of telomere elongation helicase 1 (RTEL1) protein, each with great relevance to cancer cell biology: control of homologous replication, maintenance of telomere stability, and stabilization of DNA replication forks.[43] The glioma association peak near *RTEL1* contains 2 glioma risk alleles that do not reside on a shared haplotype block and that are independently associated with glioma risk.[3] The first of these variants (rs6010620) is located in intron 12 of *RTEL1*, and the second (rs4809324) is located 8.4 kb away in intron 17. In contrast to the effects observed near *TERC* and *TERT*, glioma risk alleles in *RTEL1* are inconsistently associated with LTL and suggest the presence of

Table 1. Validated glioma risk loci from GWAS, hypothesized functional impact, and associated glioma subtypes

Gene (chromosome)	Lead SNP (risk allele)	Risk Allele Frequency[a]	Odds Ratio[b]	Hypothesized Function	Associated Subtype
TERC (3q26.2)	rs1920116 (G)	0.71	1.27	Increased telomere length/telomerase activity	Astrocytoma III–IV
TERT (5p15.33)	rs2736100 (C)	0.50	1.33	Increased telomere length/telomerase activity	All glioma subtypes
EGFR (7p11.2)	rs2252586 (A)	0.28	1.15	Undetermined	Astrocytoma III–IV
EGFR (7p11.2)	rs11979158 (A)	0.81	1.22	Undetermined	Astrocytoma III–IV
CCDC26 (8q24.21)	rs55705857 (G)	0.07	6.10	Undetermined	Oligodendroglial tumors, IDH-mutant astrocytomas
CDKN2B (9p21.3)	rs1412829 (G)	0.41	1.43	Increased ANRIL expression	Astrocytoma II–IV
PHLDB1 (11q23.3)	rs498872 (A)	0.28	1.52	Undetermined	IDH-mutant glioma
TP53 (17p13.1)	rs78378222 (C)	0.01	2.65	Alteration of *TP53* polyadenylation signal	All glioma subtypes
RTEL1 (20q13.33)	rs6010620 (G)	0.77	1.42	Alteration of RTEL1-PCNA interaction domain	All glioma subtypes
RTEL1 (20q13.33)	rs4809324 (C)	0.10	1.66	Increased telomere length/telomerase activity	Astrocytoma III–IV

Abbreviations: ANRIL, antisense noncoding RNA in the Ink4 locus; PCNA, proliferating cell nuclear antigen.
Variants in known telomere-related genes are highlighted.
[a]Risk allele frequency extracted from 1000 Genomes European data.
[b]To prevent inflation of estimates due to winner's curse, odds ratios are from replication datasets where available.[2,3,42,56]

multiple causal alleles.[2] While rs6010620 is associated with significantly shorter LTL ($P = 1.1 \times 10^{-3}$), rs4809324 is associated with a modest increase in LTL ($P = .039$).[2] Thus, genetic variation near *RTEL1* may impact gliomagenesis through multiple mechanisms, not all of which are necessarily telomere dependent.

Studies that directly assess the relationship between telomere length and cancer risk are frequently confounded by the effects of age. Because telomere length decreases with age and cancer risk increases with age, comparing telomere length in a case-control study can lead to confounded conclusions, even with careful matching. In the case of glioma, there is the additional confounding effect of sex, as men have shorter telomere length than women as well as a 30% increased risk of glioma.[44,45] Using inherited SNPs as biomarkers of telomere length avoids these confounders. The identification of glioma risk alleles in the 2 telomerase component genes *TERC* and *TERT*, all of which were associated with increased glioma risk and longer telomere length, suggests that heritable variation in telomere length or telomerase activity may be causally associated with glioma development.

LTL-Associated Glioma Risk Alleles Are the More Common Allele

Disease risk alleles are typically less common in the general population than the alternate (ie, protective) allele.[46] This is not the case for top glioma risk SNPs in *TERC*, *TERT*, and *RTEL1*, which have risk allele frequencies >50% among healthy controls (Table 1). Considering that increased telomere length protects against cardiovascular disease and pulmonary fibrosis[26,47] but may concurrently increase risk of glioma and melanoma,[2,48] these alleles are likely subject to balancing selection at the population level. While the interplay of positive and negative selective pressures underscores the complexity of telomere-based pathways of disease susceptibility, the direction of association between telomere length and disease risk appears consistent within each disease entity.

