SSBP2 Variants Are Associated with Survival in Glioblastoma Patients

Yuanyuan Xiao1, Paul A. Decker5, Terri Rice6, Lucie S. McCoy2, Ivan Smirnov2, Joseph S. Patoka2, Helen M. Hansen2, Joe L. Wiemels1,4, Tarik Tihan3, Michael D. Prados2, Susan M. Chang2, Mitchel S. Berger2, Matthew L. Kosel5, Brooke L. Fridley5, Daniel H. Lachance7,8, Brian Patrick O’Neill7, Jan C. Buckner6, Reid C. Thompson9, Louis Burt Nabors10, Jeffrey J. Olson11, Steve Brem13, Melissa H. Madden12, James E. Browning12, John K. Wiencke1,4, Kathleen M. Egan12, Robert B. Jenkins8, and Margaret R. Wrensch2,4

Abstract

**Purpose:** Glioblastoma is a devastating, incurable disease with few known prognostic factors. Here, we present the first genome-wide survival and validation study for glioblastoma.

**Experimental Design:** Cox regressions for survival with 314,635 inherited autosomal single-nucleotide polymorphisms (SNP) among 315 San Francisco Adult Glioma Study patients for discovery and three independent validation data sets [87 Mayo Clinic, 232 glioma patients recruited from several medical centers in Southeastern United States (GliomaSE), and 115 The Cancer Genome Atlas patients] were used to identify SNPs associated with overall survival for Caucasian glioblastoma patients treated with the current standard of care, resection, radiation, and temozolomide (total n = 749). Tumor expression of the gene that contained the identified prognostic SNP was examined in three separate data sets (total n = 619). Genotype imputation was used to estimate hazard ratios (HR) for SNPs that had not been directly genotyped.

**Results:** From the discovery and validation analyses, we identified a variant in single-stranded DNA-binding protein 2 (SSBP2) on 5q14.1 associated with overall survival in combined analyses (HR, 1.64; 95% CI, 1.45–2.22; P = 1.3 × 10^{-6}). Expression of SSBP2 in tumors from three independent data sets also was significantly related to patient survival (P = 5.3 × 10^{-4}). Using genotype imputation, the SSBP2 SNP rs17296479 had the strongest statistically significant genome-wide association with poorer overall patient survival (HR, 1.79; 95% CI, 1.45–2.22; P = 1.0 × 10^{-7}).

**Conclusion:** The minor allele of SSBP2 SNP rs17296479 and the increased tumor expression of SSBP2 were statistically significantly associated with poorer overall survival among glioblastoma patients. With further confirmation, previously unrecognized inherited variations influencing survival may warrant inclusion in clinical trials to improve randomization. Unaccounted for genetic influence on survival could produce unwanted bias in such studies. Clin Cancer Res; 18(11); 1–9. ©2012 AACR.

**Authors’ Affiliations:** Departments of 1Epidemiology and Biostatistics, 2Neurological Surgery, 3Pathology, and Institute of Human Genetics, University of California, San Francisco, San Francisco, California; Divisions of 4Biomedical Statistics and Informatics and 5Medical Oncology; Departments of 6Neurology and 7Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota; 8Department of Neurological Surgery, Vanderbilt University Medical Center, Nashville, Tennessee; 9Neuro-oncolgy Program, University of Alabama at Birmingham, Birmingham, Alabama; 10Department of Neurosurgery, Emory School of Medicine, Atlanta, Georgia; 11Department of Cancer Epidemiology & Genetics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida; and 12Department of Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

J.K. Wiencke, K.M. Egan, R.B. Jenkins, and M.R. Wrensch are senior authors.

**Corresponding Author:** Yuanyuan Xiao, Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco 185 Berry St, Suite 5700, San Francisco, CA 94107. Phone: 415-514-8148; Fax: 415-514-8150; E-mail: yuanyuan.xiao@ucsf.edu
doi: 10.1158/1078-0432.CCR-11-2778
©2012 American Association for Cancer Research.

