# Variants in the *CDKN2B* and *RTEL1* regions are associated with high grade glioma susceptibility

## Supplementary Material

Margaret Wrensch[1,2,3], Robert B. Jenkins[3,4], Jeffrey S. Chang[3,5], Ru-Fang Yeh[3,5], Yuanyuan Xiao[5], Karla V. Ballman[6], Mitchel Berger[1], Jan C. Buckner[7], Susan Chang[1], Paul A. Decker[6], Caterina Giannini[4], Chandralekha Halder[4], Thomas M. Kollmeyer[4], Matthew L. Kosel[6], Daniel H. LaChance[8], Lucie McCoy[1], Brian O'Neill[8], Joe Patoka[1], Alexander R. Pico[9], Michael Prados[1], Charles Quesenberry[10], Terri Rice[1], Amanda Rynearson[4], Ivan Smirnov[1], Tarik Tihan[11], Joe Wiemels[2,5], Ping Yang[12,13], John K. Wiencke[1,2,13]

1. Department of Neurological Surgery, University of California, San Francisco, San Francisco, California 94143, USA
2. Institute of Human Genetics, University of California, San Francisco, San Francisco, California 94143, USA.
3. These authors contributed equally to this work.
4. Department of Experimental Pathology, Mayo Clinic, Rochester, MN 55905, USA
5. Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco , California 94143, USA
6. Division of Biostatistics, Mayo Clinic, Rochester, MN 55905, USA
7. Department of Oncology, Mayo Clinic, Rochester, MN 55905, USA
8. Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA
9. Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, San Francisco, California 94143, USA
10. Division of Research, Kaiser Permanente, Oakland, California 94612, USA
11. Department of Pathology, University of California, San Francisco, San Francisco, California 94143, USA
12. Division of Epidemiology, Mayo Clinic, Rochester, MN 55905, USA
13. These authors represent the senior authors from the Mayo Clinic and University of California, San Francisco, respectively.

Address Correspondence to:
Margaret Wrensch, PhD
Department of Neurological Surgery
44 Page St, Suite 503
University of California, San Francisco
San Francisco, CA 94102
(margaret.wrensch@ucsf.edu)

## TABLE OF CONTENTS


| Supplementary Tables | Abbreviated title or description | Page |
|---|---|---|
| **1** | Subject characteristics from UCSF and Mayo. | **1** |
| **2** | UCSF genome wide and Mayo replication results for glioma associated SNPs with $p<10^{-6}$ in genome wide phase. | **2-4** |
| **3** | Multivariable analysis of glioma associated SNPs from UCSF study. | **5** |
| **4** | Linkage disequilibrium among glioma associated SNPs in 9p21 and *RTEL1* from UCSF study. | **6** |
| **5** | Interaction of chromosome 9p21 SNP, rs1412829, with *TERT* SNP, rs2736100 with glioma case-control status from UCSF study. | **7** |
| **6** | Mantel-Haenszel combined odds ratios for high grade glioma risk from UCSF and Mayo studies. | **8-10** |
| **Supplementary Figures** | | |
| **1** | Chromosome 9p21 linkage disequilibrium relationships for glioma associated SNPs and those associated with coronary artery disease, myocardial infarction or type 2 diabetes. | **11** |
| **2** | Ancestry checks for UCSF, the Cancer Genome Atlas and Illumina study subjects. | **12** |
| **3** | Evaluation of potential relatedness among UCSF, Cancer Genome Atlas and Illumina subjects. | **13** |
| **4** | Percent heterozygosity for UCSF study subjects. | **14** |
| **5** | Percent missingness of genotype calls for UCSF study subjects. | **15** |
| **6** | Distribution of Hardy-Weinberg p-values* for UCSF study subjects. | **16** |
| **7** | QQ plots for cases versus controls for UCSF, Cancer Genome Atlas and Illumina subjects. . | **17** |
| **8** | QQ plots for UCSF Adult Glioma Study controls versus Illumina controls. | **18** |

**Supplementary Table 1A. Subject characteristics of white high grade astrocytic glioma patients and controls, the San Francisco Bay Area Adult Glioma Study (AGS) 1997-2006, Illumina controls and The Cancer Genome Atlas glioblastoma patients.**

| | Adult Glioma Study[$] | | Other subjects | |
|---|---|---|---|---|
| | Controls | High Grade Astrocytic Glioma* | Illumina Controls | The Cancer Genome Atlas |
| **Total** | 602 | 622 | 3390 | 70 |
| **Age** | | | | |
| **Mean** | 56 | 55 | 29 | 54 |
| **Stderr** | 0.6 | 0.5 | 0.4 | 1.7 |
| **Median** | 57 | 56 | 31 | 55 |
| **Gender** | | | | |
| **% Male** | 53% | 64% | 37% | 57% |

*High grade astrocytic glioma includes glioblastoma (grade 4 astrocytoma; n=525) and grade 3 anaplastic astrocytoma, (n=97). [$] Participation rates for eligible whites were: Controls: 810/872 (92%) participated of whom 614 provided blood; 602 of these were included in this study (602/872=69%), High grade astrocytic glioma patients: 938/1177 (80%) participated of whom 659 provided blood; 622 of these were included in this study (53%). More details about participating rates for AGS were published previously [17,18]. Participation rates are not available for either TCGA cases or Illumina controls. Median, Mean ± standard error of days between diagnosis and blood draw: High grade astrocytic glioma patients: 80, 106.5±4.5, Glioblastoma patients: 80, 102.1±4.3.

**Supplementary Table 1B. Characteristics of Mayo Clinic study subjects.***

| | High Grade Astrocytic Glioma | Controls |
|---|---|---|
| **Total** | 176 | 174 |
| **Age** | | |
| **Mean** | 54 | 54 |
| **Stddev** | 12.6 | 12.5 |
| **Gender** | | |
| **% Male** | 62% | 63% |
| **Race** | | |
| **White** | 98% | 100% |
| **Other** | 1% | 0% |
| **Unknown** | 1% | 0% |

*Participation rates were 86% for cases and 90% for controls. Median days between diagnosis and blood draw for cases was 87. Of patients with high grade astrocytic glioma, 114 had glioblastoma and 62 had anaplastic astrocytoma.

**Supplementary Table 2. A. Thirteen SNPs with principal component* adjusted p-values <$10^{-6}$ for San Francisco Bay Area Adult Glioma Study (AGS) and The Cancer Genome Atlas (TCGA) high grade glioma cases versus AGS and Illumina controls (iControls). B. Replication data from Mayo Clinic high grade glioma cases versus Mayo general medical exam controls.**

