Published in final edited form as:
J Med Genet. 2012 July ; 49(7): 420–421. doi:10.1136/jmedgenet-2012-100941.

Rare *TP53* genetic variant associated with glioma risk and outcome

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Abstract

Validation of a recent finding linking a rare variant in *TP53* to the risk of glioma, the most common primary brain tumour, is reported here. This study genotyped the single nucleotide polymorphism (SNP) rs78378222 in 566 glioma cases and 603 controls. The variant 'C' allele (with an allelic frequency of 1.1% in controls) was associated with a 3.5-fold excess in glioma risk (odds ratio 3.54; p=0.0001). Variant carriers had significantly improved survival (hazard ratio 0.52; p=0.009) when compared to non-carriers. The rs78378222 SNP is the first confirmed rare susceptibility variant in glioma. Results may shed light on the aetiology and progression of these tumours.

Keywords

glioma; glioblastoma; risk; prognosis; single nucleotide polymorphism

Rare (minor allele frequency <5%) variants have been proposed to contribute to the "missing heritability" in cancer (1) and may contribute to recently identified signals reported in genome-wide association studies (2). Rare variants are more likely than common variants to have a functional impact, and tend to have a stronger effect size than do common variants (3). For these reasons, rare variants are likely to be a crucial element of the genetic architecture of common human diseases. However, few rare variants have yet been definitively linked to cancer risk.

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Competing Interests

The authors declare that they have no competing interests.

Contributorship Statement

K. Egan participated in designing the study, generated and gathered data for the study, analyzed the data, and wrote the majority of the original draft of the paper. She is the corresponding author and guarantor. L.B. Nabors, J. Olson and R. Thompson participated in gathering data for the study and in writing the paper. A Monteiro participated in designing the study, in writing the paper and in reviewed the pertinent raw data on which the study was based. J. Browning analyzed the data and participated in writing the paper. M. Madden gathered data for the study, participated in writing the paper and reviewed the pertinent raw data on which the study was based. All authors reviewed and approved the final version.

A rare variant conferring glioma risk was recently reported in the Icelandic population and provisionally validated in two separate US case-control studies (4). The implicated single nucleotide polymorphism (SNP), rs78378222, occurs in the sole polyadenylation signal of *TP53* and is predicted to disrupt the signal sequence. In functional assays, the rs78378222[C] variant was shown to impair proper termination and polyadenylation of the *TP53* transcript (4). The SNP was linked to risk of a spectrum of diverse cancers including glioma. This is the first rare variant linked to glioma risk.

We genotyped the rs78378222 SNP in a large, ongoing, clinic based, case-control study and considered associations according to glioma histological subtype. We also examined for the first time the prognostic impact of this new candidate susceptibility allele in glioma and other primary tumours.

A description of the study population has been published (5). Briefly, glioma cases were individuals aged 18 years and older with a recent diagnosis of glioma identified in neurosurgery and neuro-oncology clinics at medical centres in the southeastern USA. Controls were persons sampled from communities giving rise to the cases with no personal history of brain tumour supplemented with friends and non-blood relatives of the cases. Glioma cases were enrolled a median of 1.0 month following glioma diagnosis (interquartile range 2 weeks to 1.7 months). Oral genomic DNA was available for all subjects. Study protocols were approved by the institutional review committees at each participating centre and all study participants provided written informed consent.

A total of 566 cases and 603 controls, all Caucasian, were genotyped for the rs78378222 variant using TaqMan. Laboratory personnel were masked to the case-control status of the samples. A single homozygous carrier of the variant ‘C’ allele, a case with glioblastoma, was identified in the series of 1169 genotyped subjects. All remaining variant allele carriers were heterozygous at this locus. The minor allele frequency was 0.037 in the cases and 0.011 in the controls. Genotype frequencies were in Hardy-Weinberg equilibrium (p=0.789).

Results for the examination of risk associations are shown in the table 1. Odds of glioma were increased 3.5-fold among variant allele carriers (odds ratio (OR) 3.54, 95% confidence interval (CI) 1.87 to 6.71; p=0.0001) compared to non-carriers. An increased risk associated with the C allele was observed regardless of glioma histologic subtype (test for heterogeneity in multinomial regression: p=0.779).

We further examined the impact of the rs78378222 variant allele on survival among the 413 patients with high grade gliomas (316 glioblastomas and 97 grade III astrocytomas or oligodendrogliomas) in whom 328 glioma related deaths were documented (figure 1). Carriers of the variant ‘C’ allele had longer survival times when compared to persons homozygous for the wild type ‘A’ allele (median Kaplan-Meier survival probability: 19.4 months and 15.2 months, respectively), with an approximately 50% reduction in death rates observed among variant allele carriers (hazard ratio adjusted for patient age and gender: 0.52, 95% CI 0.32 to 0.85; p=0.0094).

The present study confirms the reported association of the rare *TP53* variant with glioma risk and demonstrates that the association is consistent across glioma subtypes. Odds ratios in the present study (OR 3.54 for all gliomas combined) are more prominent than those from the Icelandic population (OR 2.36) and the two validation studies from the USA in the study by Stacey et al (combined OR 2.34) (4). Similar to the previous analyses, all of the subjects in the present study were Caucasian with the great majority reporting European ancestry.