**Introduction**

Glioblastoma is a rapidly fatal form of primary brain cancer with few known prognostic factors. Major challenges of achieving complete patient follow-up, treatment heterogeneity, and changing patterns of patient care over time have limited the feasibility of genome-wide cancer survival discovery with very few such studies published for any cancer site (1) and none thus far for glioblastoma. Moreover, candidate gene studies for glioblastoma survival have provided equivocal results (2–9) possibly due to the factors above or to inadequate gene coverage. To minimize these challenges, we focused this first genome-wide discovery and validation study for glioblastoma patient survival on carefully selected glioblastoma patient groups with follow-up and initial treatment with current standard of care.
Translational Relevance

Glioblastoma is the most fatal form of primary brain cancer and only a few prognostic factors, age, initial Karnofsky performance status, and some treatments, are known. Reliable genetic prognostic markers are still not well established. We present the first genome-wide survival and validation study for glioblastoma patients treated with the current standard of care, resection, radiation, and temozolomide. Using Cox regressions for genome-wide survival analysis, followed by functional validation in tumor expression and genotype imputation, we identified a variant in single-stranded DNA-binding protein 2 (SSBP2) and the tumor expression of SSBP2 to be significantly associated with patient survival. Identification and characterization of the role of genetic variation in predicting glioblastoma patient survival may help optimize clinical trial study design and individualize patient treatment plans.

Methods

Study subjects

Informed consent was obtained from each subject. The subject recruitment and studies were conducted after approval was obtained from the Institutional Review Boards at each participating site in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services (10, 11).

Discovery study. Details of subject ascertainment for the San Francisco Adult Glioma Study (AGS) have been previously described (10, 12, 13). The 315 glioblastoma patients in this study are the subset who had received current standard-of-care treatment (resection, radiation, and temozolomide) of the 525 glioblastoma patients whose results were used in the genome-wide association study reported by Wrensch and colleagues (10) after stringent sample quality control filtering. Among these patients, tumor characteristics [IDH1 (n = 173) and TP53 (n = 151) mutation status and EGFR copy number (n = 173)] were available from ongoing studies (14–16).

Validation study. The Mayo Clinic study included 87 glioblastoma patients newly diagnosed between 2005 and 2008. Most cases were identified within 24 hours of diagnosis; some were initially diagnosed elsewhere and later had their diagnosis verified at the Mayo Clinic. Pathologic diagnosis was confirmed by review of the primary surgical material for all cases by 2 Mayo Clinic neuropathologists based on surgically resected material.

The glioma patients recruited from several medical centers in Southeastern United States (GliomaSE) study included glioblastoma patients enrolled in a case–control study conducted at medical centers in the Southeast and diagnosed with a primary (e.g., nonrecurrent) glioma between 2005 and 2010 (11). Patients were enrolled a median of 1 month following glioblastoma diagnosis (and a maximum of 4 months according to study protocol). The glioblastoma diagnosis was based on diagnostic pathology reports available for all patients in the study.

The Cancer Genome Atlas (TCGA) data set was downloaded from http://cancergenome.nih.gov/ (17). At the time of data retrieval from TCGA, alignment of sample identifiers yielded 181 glioblastoma patients with both genotype and clinical data, 115 of whom had resection, radiation, and temozolomide treatment. The subject IDs of these 115 TCGA patients are listed in Supplementary Table S1.

Genotyping

Genotyping for the AGS discovery subjects was conducted by deCODE Genetics using Illumina’s HumanCNV370-duo BeadChip as previously described (10). After excluding single-nucleotide polymorphisms (SNP) with $P < 10^{-5}$ for Hardy–Weinberg equilibrium in the AGS control samples (AGS participants that did not have glioma), or minor allele frequency less than 5%, or missing genotyping data more than 5% in the case groups, there were 314,635 autosomal SNPs to consider in the survival tests. Genotyping for the Mayo Clinic study subjects was carried out with Illumina 610Quad SNP arrays as previously described (10). Genotyping for the GliomaSE study subjects was conducted with the Illumina Goldengate assay as previously described (11). Genotyping for the TCGA study subjects was conducted with Illumina 550 platform (17).

Statistical analysis

Supplementary Fig. S1 provides an overview of the 3 types of analyses conducted: (i) genome-wide constitutive discovery and validation of SNPs associated with glioblastoma patient overall survival, (ii) functional validation of survival loci (association of gene expression in tumors with glioblastoma overall patient survival), and (iii) fine mapping via genotype imputation.