**A. Discovery set: 692 UCSF AGS and TCGA cases and 3992 AGS and iControls**

| **SNP** | rs11163687 | rs7530361 | rs501700 | rs2736100 | rs10079250 |
|---|---|---|---|---|---|
| **Chromosome** | 1 | 1 | 1 | 5 | 5 |
| **Position** | 83437707 | 100235448 | 100292899 | 1339516 | 149430325 |
| **Entrez Gene ID** | | 23443 | 64645 | 7015 | 1436 |
| **Gene Symbol** | | *SLC35A3* | *HIAT1* | *TERT* | *CSF1R* |
| **Function** | | intron | intron | intron | cds-reference, missense |
| **Number genotyped** | | | | | |
| AGS glioblastoma | 516 | 525 | 525 | 525 | 525 |
| TCGA glioblastoma | 68 | 70 | 69 | 69 | 70 |
| AGS Anaplastic Astrocytoma | 93 | 97 | 97 | 97 | 96 |
| AGS Controls | 590 | 602 | 601 | 602 | 601 |
| iControls | 3232 | 3390 | 3384 | 3382 | 3370 |
| **Allele 1** | A | T | T | T | T |
| **Allele 2** | G | C | C | G | C |
| **Minor Allele** | G | C | T | T | C |
| **Minor allele frequencies** | | | | | |
| AGS glioblastoma | 0.16 | 0.18 | 0.18 | 0.39 | 0.10 |
| TCGA glioblastoma | 0.18 | 0.27 | 0.27 | 0.35 | 0.09 |
| AGS Anaplastic Astrocytoma | 0.17 | 0.19 | 0.19 | 0.43 | 0.10 |
| **Combined cases** | **0.17** | **0.19** | **0.19** | **0.39** | **0.10** |
| AGS Controls | 0.12 | 0.15 | 0.15 | 0.48 | 0.08 |
| iControls | 0.11 | 0.14 | 0.14 | 0.50 | 0.06 |
| **Combined controls** | **0.11** | **0.14** | **0.14** | **0.50** | **0.06** |
| **Principal component* adjusted p-value cases versus controls** | **3.60E-08** | 6.50E-07 | 7.10E-07 | **5.30E-13** | 4.40E-07 |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.56 (1.33-1.83) | 1.45 (1.25-1.69) | 1.45 (1.25-1.69) | 0.65 (0.58-0.73) | 1.68 (1.38-2.05) |

**B. Replication set: 176 Mayo Clinic glioblastoma and anaplastic astrocytoma cases and 174 Mayo Clinic general medical exam controls**

| | | | | | |
|---|---|---|---|---|---|
| **Number genotyped** | | | | | |
| Cases | 175 | 176 | 176 | 176 | 175 |
| Controls | 173 | 174 | 174 | 173 | 173 |
| **Minor allele frequencies** | | | | | |
| Cases | 0.14 | 0.16 | 0.16 | 0.43 | 0.07 |
| Controls | 0.09 | 0.14 | 0.14 | 0.5 | 0.04 |
| **Principal component* adjusted p-value cases versus controls** | 0.03 | 0.52 | 0.52 | 0.06 | 0.15 |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.76 (1.07-2.91) | 1.15 (0.75-1.76) | 1.15 (0.75-1.76) | 0.73 (0.53-1.02) | 1.65 (0.83-3.29) |

Bolded p-values in A were statistically significant for genome wide association discovery phase with p≤$1.8*10^{-7}$. Bolded p-values in the replication set B were statistically significant with p≤0.0038 (0.05/13).

* Principal component analysis implemented with Eigenstrat software.

**Supplementary Table 2 (continued). A. Thirteen SNPs with principal component* adjusted p-values <10-6 for San Francisco Bay Area Adult Glioma Study (AGS) and The Cancer Genome Atlas (TCGA) high grade glioma cases versus AGS and Illumina controls (iControls). B. Replication data from Mayo Clinic high grade glioma cases versus Mayo General Medicine controls.**

**A. Discovery set: 692 UCSF AGS and TCGA cases and 3992 AGS and iControls**

| **SNP** | rs1063192 | rs2157719 | rs1412829 | rs4977756 |
|---|---|---|---|---|
| **Chromosome** | 9 | 9 | 9 | 9 |
| **Position** | 21993367 | 22023366 | 22033926 | 22058652 |
| **Entrez Gene ID** | 1030 | | | |
| **Gene Symbol** | *CDKN2B* | | | |
| **Function** | UTR-3 | | | |
| **Number genotyped** | | | | |
| AGS glioblastoma | 523 | 525 | 525 | 524 |
| TCGA glioblastoma | 70 | 70 | 70 | 70 |
| AGS Anaplastic Astrocytoma | 97 | 97 | 97 | 97 |
| AGS Controls | 602 | 602 | 601 | 602 |
| iControls | 3388 | 3387 | 3388 | 3390 |
| **Allele 1** | T | A | T | A |
| **Allele 2** | C | G | C | G |
| **Minor Allele** | C | G | C | G |
| **Minor allele frequencies** | | | | |
| AGS glioblastoma | 0.49 | 0.48 | 0.48 | 0.45 |
| TCGA glioblastoma | 0.51 | 0.50 | 0.50 | 0.48 |
| AGS Anaplastic Astrocytoma | 0.47 | 0.45 | 0.45 | 0.42 |
| **Combined cases** | **0.49** | **0.48** | **0.47** | **0.45** |
| AGS Controls | 0.43 | 0.42 | 0.41 | 0.40 |
| iControls | 0.40 | 0.39 | 0.38 | 0.36 |
| **Combined controls** | **0.40** | **0.39** | **0.39** | **0.37** |
| **Principal component* adjusted p-value cases versus controls** | **9.20E-08** | **6.10E-08** | **3.40E-08** | 4.20E-07 |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.38 (1.23-1.55) | 1.38 (1.23-1.55) | 1.39 (1.24-1.57) | 1.36 (1.21-1.53) |

**B. Replication set: 176 Mayo Clinic glioblastoma and anaplastic astrocytoma cases and 174 Mayo Clinic general medical exam controls**

| **Number genotyped** | | | | |
|---|---|---|---|---|
| Cases | 176 | 176 | 175 | 176 |
| Controls | 174 | 172 | 173 | 174 |
| **Minor allele frequencies** | | | | |
| Cases | 0.55 | 0.54 | 0.53 | 0.52 |
| Controls | 0.42 | 0.42 | 0.41 | 0.38 |
| **Principal component* adjusted p-value cases versus controls** | **0.0022** | **0.0022** | **0.0038** | **0.00047** |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.6 (1.19-2.17) | 1.61 (1.19-2.17) | 1.56 (1.16-2.12) | 1.72 (1.27-2.32) |

Bolded p-values in A were statistically significant for genome wide association discovery phase with $p \leq 1.8*10^{-7}$. Bolded p-values in the replication set B were statistically significant with $p \leq 0.0038$ (0.05/13).

* Principal component analysis implemented with Eigenstrat software.

**Supplementary Table 2 (continued). A. Thirteen SNPs with principal component* adjusted p-values <10-6 for San Francisco Bay Area Adult Glioma Study (AGS) and The Cancer Genome Atlas (TCGA) high grade glioma cases versus AGS and Illumina controls (iControls). B. Replication data from Mayo Clinic high grade glioma cases versus Mayo general medical exam controls.**

**A. Discovery set: 692 UCSF AGS and TCGA cases and 3992 AGS and iControls**

| **SNP** | rs11823971 | rs6089953 | rs6010620 | rs4809324 |
|---|---|---|---|---|
| **Chromosome** | 11 | 20 | 20 | 20 |
| **Position** | 72066209 | 61761452 | 61780283 | 61788664 |
| **Entrez Gene ID** | | 51750 | 51750 | 51750 |
| **Gene Symbol** | | *RTEL1* | *RTEL1* | *RTEL1* |
| **Function** | | intron | intron | intron |
| **Number genotyped** | | | | |
| AGS glioblastoma | 525 | 524 | 525 | 525 |
| TCGA glioblastoma | 70 | 69 | 70 | 70 |
| AGS Anaplastic Astrocytoma | 97 | 97 | 97 | 97 |
| AGS Controls | 602 | 602 | 602 | 601 |
| iControls | 3342 | 3310 | 3389 | 3378 |
| **Allele 1** | A | A | A | T |
| **Allele 2** | G | G | G | C |
| **Minor Allele** | A | A | A | C |
| **Minor allele frequencies** | | | | |
| AGS glioblastoma | 0.11 | 0.16 | 0.16 | 0.16 |
| TCGA glioblastoma | 0.10 | 0.16 | 0.19 | 0.09 |
| AGS Anaplastic Astrocytoma | 0.13 | 0.21 | 0.21 | 0.16 |
| **Combined cases** | **0.11** | **0.16** | **0.17** | **0.15** |
| AGS Controls | 0.08 | 0.22 | 0.22 | 0.10 |
| iControls | 0.07 | 0.22 | 0.23 | 0.10 |
| **Combined controls** | **0.07** | **0.22** | **0.23** | **0.10** |
| **Principal component* adjusted p-value cases versus controls** | **6.50E-09** | 7.90E-07 | **1.50E-07** | **1.50E-07** |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.72 (1.43-2.08) | 0.69 (0.59-0.8) | 0.68 (0.58-0.79) | 1.54 (1.31-1.82) |