We also report an apparent survival advantage in carriers of the rare allele. Prolongation of survival among carriers of a genetic variant that increases the incidence of the tumour is an

unexpected finding. (We attempted to validate this finding in The Cancer Genome Atlas (6) which includes mortality information and results of a genome-wide scan on approximately 300 patients with glioblastoma; however, neither rs78378222 nor any suitable proxy SNP was included in the The Cancer Genome Atlas array.). We note that in the report of Stacey et al (4), the rs78378222 variant was associated with the risk of colorectal adenoma but not colorectal cancer, suggesting the SNP may select for neoplasms with more indolent behaviour. If not due to chance, the observed association may offer some insights into the mechanistic aspects of cancer development and progression. Since the risk allele affects a regulatory sequence in the untranslated region (3′UTR), the likely impact of this variant is a reduction in *TP53* gene dosage and not in the production of a mutated protein. It is tempting to speculate that the presence of the risk allele could direct tumour development into a less aggressive path by not requiring loss of the wild-type *TP53* allele for tumour development. Alternatively, in tumours that undergo loss of the wild-type *TP53* allele, the reduced levels of wild-type *TP53* protein produced by the variant allele could provide residual *TP53* activity sufficient to maintain a less aggressive phenotype.

Glioma remains a poorly understood neoplasm with a high morbidity and devastating outcome. The discovery of the association of the *TP53* variant rs78378222 with glioma offers new insights into these tumours and the prospects for better delineating populations at risk.

Acknowledgments

Funding Source

Financial support was received from Public Health Service Grants R01CA116174 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services and institutional funding from the Moffitt Cancer Center, Tampa, FL and the Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN.

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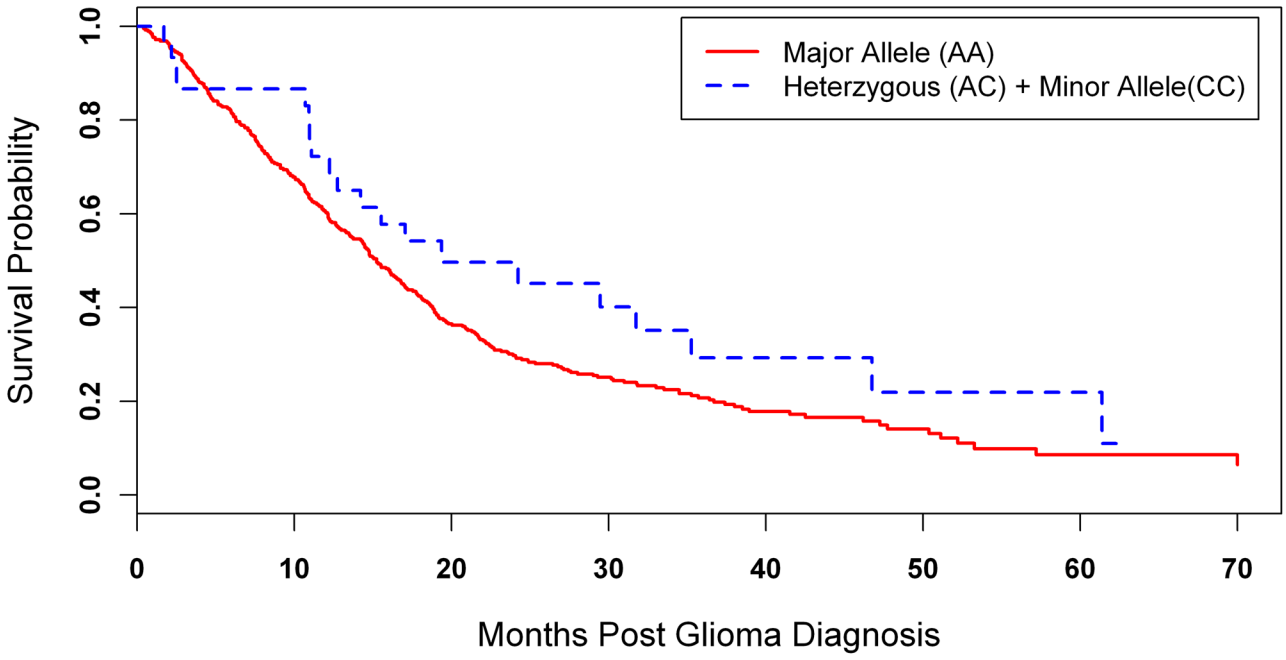

Figure 1.
Kaplan-Meier curves depicting probability of survival following diagnosis of high grade glioma according to rs78378222 genotype.

Table 1

Risk associations for rs78378222 overall and according to glioma histologic subtype

Glioma subtype*	Cases (AA/AC or CC)	Controls (AA/AC or CC)	OR (95% CI)†	P value
All Gliomas	525/41	590/13	3.54 (1.87, 6.71)	0.0001
Glioblastoma	292/24	590/13	3.51 (1.75, 7.04)	0.0006
Astrocytic tumors	130/11	590/13	4.04 (1.72, 9.50)	0.0016
Oligodendrogliomas	85/5	590/13	2.83 (0.95, 8.40)	0.0610

*Histology was unknown in 19 of 566 glioma cases.

†Odds ratio (OR) and 95% confidence interval (CI) under a dominant model adjusting for age and sex.