Genome-wide survival and validation analyses. Due to human subject IRB constraints, analyses on the raw genotype data were carried out separately at the AGS, Mayo Clinic, and GliomaSE sites (TCGA data were analyzed at the AGS site). Summary statistics were then submitted to the AGS site for combined analysis. For the AGS discovery study, we conducted Cox proportional hazards regression models to assess the association of each of the 314,635 SNPs with overall survival, adjusting for age (on a continuous scale) and sex. The SNP variable used in the model is coded as a continuous count of the number of minor alleles based on the additive genetic model. Per-allele HR and 95% CI were obtained for each SNP. Statistical significance for each SNP was assessed with the Wald test. The same Cox proportional hazard models were used for all ensuing analyses of the validation data sets. The genomic inflation factor based on the genome-wide $P$ values for the AGS discovery study was 1.04 indicating that systematic inflation of our survival association signals due to model misspecification, undetected genotyping error, or hidden ancestry relationship was highly unlikely. The proportional hazards...
SSBP2 Variants Are Associated with Survival in GBM Patients

Functional validation of survival loci. To examine associations of expression of the candidate gene, with survival, we assembled data from 619 primary glioblastoma samples from 3 published studies (20–22). The Lee and colleagues (20) data set described 218 glioblastoma expression samples including 132 samples from 3 previously published data sets as well as 86 new samples assembled into a single, unified data set with Affymetrix U133A. The Murat and colleagues (21) data set contains 75 glioblastoma expression samples using the Affymetrix U133. Normalized expression values using the standard RMA method for the Lee and Murat data sets were downloaded from the National Center for Biotechnology Information Gene Expression Omnibus database (GSE13041 and GSE7696). The TCGA data set (22) has 326 primary glioblastoma expression samples using the Affymetrix U133A expression platform. Transcriptional class labels were obtained from the TCGA Advanced Working Group (23). The updated labeling extends the original labeled set presented in Verhaak and colleagues (22) to previously unclassified samples. In total, we obtained 74 proneurals, 45 neurals, 93 mesenchymals, and 91 classicals. For each of the 3 expression data sets, we carried out age and sex adjusted study specific survival analysis employing Cox models relating continuous gene expression data to patient survival and then combined the study-specific HR estimates with a fixed effect model using the inverse variance approach (19). Within the TCGA expression data set, we also conducted expression subtype (proneural, neural, classical, and mesenchymal) stratified survival analysis using a Cox model with the same specification. As treatment data were either missing or incomplete for these patients, we did not restrict the tumor gene expression analyses to patients with the current standard of care.

Fine mapping via imputation. Using MACH (24) and data from release 22 phase II CEU HapMap data (MACH version 1.0.16), we imputed SNPs separately within each of the 3 studies with sufficient tagging SNPs (AGS, Mayo, and TCGA). MACH implements a Markov chain–based algorithm to infer possible pairs of haplotypes for each individual’s genotypes (including untyped genotypes). We ran MACH with the default parameter values with the number of iterations of the Markov Chain set to 50 and the “greedy” option turned on. We then carried out study-specific Cox survival analysis with expected allele counts as the predictor for a total of 159 SNPs, whose variance ratios were larger than 0.5 for all 3 studies to exclude SNPs with poor quality imputed genotypes. Meta-analysis of the imputed data was carried out in the same way as described above. To obtain survival signals independent of the most significant (imputed) SNP in the region, we included its expected counts in the Cox model as an additional covariate, along with the other covariates such as age and sex. All analyses were conducted by the R statistical package.

Results

Patient characteristics (age, sex, and median survival) for the 4 data sets (AGS, the Mayo Clinic, GliomaSE, and TCGA) are described in Table 1. The majority of the observed survival Cox regression P values for 314,635 SNPs from the AGS discovery data set conformed to the identity line in the Q-Q plot, whereas 90 SNPs showed significant deviation from expectation at $P = 10^{-5}$ (Supplementary Fig. S2). We submitted these 90 SNPs for validation in Mayo Clinic patients of which 78 passed quality control. Ten of these SNPs had $P < 10^{-5}$ in the combined analysis using a fixed effect model (25). Examination of these 10 SNPs in 2 additional patient groups, GliomaSE and TCGA patients, yielded one SNP, rs7732320, that had discovery and validation combined $P < 10^{-5}$ for survival and had proportionality of hazards in all 4 data sets (Table 2 and Supplementary Table S3). The associations of this SNP with patient survival were in the same direction across the studies and had a combined validation $P = 0.008$ and a combined discovery validation $P = 1.3 \times 10^{-6}$. There was no evidence of heterogeneity of the HR estimates across the 4 studies (Table 2). Effect modification by age at diagnosis for rs7732320 was evaluated in the AGS discovery data by the significance of the interaction term between age at diagnosis and the SNP; no statistical significant interaction was detected. In the AGS discovery data, the median survival time for the 3 groups of patients with 0, 1, and 2 adverse alleles of rs7732320 were 17.8, 13.4, and 10.6 months, respectively.