**B. Replication set: 176 Mayo Clinic glioblastoma and anaplastic astrocytoma cases and 174 Mayo Clinic general medical controls**

| **Number genotyped** | | | | |
|---|---|---|---|---|
| Cases | 176 | 175 | 175 | 176 |
| Controls | 174 | 174 | 174 | 174 |
| **Minor allele frequencies** | | | | |
| Cases | 0.1 | 0.15 | 0.15 | 0.16 |
| Controls | 0.09 | 0.25 | 0.26 | 0.1 |
| **Principal component* adjusted p-value cases versus controls** | 0.79 | **0.00073** | **0.00035** | 0.03 |
| **Odds ratio and 95% confidence intervals for 0,1, or 2 minor alleles** | 1.07 (0.63-1.81) | 0.5 (0.34-0.75) | 0.48 (0.32-0.72) | 1.66 (1.06-2.61) |

Bolded p-values in A were statistically significant for genome wide association discovery phase with $p \leq 1.8*10^{-7}$. Bolded p-values in the replication set B were statistically significant with $p \leq 0.0038$ (0.05/13).

* Principal component analysis implemented with Eigenstrat software.

**Supplementary Table 3. Eight SNPs independently associated with high grade glioma risk from the analysis of a backward selection procedure in the multivariate logistic regression framework using the 13 SNPs with individual $p<10^{-6}$; San Francisco Bay Area Adult Glioma Study (AGS) and The Cancer Genome Atlas (TCGA) high grade glioma cases versus AGS and Illumina controls (iControls).**

| | | | | Adjusted for other SNPs | | |
|---|---|---|---|---|---|---|
| **SNP** | **Chromosome** | **Position** | **Entrez Symbol** | **p-value** | **OR** | **95%CI** |
| rs11163687 | 1 | 83437707 | | 3.69E-07 | 1.52 | 1.3-1.78 |
| rs7530361 | 1 | 100235448 | SLC35A3 | 2.03E-05 | 1.40 | 1.2-1.64 |
| rs2736100 | 5 | 1339516 | TERT | 1.96E-11 | 0.66 | 0.59-0.75 |
| rs10079250 | 5 | 149430325 | CSF1R | 3.48E-06 | 1.62 | 1.32-1.99 |
| rs1412829 | 9 | 22033926 | | 2.52E-09 | 1.45 | 1.29-1.63 |
| rs11823971 | 11 | 72066209 | | 8.69E-09 | 1.79 | 1.47-2.17 |
| rs6010620 | 20 | 61780283 | RTEL1 | 6.65E-04 | 0.76 | 0.65-0.88 |
| rs4809324 | 20 | 61788664 | RTEL1 | 2.27E-05 | 1.46 | 1.23-1.74 |

**Supplementary Table 4. Linkage disequilibrium among glioma associated SNPs in 9p21 and those in RTEL1 using data from the San Francisco Bay Area Adult Glioma Study (AGS) and the Cancer Genome Atlas (TCGA) cases and AGS and Illumina controls.**

$R^2$ for four SNPs in 9p21 with $p<10^{-6}$ for glioma risk

| | rs2157719 | rs1412829 | rs4977756 |
|---|---|---|---|
| rs1063192 | 0.94 | 0.91 | 0.79 |
| rs2157719 | - | 0.94 | 0.81 |
| rs1412829 | - | - | 0.78 |

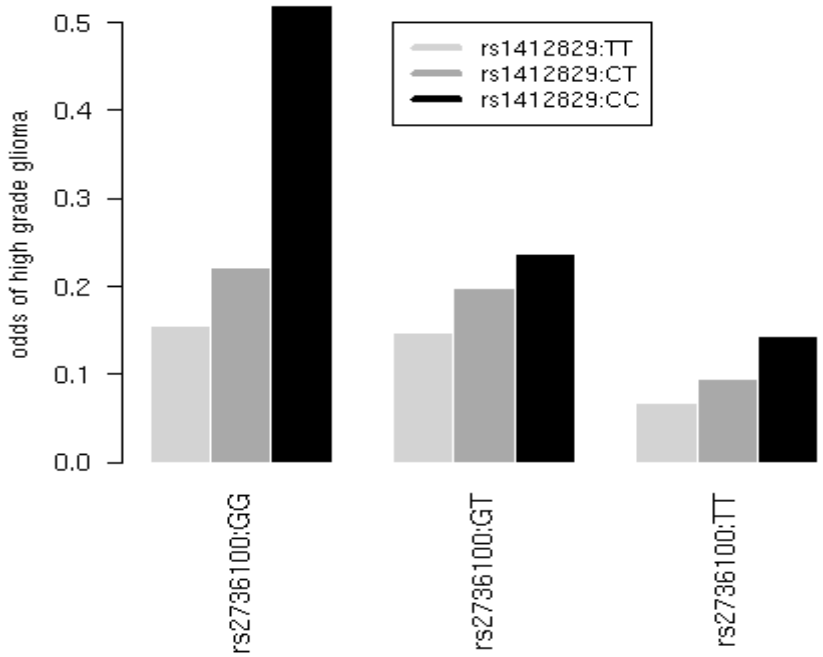
$R^2$ for three SNPs intronic to *RTEL1* with $p<10^{-6}$ for glioma risk

| | rs6010620 | rs6089953 |
|---|---|---|
| rs4809324 | 0.03 | 0.03 |
| rs6010620 | - | 0.95 |

**Supplementary Table 5. Odds ratios for high grade glioma, 95% confidence intervals and p-values from Eigenstrat adjusted model for interaction of chromosome 9p21 SNP, rs1412829, with *TERT* SNP, rs2736100 using data from the San Francisco Bay Area Adult Glioma Study (AGS) and the Cancer Genome Atlas (TCGA) cases and AGS and Illumina controls.**

| rs1412829 | rs2736100 | Cases | Controls | OR | 95% CI | p-value | Adjusted p-value (Bonferroni) |
|---|---|---|---|---|---|---|---|
| TT | GG | 65 | 420 | 1.00 | Ref* | | |
| CT | GG | 114 | 515 | 1.43 | 1.03-2.00 | 0.034 | 0.27 |
| CC | GG | 63 | 121 | 3.35 | 2.27-4.96 | 3.09e-09 | 2.5e-08 |
| TT | GT | 104 | 701 | 0.96 | 0.69-1.34 | 0.80 | 1.00 |
| CT | GT | 180 | 907 | 1.28 | 0.94-1.74 | 0.11 | 0.88 |
| CC | GT | 70 | 296 | 1.52 | 1.05-2.20 | 0.024 | 0.19 |
| TT | TT | 24 | 358 | 0.43 | 0.26-0.70 | 8.0e-04 | 6.4e-03 |
| CT | TT | 48 | 504 | 0.62 | 0.42-0.91 | 0.016 | 0.13 |
| CC | TT | 23 | 159 | 0.93 | 0.56-1.56 | 0.80 | 1.00 |

*Ref is referent group.