Inherited Variants Near *TERC*, *TERT*, and *RTEL1* Are Associated With Clinical Presentation and Tumor Histology

Risk alleles in *TERC*, *TERT*, and *RTEL1* are significantly associated with older age at diagnosis in glioma patients, even after controlling for tumor grade and histology, suggesting that gliomas developing in the presence of altered telomerase activity may present later in life.[2,49] Several mechanisms exist that could explain this phenomenon. Cells with increased telomere length or increased telomerase activity may be better able to delay senescence. The extra replicative divisions this allows could permit accumulation of further mutations and increase the chance of malignant transformation. These telomere-associated risk alleles may also place cells in a preactivated state, making them more liable to reactivate telomerase activity following normal growth arrest. Both potential mechanisms correspond with a tumor that develops later in life through acquired mutations and an inherent predisposition to delay growth arrest.[49]

Age at diagnosis is one of the strongest prognostic factors for glioblastoma patients,[50] and variants in *TERC*, *TERT*, and *RTEL1* are associated with older ages at diagnosis. This suggests that these risk alleles may also be associated with poor patient outcomes. Liu et al[51] examined this hypothesis by testing for association between 100 top-ranking glioma susceptibility SNPs from previous GWAS, including those in *TERT* and *RTEL1*, and glioblastoma patient survival. They observed that glioma risk alleles in *RTEL1*, including the rs6010620 variant associated with older age at diagnosis, were associated with worse overall survival among 590 glioblastoma patients after adjusting for age and extent of resection. Another study suggested that inherited and acquired genetic variation in the *TERT* locus may interact with age at diagnosis to influence glioma patient survival.[52] Prognostic models that integrate somatic mutations, inherited variants, and clinical data (eg, extent of resection) can rapidly translate neuro-oncology research into neuro-oncology practice.

The inherited *TERT* SNP most strongly associated with glioblastoma risk, rs2736100, is also associated with increased risk of lung cancer,[53] testicular cancer,[54] and myeloproliferative disorders.[55] Furthermore, it is associated with risk of both WHO grades II–III astrocytoma and oligodendroglioma[56] and with risk of glioblastoma irrespective of *TERT* promoter mutation status.[15] Heritable variants near *TERC* have been associated with risk of colorectal cancer,[57] chronic lymphocytic leukemia,[58] and multiple myeloma,[59] but glioma associations to date are limited to patients with high-grade astrocytic tumors, especially those harboring *TERT* promoter mutation and lacking isocitrate dehydrogenase (IDH) mutation.[2,15] *RTEL1* variants have been associated with all glioma grades and histologies,[56] although the magnitude of this association also appears largest in patients with *TERT*-mutated glioblastoma.[15]

POT1 Mutations and Familial Glioma

Between 2007 and 2011, the Gliogene Consortium recruited 435 families in which multiple members had diagnosed gliomas. Whole-exome sequencing was performed on genomic DNA from 90 individuals with familial glioma, drawn from 55 independent kindreds, identifying 2 families with rare missense mutations in the gene for protection of telomeres protein 1 (*POT1*).[60] The POT1 protein prevents DNA damage response pathways from recognizing exposed telomeric ends and regulates the access of telomerase to the telomere.[61,62] Screening of *POT1* in an additional 264 glioma patients from 246 Gliogene families identified a *POT1* missense mutation in one additional family. Two of the families harboring *POT1* mutations had 2 affected members, while the third had 4 affected members. Of 8 *POT1* mutation carriers with diagnosed gliomas, 6 had oligodendroglial tumors (4 oligodendroglioma and 2 mixed oligoastrocytoma).

POT1 is one of 6 members of shelterin, a protein complex that binds telomeres. Additional shelterin complex proteins are encoded by *TERF1*, *TERF2*, *TINF2*, *TERF2IP*, and *ACD*. Three shelterin subunit proteins (telomeric repeat-binding factor 1[TERF1], TERF2, and POT1) directly recognize telomeric TTAGGG repeats.[63] Because of the integral role of *POT1* in telomere integrity, the Gliogene investigators assessed whether *POT1* mutation carriers had alterations in LTL. *POT1* mutation carriers had significantly longer LTL than noncarriers, even after adjustments for age and sex and after excluding subjects with diagnosed glioma. These results are consistent with the GWAS findings that link common *TERC* and *TERT* variants to longer LTL and increased glioma risk.[2]

Inherited mutations of *POT1* have also been detected in melanoma-prone kindreds from the UK and Italy.[64,65] Remarkably, of 4 melanoma-prone families with *POT1* mutations identified in the UK study, 3 pedigrees contained an adult-onset malignant brain tumor.[64] One of these families contained a proband with 3 cutaneous malignant melanomas, a sibling with a malignant brain tumor diagnosed at age 35, and a grandparent with a malignant brain tumor diagnosed at age 65. Melanoma-prone kindreds with inherited mutations of another shelterin complex gene, *ACD*, have also been shown to contain glioma diagnoses within the pedigree.[66] These data strongly support the findings of the Gliogene Consortium and suggest a role for *POT1* mutations in diverse malignancies.