Rs7732320 is located in the intronic region of SSBP2; we therefore investigated whether patient survival was associated with the transcript levels of SSBP2 among 619 patients in 3 publically available glioblastoma gene expression data sets [Lee and colleagues (20), Murat and colleagues (21), and TCGA (22); see Methods and Supplementary Fig. S1)]. We observed a strong and significant association of SSBP2 expression with poorer overall survival (HR, 1.22; 95% CI, 1.09–1.36; $P = 5.3 \times 10^{-4}$), and the association was consistent across the 3 expression data sets (Table 3). No effect modification by age at diagnosis was found for the association of SSBP2 tumor expression with survival in any
of the 3 expression data sets. In addition, among TCGA glioblastoma patients, the HR for patient survival associated with tumor SSBP2 expression was highest and statistically significant only among patients with the previously described (22) proneural signature (HR, 1.44; 95% CI, 1.10–1.89; \( P = 0.007 \); Table 3). Consistent with this finding, we found that proneural glioblastoma patients expressed the lowest amount of SSBP2 compared with the other subtypes (Wilcoxon \( P = 2.16 \times 10^{-12} \); Fig. 1A). Intriguingly, even though the overall survival for patients of the proneural subtype was not significantly different from the other gene expression subtypes (log-rank \( P = 0.21 \); Fig. 1B), significant survival differences were observed for the proneural SSBP2-negative patients (Fig. 1C), arbitrarily defined as the subset of patients with lower than 25 percentile of SSBP2 expression in the proneural group. We observed significantly better survival for proneural SSBP2-negative patients (median survival time, 28.8 months) than proneural SSBP2-positive patients (median survival time, 12.4 months) and all other nonproneural glioblastoma patients (median survival time, 13.8 months). Proneural SSBP2-negative status remained a significant prognostic factor for longer survival (Cox \( P = 9.7 \times 10^{-3} \)) in Cox multivariate analysis after adjusting for patient age at diagnosis and sex.

### Table 1. Characteristics of glioblastoma patients used in discovery (University of California, San Francisco, 1997–2008) and validation sets (Mayo Clinic, GliomaSE, and TCGA)

<table>
<thead>
<tr>
<th></th>
<th>Discovery: AGS</th>
<th>Validation I: Mayo</th>
<th>Validation II: GliomaSE</th>
<th>Validation III: TCGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N ) (events/total)</td>
<td>Median survival (mo)</td>
<td>( N ) (events/total)</td>
<td>Median survival (mo)</td>
</tr>
<tr>
<td>Total</td>
<td>270/315</td>
<td>17.1</td>
<td>64/87</td>
<td>16.3</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 (17.3)</td>
<td></td>
<td>54 (15.0)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI), ( P^a )</td>
<td>1.03 (1.02–1.04), 7.3E-09</td>
<td></td>
<td>1.03 (1.01–1.08), 4.3E-03</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92/101</td>
<td>15.4</td>
<td>22/35</td>
<td>16.3</td>
</tr>
<tr>
<td>Male</td>
<td>178/214</td>
<td>17.2</td>
<td>42/52</td>
<td>16.8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>315 (100%)</td>
<td>87 (100%)</td>
<td>232 (100%)</td>
<td>115 (100%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** GliomaSE, glioma patients recruited from several medical centers in Southeastern United States; TCGA, The Cancer Genome Atlas.

\( ^a P \) values from log-additive Cox Proportional Hazards model adjusted for age at diagnosis (on a continuous scale) and sex.

### Table 2. Association of rs7732320 genotype with overall survival for glioblastoma multiforme patients with initial standard of care (resection, radiation, and temozolomide) treatment

<table>
<thead>
<tr>
<th>SNP</th>
<th>Discovery AGS ( \text{HR (95% CI), } P^a )</th>
<th>Combined validation (3 sites) ( \text{HR (95% CI), } P^b )</th>
<th>Heterogeneity test (4 sites) ( Q, P )</th>
<th>Combined statistics (4 sites) ( \text{HR (95% CI), } P^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7732320 (SSBP2, Chr 5, MA = T, MAF = 0.11)</td>
<td>1.80 (1.36–2.30), 3.07E-05</td>
<td>1.48 (1.11–1.99), 0.008</td>
<td>0.66 (1.34–2.00), 1.30E-06</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** SNP discovered in a genome-wide survival association study [University of California, San Francisco, 1997–2008, AGS (10)] and validated in 3 independent studies [Mayo Clinic (10), GliomaSE (11), and TCGA (17)] based on combined \( P < 1E-5 \). Abbreviations: GliomaSE, glioma patients recruited from several medical centers in Southeastern United States; MA, minor allele; MAF, minor allele frequency.