**Please note that the y-axis is the odds rather the odds ratio of disease.**

As shown above, the minor allele (T) of rs2736100 decreases, whereas the minor allele (C) of rs1412829 increases, the risk of high grade glioma. The interaction which is evident from the elevated odds in those with rs1412829 genotype CC (two minor alleles) and rs2736100 genotype GG (no minor alleles), can not be explained completely by the main effects of these two SNPs. Though the increased risk of high grade glioma associated with the minor allele (C) of rs1412829 is seen across the three genotypes of rs2736100, this increase appears greater for subjects with rs2736100 genotype GG, indicating a SNP-SNP interaction. However, the apparent increase probably is due to an association of the 2 SNPs in controls (chi-square test p-value for independence of rs1412829 and rs2736100 in controls p=0.013) with there being fewer than expected control subjects with rs1412828 CC and rs2736100 GG genotypes.

**Supplementary Table 6. Mantel-Haenszel combined odds ratios, 95% confidence intervals and p-values for associations of SNPs with high grade glioma risk from UCSF and Mayo studies. Tests of associations are for equality of allele frequencies between cases and controls.**

| **SNP** | rs11163687 | rs7530361 | rs501700 | rs2736100 | rs10079250 |
|---|---|---|---|---|---|
| **Chromosome** | 1 | 1 | 1 | 5 | 5 |
| **Position** | 83437707 | 100235448 | 100292899 | 1339516 | 149430325 |
| **Entrez Gene** | 5380 | 23443 | 64645 | 7015 | 1436 |
| **Gene Symbol** | | *SLC35A3* | *HIAT1* | *TERT* | CSF1R |
| **Function** | | intron | intron | intron | cds-reference,missense |
| **Allele 1** | A | T | T | T | T |
| **Allele 2** | G | C | C | G | C |
| **Minor Allele** | G | C | T | T | C |
| | | | | | |
| **UCSF** | | | | | |
| Number | | | | | |
| Case | 677 | 692 | 691 | 691 | 691 |
| Control | 3822 | 3992 | 3985 | 3984 | 3971 |
| Frequency | | | | | |
| Case | 0.17 | 0.19 | 0.19 | 0.39 | 0.1 |
| Control | 0.11 | 0.14 | 0.14 | 0.5 | 0.06 |
| OR | 1.66 (1.41-1.94) | 1.44 (1.24-1.67) | 1.44 (1.24-1.68) | 0.634 (0.57-0.72) | 1.74 (1.41-2.12) |
| p-value | 2.07E-09 | 2.70E-06 | 2.20E-06 | 3.76E-14 | 1.99E-07 |
| | | | | | |
| **Mayo** | | | | | |
| Number | | | | | |
| Case | 175 | 176 | 176 | 176 | 175 |
| Control | 173 | 174 | 174 | 173 | 173 |
| Frequency | | | | | |
| Case | 0.14 | 0.16 | 0.16 | 0.43 | 0.07 |
| Control | 0.09 | 0.14 | 0.14 | 0.5 | 0.04 |
| OR | 1.65 (1.00-2.76) | 1.15 (0.75-1.79) | 1.15 (0.75-1.79) | 0.75 (0.55-1.02) | 1.82 (0.89-3.85) |
| p-value | 4.31E-02 | 5.26E-01 | 5.26E-01 | 6.85E-02 | 9.86E-02 |
| | | | | | |
| **Combined** | | | | | |
| OR | 1.66 (1.42-1.93) | 1.40 (1.22-1.62) | 1.40 (1.22-1.62) | 0.65 (0.59-0.73) | 1.75 (1.44-2.11) |
| p-value | 3.95E-11 | 1.72E-06 | 1.76E-06 | 1.21E-14 | 6.98E-09 |

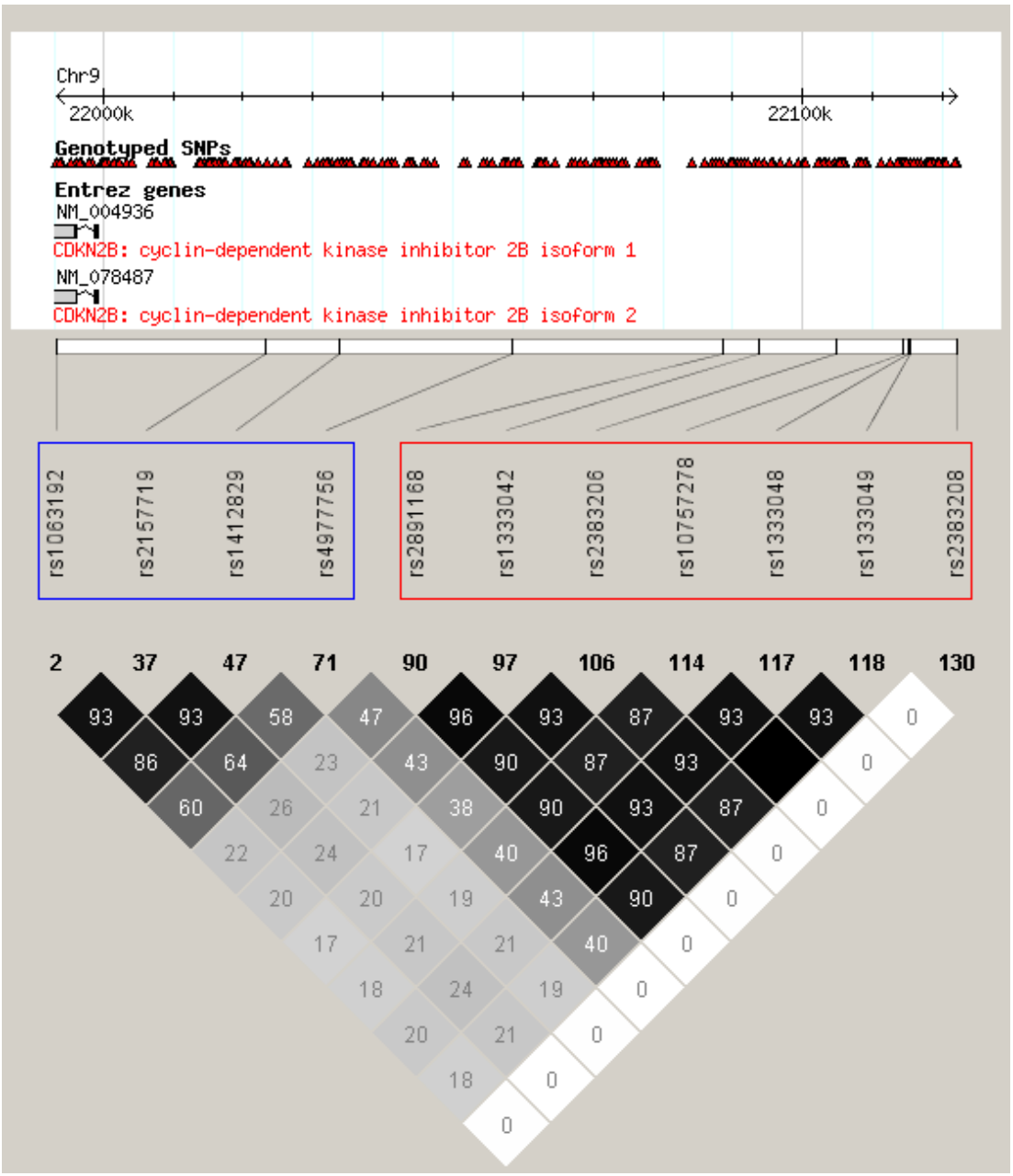
**Supplementary Table 6 (continued). Mantel-Haenszel combined odds ratios, 95% confidence intervals and p-values for associations of SNPs with high grade glioma risk from UCSF and Mayo studies. Tests of associations are for equality of allele frequencies between cases and controls.**