POT1 mutations have also been implicated in chronic lymphocytic leukemia (CLL), with somatic mutations detected in ~5% of cases.[67] Localization of mutant POT1 to the telomere causes dominant-negative telomere lengthening and telomere uncapping, leading to unprotected telomere ends and chromosomal fusions.[67] Common inherited variants (minor allele frequency >5%) in *POT1* have also been associated with increased risk of CLL in GWAS,[58] indicating that multiple types of *POT1* variants (common and rare, low-penetrance and high-penetrance, heritable and somatic) are involved in the etiology of diverse cancers.[58,60,64,65,67] While neither common nor somatic variants in *POT1* have yet been implicated in gliomagenesis, rare loss-of-function mutations in this gene are the first Mendelian cause of glioma to be discovered since *CHK2* mutations were identified as a cause of Li–Fraumeni syndrome and *CDKN2A* deletions were identified as a cause of familial melanoma-astrocytoma syndrome at the turn of the century.[68,69]

Convergence of Inherited and Acquired Somatic Variants on Telomere-Maintenance Genes

Telomere maintenance is a universal requirement of most human cancers, as it enables premalignant cells to continue replicating and reach a more fully malignant endpoint.[70] Telomere maintenance in tumors occurs in at least 2 different ways: through reactivation of telomerase or through a homologous recombination-based mechanism known as alternative lengthening of telomeres (ALT).[70,71] How telomerase is reactivated by tumors remained unknown until recently, when sequencing of germline DNA in melanoma-prone families identified 2 different activating mutations in the promoter of *TERT*.[72] Somatic mutations at these same positions were identified in tumor DNA from sporadic melanoma cases.[73] Soon after, targeted sequencing of the *TERT* promoter was carried out in a diverse set of human tumors.[8] Mutations of the *TERT* promoter are observed in ~75% of glioblastomas and 20% of grades II and III astrocytomas, where they generate a novel transcription factor binding site and upregulate *TERT* mRNA expression. Strikingly, 75% of oligodendrogliomas also harbor *TERT* promoter mutations, despite otherwise being largely molecularly dissimilar from primary glioblastomas.[8,15] The recent emergence of etiologically and prognostically distinct subgroups of glioma patients, defined by the presence/absence of *TERT* promoter mutation, IDH mutation, and 1p/19q codeletion, provides a simple model that can expedite adoption of genomics into the clinic.[15]

Tumors that do not maintain telomere length through activation of telomerase typically activate the ALT pathway, which strongly correlates with loss of either *ATRX* or *DAXX*.[71] More than half of all adult grade II and grade III astrocytomas have mutations in *ATRX*, and this proportion is even higher when limited to IDH-mutated astrocytoma.[10,74] *DAXX* mutations, which also activate the ALT pathway, are primarily limited to pediatric gliomas.[74]

The interactions between heritable variants in *TERC, TERT, RTEL1*, and *POT1* and somatic alterations in *TERT* and *ATRX* are not yet fully understood. However, compelling evidence that certain heritable glioma risk alleles are associated with specific somatic alterations has already been generated,