\( ^a P \) values from log-additive Cox Proportional Hazards model adjusted for age at diagnosis (on a continuous scale) and sex.

\( ^b P \) values based on combining summary statistics from the 3 validation studies of Mayo, GliomaSE, and TCGA using a fixed effect model with inverse variance weights.

\( ^c P \) values based on combining summary statistics from all 4 study sites (AGS, Mayo, GliomaSE, and TCGA) using a fixed effect model with inverse variance weights.
methylator phenotype (G-CIMP; ref. 26). To understand the relationship between SSBP2 and the G-CIMP signature, we compared the SSBP2 genotype and tumor expression in the set of TCGA glioblastoma samples with available G-CIMP status. Of the 241 TCGA samples with concomitant tumor expression and G-CIMP information, 24 were G-CIMP positive and they expressed a much lower level of SSBP2 than the 217 G-CIMP–negative tumors (Wilcoxon $P = 3.54$

### Table 3. Association of gene expression and survival in glioblastoma multiforme cases with data from 3 different sources

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events/N MST</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (20)</td>
<td>218</td>
<td>1.18 (1.01–1.38)</td>
<td>0.034</td>
<td>0.14</td>
<td>1.24 (1.05–1.47)</td>
</tr>
<tr>
<td>Murat et al. (21)</td>
<td>75</td>
<td>1.44 (1.10–1.89)</td>
<td>0.007</td>
<td>65/74</td>
<td>14.7 (11.3–23.0)</td>
</tr>
<tr>
<td>TCGA (22) N = 326</td>
<td></td>
<td>1.19 (0.88–2.51)</td>
<td>0.14</td>
<td>38/45</td>
<td>11.9 (10.4–15.4)</td>
</tr>
<tr>
<td>Combined N = 619</td>
<td></td>
<td>1.27 (0.77–2.07)</td>
<td>0.35</td>
<td>86/93</td>
<td>13.9 (12.1–17.6)</td>
</tr>
</tbody>
</table>

Abbreviations: MST, median survival time (in mo).

*Adjusted for age.

**Figure 1.** A, Boxplots of SSBP2 tumor expression by previously assigned TCGA expression groups in 303 glioblastomas: C, classical; M, mesenchymal; N, neural; and P, proneural. B, Kaplan–Meier survival curves for the 4 TCGA expression groups. C, Kaplan–Meier survival curves based on SSBP2 expression and TCGA expression groups. The “Proneural SSBP2-” group is designated as the subset of 20 patients with lower than 25 percentile expression of SSBP2 expression in the proneural group versus the rest of the TCGA patients.
TCGA patients with standard-of-care treatment had both EFGR amplification. Unfortunately, only 35 of the 115 treatment had data on for whom 143 of the 315 patients with standard-of-care survival in glioblastoma patients, we used the AGS data set, patient genotypes and tumor markers that are related to this association was not found in the AGS data set. Next, to further localize the association with survival in the 5q14.1 region around rs7732320, we imputed nongenotyped SNPs in the entire genomic locus of SSBP2 with a 100 kb extension at its 3' end from 80,680,000–80,980,000 on chromosome 5. The Hapmap II CEU data set (27) contained 217 SNPs in this region (the AGS data set had 31 SNPs). Out of the 186 (217 minus 31) imputed SNPs, 159 had good imputation quality for AGS, Mayo, and TCGA. Meta-analysis using a fixed effect model to combine study-specific HR estimates from age-gender adjusted Cox models shows a genome-wide statistically significant association of patient survival with the SNP rs17296479 (P = 1.0 × 10⁻⁷; see Fig. 2 and Supplementary Table S4), which is located approximately 8 kb centromeric of rs7732320. Two SNPs, rs12187089 and rs11738172, located between these 2 SNPs, are highly linked with each other (r² > 0.8). The smallest combined nominal P value from multivariate Cox models of patient survival with the remaining SNPs adjusting for rs17296479 genotype was 0.061, suggesting that there were no residual independent survival signals remaining.