| **SNP** | rs1063192 | rs2157719 | rs1412829 | rs4977756 |
|---|---|---|---|---|
| **Chromosome** | 9 | 9 | 9 | 9 |
| **Position** | 21993367 | 22023366 | 22033926 | 22058652 |
| **Entrez Gene** | 1030 | | | |
| **Gene Symbol** | *CDKN2B* | | | |
| **Function** | UTR-3 | | | |
| **Allele 1** | T | A | T | A |
| **Allele 2** | C | G | C | G |
| **Minor Allele** | C | G | C | G |
| | | | | |
| **UCSF** | | | | |
| Number | | | | |
| Case | 690 | 692 | 692 | 691 |
| Control | 3990 | 3989 | 3989 | 3992 |
| Frequency | | | | |
| Case | 0.49 | 0.48 | 0.47 | 0.45 |
| Control | 0.4 | 0.39 | 0.39 | 0.37 |
| OR | 1.44 (1.28-1.62) | 1.44 (1.28-1.62) | 1.39 (1.23-1.56) | 1.39 (1.24-1.57) |
| p-value | 5.73E-10 | 4.32E-10 | 3.18E-08 | 1.99E-08 |
| | | | | |
| **Mayo** | | | | |
| Number | | | | |
| Case | 176 | 176 | 175 | 176 |
| Control | 174 | 172 | 173 | 174 |
| Frequency | | | | |
| Case | 0.55 | 0.54 | 0.53 | 0.52 |
| Control | 0.42 | 0.42 | 0.41 | 0.38 |
| OR | 1.70 (1.24-2.32) | 1.63 (1.19-2.22) | 1.63 (1.19-2.22) | 1.77 (1.30-2.42) |
| p-value | 5.12E-04 | 1.45E-03 | 1.44E-03 | 1.98E-04 |
| | | | | |
| **Combined** | | | | |
| OR | 1.47 (1.32-1.64) | 1.47 (1.32-1.63) | 1.42 (1.27-1.58) | 1.44 (1.29-1.60) |
| p-value | 1.33E-12 | 2.21E-12 | 1.85E-10 | 3.52E-11 |

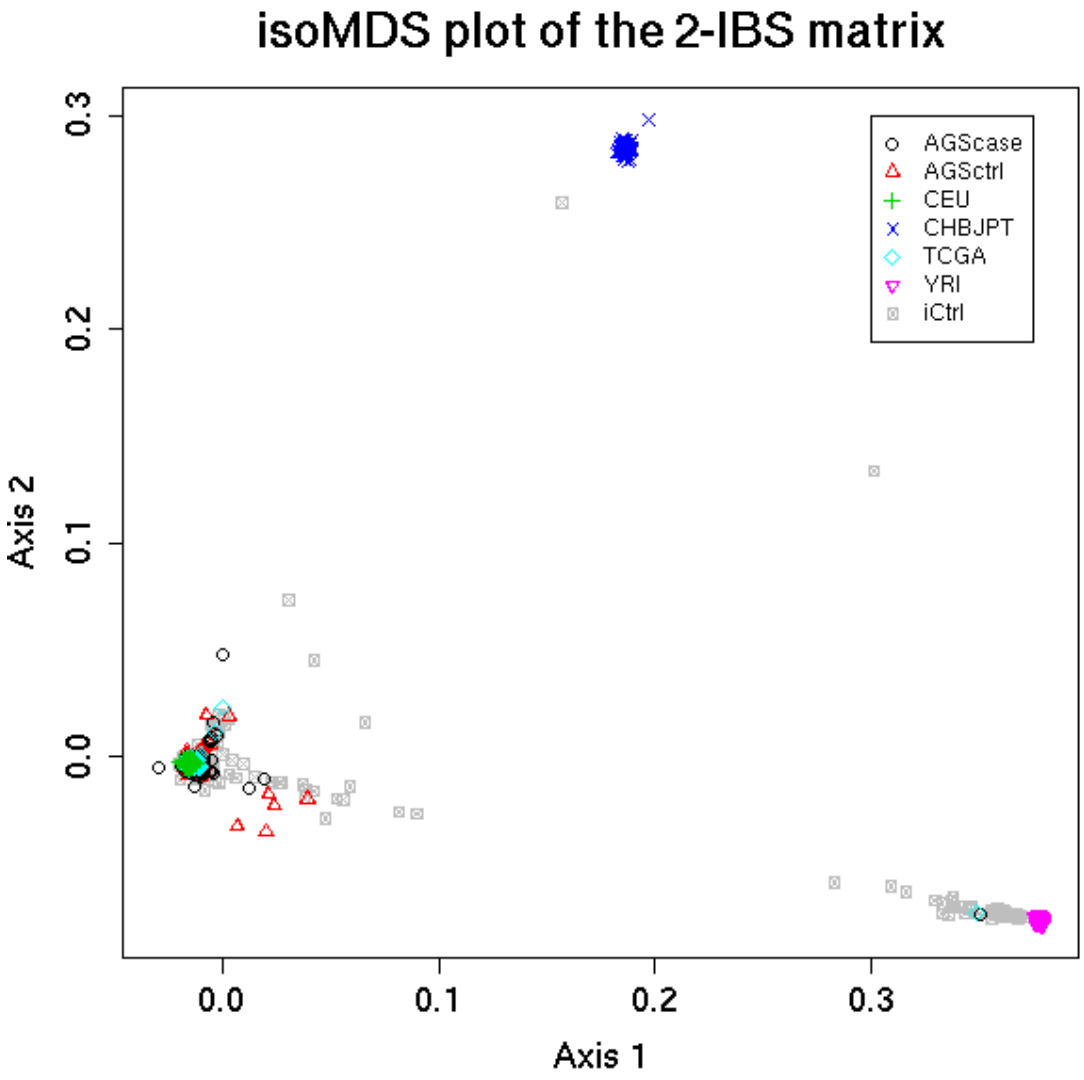
**Supplementary Table 6 (continued). Mantel-Haenszel combined odds ratios, 95% confidence intervals and p-values for associations of SNPs with high grade glioma risk from UCSF and Mayo studies. Tests of associations are for equality of allele frequencies between cases and controls.**