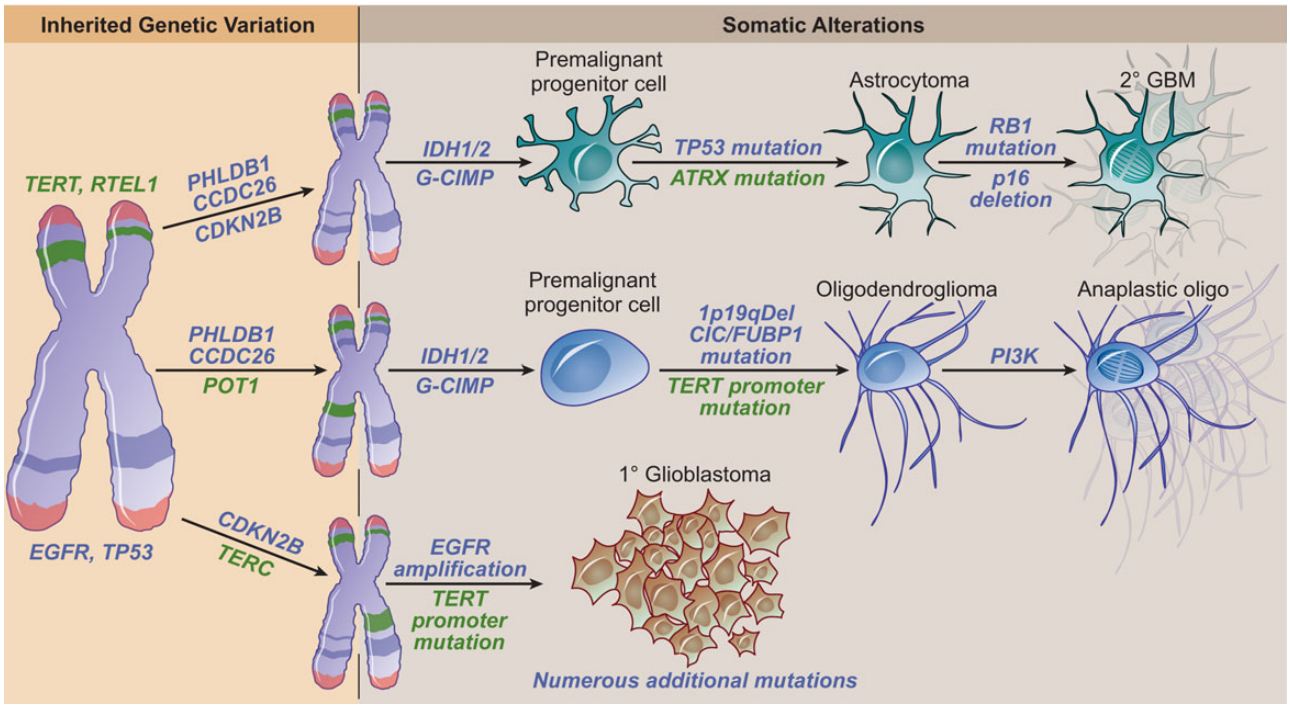

Fig. 1. Hypothesized pathways of glioma development, highlighting heritable and somatic genetic variants. From left to right: gene regions that contribute inherited risk for all histopathologic classifications of glioma. Gene regions that contribute inherited risk for specific histopathologic classifications of glioma. Somatic (ie, acquired) genetic changes that are believed to be early events in the development of glioma. Additional somatic events important for malignant progression. Gene names appearing in green font harbor glioma risk alleles associated with telomere lengthening. (Figure created with assistance from Xavier Studio.)

especially relating SNPs to IDH mutation status.[42,75] As a corollary to this, a recent publication indicates that *TERC, TERT*, and *RTEL1* SNP associations are strongest for patients whose gliomas harbor somatic *TERT* promoter mutations,[15] suggesting that telomerase dysregulation in glioma occurs at the interface of inherited and acquired genomic variation. This interface, diagrammed in Fig. 1, connects the principal inherited and acquired genetic variants that underlie gliomagenesis with the distinct grades and histologies with which they are associated.

Conclusions and Future Directions

A growing body of epidemiologic and tumor genomic research has identified an important role for telomere maintenance in glioma predisposition, initiation, and prognosis. Though future research is needed, the following points seem clear: (i) rare (*POT1*) and common (*TERC*, *TERT*, *RTEL1*) inherited variants in telomere-related genes are associated with glioma risk; (ii) mutations affecting telomere maintenance pathways (*TERT* promoter, *ATRX*) are among the most recurrent somatic events observed in gliomas; and (iii) these heritable and somatic genetic variants primarily cause *lengthening*, not shortening, of telomeres.

The mounting evidence of association between glioma and alterations in telomere maintenance genes raises the interesting possibility of viewing glioma as, at least in part, a disease of telomere dysregulation. As a parallel to this, one can again consider the example of pulmonary fibrosis, an apparent telomeropathy.[30] Pulmonary fibrosis is associated with reduced function of telomere maintenance genes, leading to critically short telomeres. Common SNPs in *TERC* and *TERT* that are associated with longer LTL decrease risk of pulmonary fibrosis,[29] yet increase glioma risk.[2] Supporting the association between telomere lengthening and gliomagenesis, rare heritable mutations in *POT1* are associated with longer telomeres and familial glioma,[60] and somatic mutations in *TERT* and *ATRX* maintain telomere length in gliomas.[8,74] The idea that glioma is a disease of telomere accretion, much like pulmonary fibrosis is a disease of telomere attrition, has great appeal. Next steps will be to expand these etiologic findings to determine if other components of the telomere maintenance pathway are involved in gliomagenesis, and to better understand the mechanisms underlying the observed genetic associations. The ultimate goal is to translate these findings to benefit patients through improved risk stratification and rational therapeutic design.

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