Discussion
Major strengths of this study include: (i) a large group of glioblastoma patients in the discovery study (AGS) with initial standard of care treatment of resection, radiation, and temozolomide; (ii) three independent validation studies.
SSBP2 Variants Are Associated with Survival in GBM Patients

Although all 4 SNPs are noncoding, their immediate proximity to the gene and the ample evidence for epigenetic modifications within the region supports a possible role in transcriptional regulation of SSBP2. First, the histone methylation marker H3K4Me1 for enhancer elements has a broad peak encompassing 3 of the 4 variants (See Supplementary Fig. S3). Second, there are 3 unannotated human transcripts (AK024171, AK054959, and CR608789) located in the same region, just downstream of SSBP2, suggestive of a transcriptionally active genomic interval. Last and most importantly, the direct functional evidence relating the variant rs7732320 to SSBP2 expression in glioblastomas and the unequivocal associations of patient survival with SSBP2 inherited variants and SSBP2 expression levels in tumors point to a cis effect of the variant(s) with the disruption of the transcriptional control of SSBP2 as the likely functional mechanism. The genotyped and imputed variants could either tag the principal association with survival attributable to this 5q14.1 locus or they themselves could be the principal culprits. Comprehensive resequencing efforts and further functional analysis will be required to unambiguously identify the causal variants.

As further evidence of the biologic plausibility of these findings, SSBP2 has been reported to be involved in the maintenance of genome stability (29) and has been implicated in transcriptional signatures in several cancers including leukemia (30), pancreatic cancer (31), oligodendrogial tumors (32), and esophageal squamous cell carcinoma (29). A direct confirmation of the link between SSBP2 and survival in brain cancer is further proffered by Shaw and colleagues (32), in which the expression of SSBP2 was shown to be associated with response to chemotherapy in patients with oligodendrogial tumors. Evidence that the genotypic association of SSBP2 with patient survival seems to be independent of tumor IDH1 mutation status and strongest among patients with a proneural/G-CIMP expression signature suggests SSBP2 may contribute to glioblastoma pathogenesis.

With further confirmation, these previously unrecognized inherited variations influencing survival may warrant inclusion in clinical trials to improve randomization and validate new therapeutic approaches. The genes identified here by SNP tags may represent potential targets for developing new drug therapies.

Disclosure of Potential Conflicts of Interest
M.S. Berger: consultant/advisory board, IVIVI Health Services and Pharmaco-Kinesis Corp. L.B. Nabors has an uncompensated position at Merck KGaA. The other authors disclosed no potential conflicts of interest.

Authors' Contributions
Development of methodology: Y. Xiao, J.L. Wiemels, M.R. Wenzsch

www.aacrjournals.org Clin Cancer Res; 18(11) June 1, 2012
OF7

Published OnlineFirst April 3, 2012; DOI: 10.1158/1078-0432.CCR-11-2778

Downloaded from clincancerres.aacrjournals.org on April 12, 2017. © 2012 American Association for Cancer Research.


Study supervision: B.L. Fridley, R.C. Thompson, J.J. Olson, M.H. Madden, K.M. Egan, R.B. Jenkins, M.R. Wensrch

Acknowledgments

The authors thank study participants, the clinicians, and research staffs at participating medical centers, Kenneth Aldape, deCODE genetics, the late Dr. Bernd Scheithauer, Dr. Caterina Gianinni, the Mayo Clinic Comprehensive Cancer Center Biorepositories and Processing, Celia Sigua, Marek Wloch, and Ms. Anna Konidari.

The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The results published here are in part based upon data generated by The Cancer Genome Atlas pilot project established by the National Cancer Institute and National Human Genome Research Institute. Information about TCGA and the investigators and institutions that constitute the TCGA research network can be found at "http://cancergenome.nih.gov."

References


22. Verhaak RG, Hoadley KA, Purdom E, Wang V, Ol Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of...
glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 2010;17:98–110.


Clinical Cancer Research

SSBP2 Variants Are Associated with Survival in Glioblastoma Patients

Yuanyuan Xiao, Paul A. Decker, Terri Rice, et al.

Clin Cancer Res  Published OnlineFirst April 3, 2012.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-2778

Supplementary Material  Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2012/04/03/1078-0432.CCR-11-2778.DC1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.