| **SNP** | rs11823971 | rs6089953 | rs6010620 | rs4809324 |
|---|---|---|---|---|
| **Chromosome** | 11 | 20 | 20 | 20 |
| **Position** | 72066209 | 61761452 | 61780283 | 61788664 |
| **Entrez Gene** | | 51750 | 51750 | 51750 |
| **Gene Symbol** | | *RTEL1* | *RTEL1* | *RTEL1* |
| **Function** | | intron | intron | intron |
| **Allele 1** | A | A | A | T |
| **Allele 2** | G | G | G | C |
| **Minor Allele** | A | A | A | C |
| | | | | |
| **UCSF** | | | | |
| Number | | | | |
| Case | 692 | 690 | 692 | 692 |
| Control | 3944 | 3912 | 3991 | 3979 |
| Frequency | | | | |
| Case | 0.11 | 0.16 | 0.17 | 0.15 |
| Control | 0.07 | 0.22 | 0.23 | 0.1 |
| OR | 1.64 (1.35-1.99) | 0.68 (0.58-0.79) | 0.68 (0.59-0.80) | 1.59 (1.34-1.88) |
| p-value | 8.67E-07 | 2.97E-07 | 3.52E-07 | 9.57E-08 |
| | | | | |
| **Mayo** | | | | |
| Number | | | | |
| Case | 176 | 175 | 175 | 176 |
| Control | 174 | 174 | 174 | 174 |
| Frequency | | | | |
| Case | 0.1 | 0.15 | 0.15 | 0.16 |
| Control | 0.09 | 0.25 | 0.26 | 0.1 |
| OR | 1.13 (0.66-1.94) | 0.52 (0.35-0.78) | 0.50 (0.33-0.74) | 1.69 (1.05-2.74) |
| p-value | 6.99E-01 | 8.84E-04 | 3.39E-04 | 2.44E-02 |
| | | | | |
| **Combined** | | | | |
| OR | 1.56 (1.30-1.86) | 0.65 (0.57-0.75) | 0.66 (0.57-0.76) | 1.60 (1.37-1.87) |
| p-value | 7.77E-07 | 4.14E-09 | 3.40E-09 | 1.70E-09 |

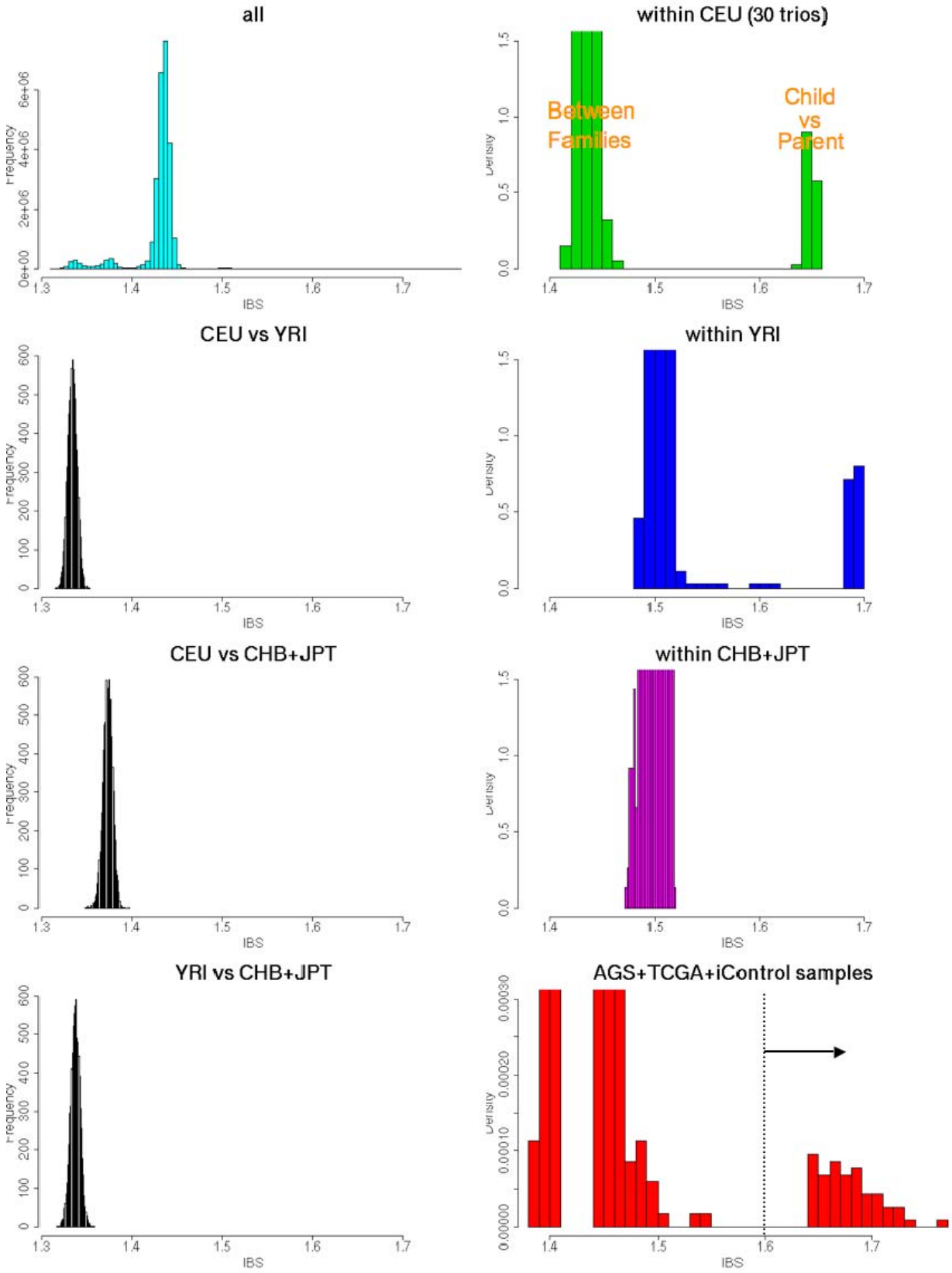
**Supplementary Figure 1:** Linkage disequilibrium relationships between the four chromosome 9 glioma associated SNPs (left box) and seven chromosome 9 SNPs associated or potentially associated with coronary artery disease, myocardial infarction or type 2 diabetes (right box).



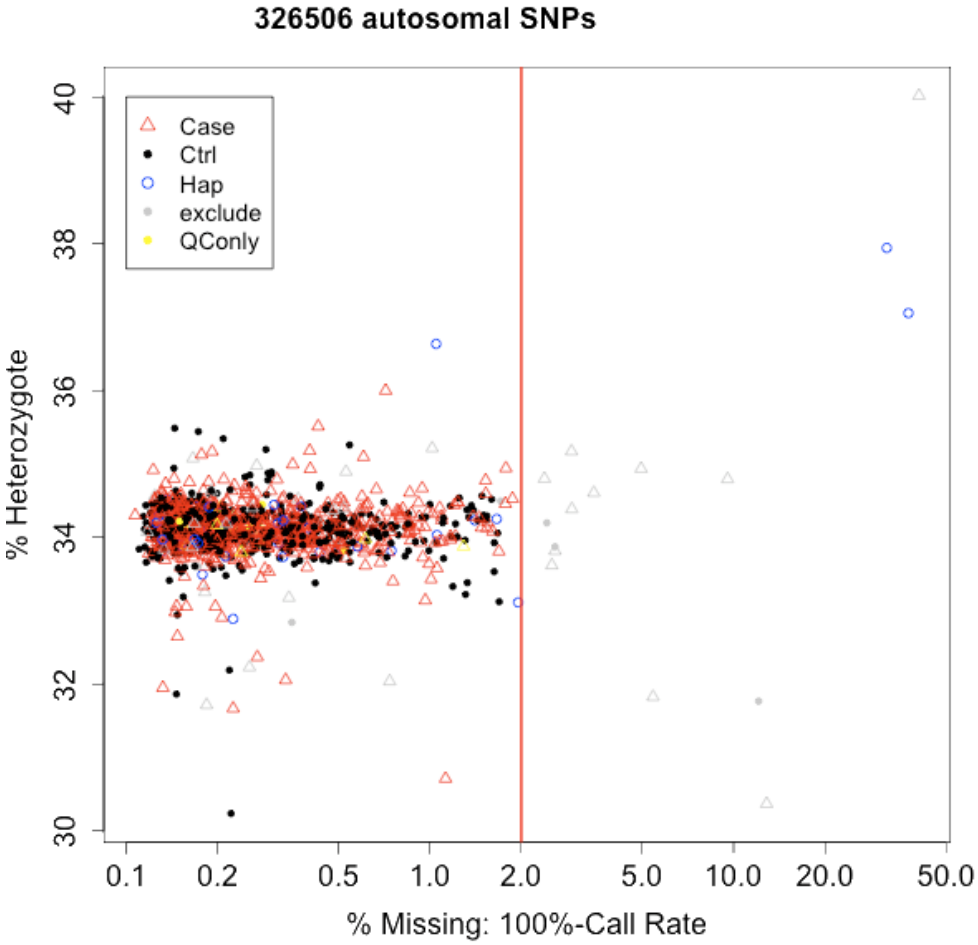
**Supplementary Figure 2.** Subject ancestry check and identity by state (IBS) analyses using Kruskal's non-metric multi-dimensional scaling (MDS) of means of 20 bootstrap runs comparing 1000 random biallelic SNPs for each pair of self-identified whites from the Adult Glioma Study (AGScase and AGSctrl) and Illumina controls (iCtrl) with Hapmap samples from individuals with known European (CEU), African (YRI), or Asian (CHB, JPT) ancestry, the San Francisco Bay Area Adult Glioma Study 1997-2006.



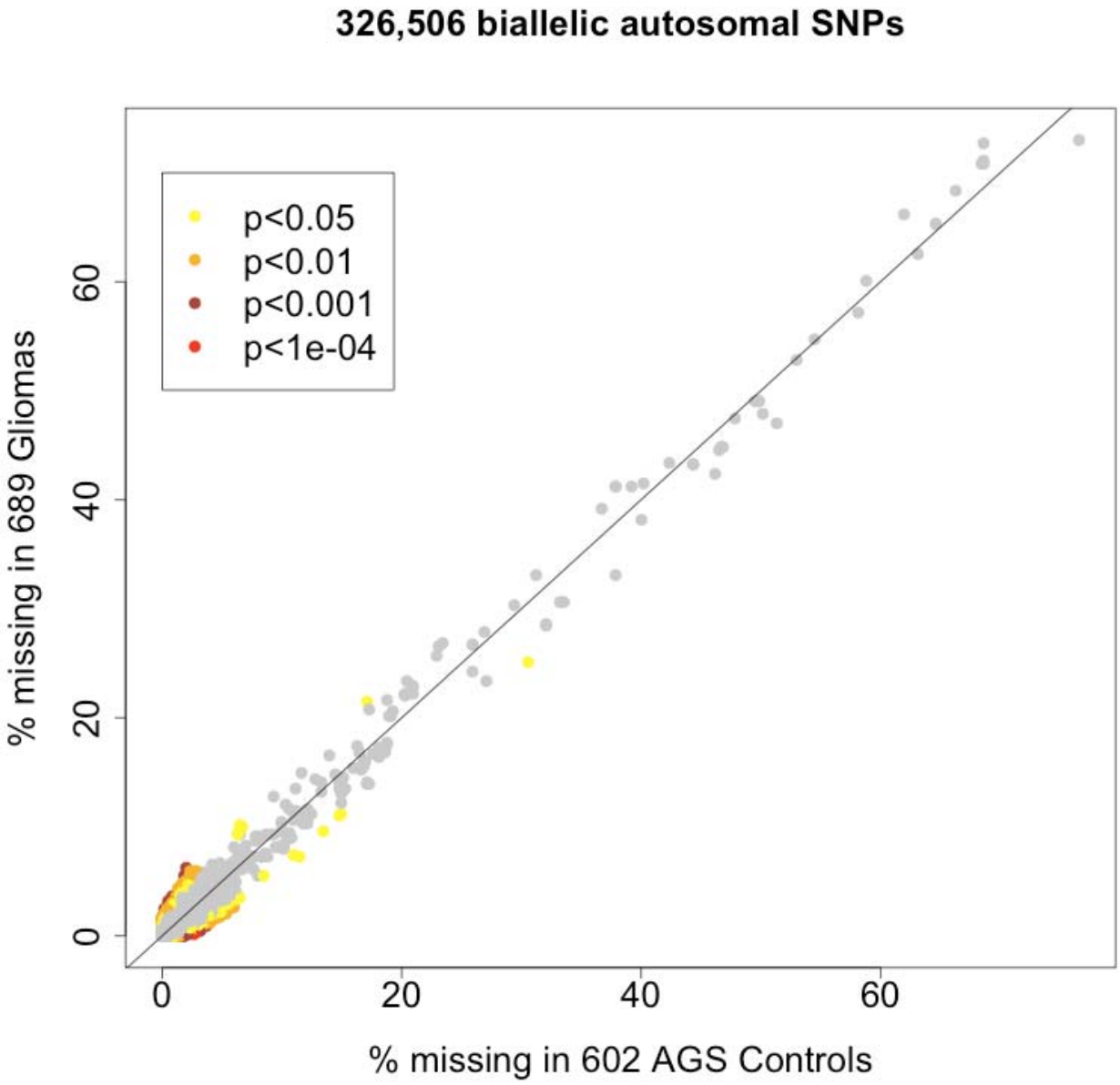
**Supplementary Figure 3.** Evaluation of identity by state (IBS) to discover potentially related individuals from the San Francisco Bay Area Adult Glioma Study (AGS) 1997-2006, Illumina controls (iControls), and the Cancer Genome Atlas (TCGA) using IBS distributions for HapMap samples from individuals with known relationship and European (CEU), African (YRI), or Asian (CHB, JPT) ancestry.



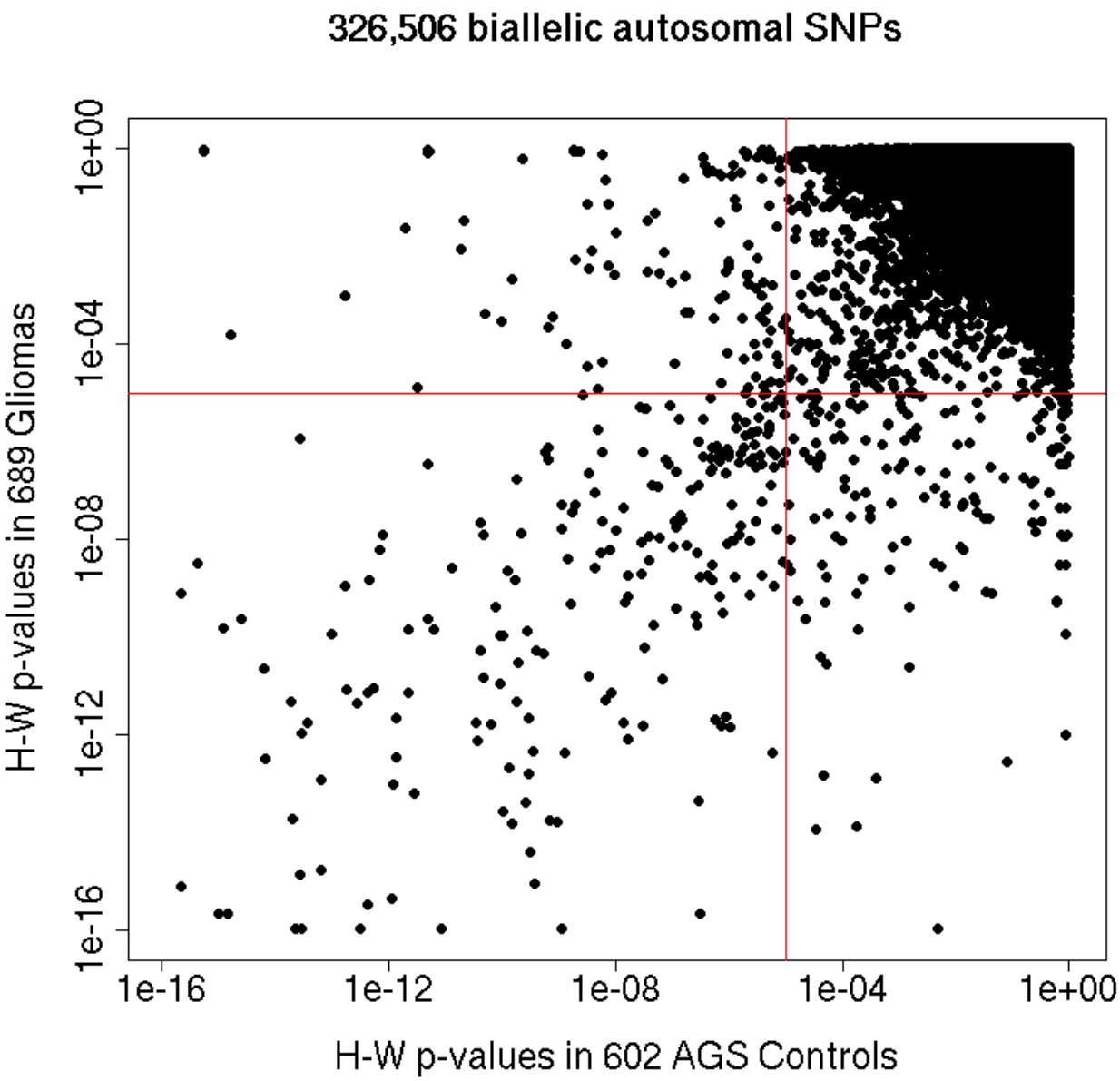
**Supplementary Figure 4.** Percent heterozygosity of 1403 samples genotyped by type of sample and call rate, for cases and controls (Ctrl) from the San Francisco Bay Area Adult Glioma Study (AGS) 1997-2006 and from Hapmap CEU controls (Hap).



**Supplementary Figure 5.** Percent of missingness for 326,506 autosomal SNPs, glioma cases vs. controls, the San Francisco Bay Area Adult Glioma Study (AGS) 1997-2006, (689 cases include 622 high grade glioma plus 67 patients with other histologies not included in case-control comparisons).

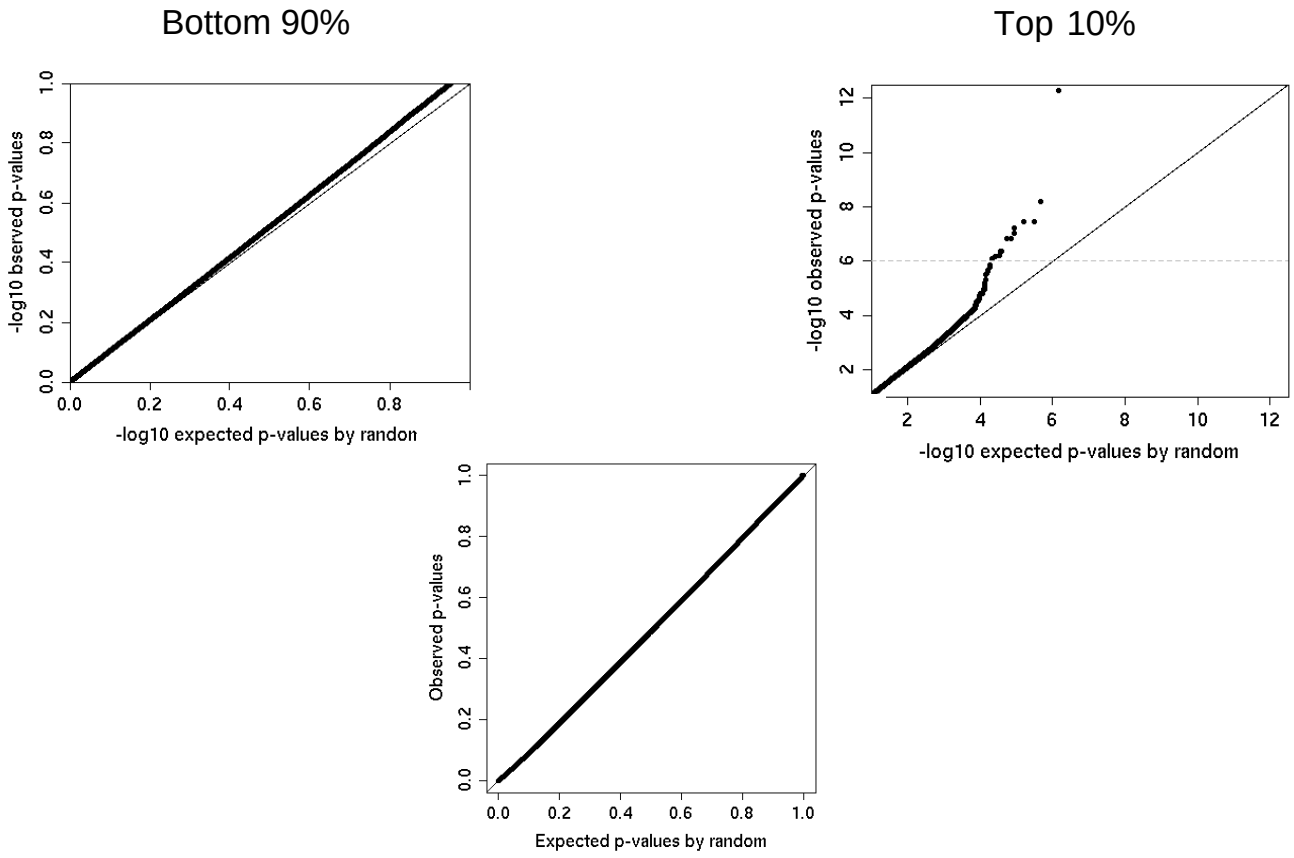


**Supplementary Figure 6.** Distribution of Hardy-Weinberg p-values* from the San Francisco Bay Area Adult Glioma Study (AGS) 1997-2006 cases vs. controls, (689 cases include 622 high grade glioma plus 67 patients with other histologies not included in case-control comparisons).




* Red lines indicate p of 0.00001

**Supplementary Figure 7:** QQ plots of observed versus expected Eigenstrat adjusted p-values across the genome for SNP associations with UCSF Adult Glioma Study (AGS) and The Cancer Genome Atlas high grade glioma cases (n=692) versus AGS and Illumina controls (n=3992); genomic control parameter=1.058.



**Supplementary Figure 8**: QQ plots of observed versus expected Eigenstrat adjusted p-values across the genome for SNP associations with UCSF Adult Glioma Study (AGS) controls (n=602) versus Illumina controls (n=3390); genomic control parameter=1.07.