**Supplementary Figure 1. CONSORT chart.**

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**Supplementary Figure 2. Q-Q plot.**

****

**Supplementary Figure 3. Mutated sequences in *AXIN1* by CRISPR.**

**Supplementary Figure 4. LocusZoom plots of A) *AXIN1* SNPs, and B) intergenic SNPs between *MGST1* and *LMO3.***

**A)**

****

**B)**

****

**Supplementary Figure 5. Kaplan-Meier plots of OS for rs11648673 (G>A) in *AXIN1* (the variant used for the functional assays) in CALGB/SWOG 80405.**



**Supplementary Tables**

**Supplementary Table 1. Oligonucleotide sequences used for CRISPR.**

|  |  |  |
| --- | --- | --- |
| **Oligonucleotide Name** | **Forward Oligonucleotide 5’-3’** | **Reverse Oligonucleotide 5’-3’** |
| **gRNA\_AXIN1\_rs11648673** | CACCGCATTTCAACAAACAGTGCTT | AAACAAGCACTGTTTGTTGAAATGC |
| **gRNA1\_AXIN1\_KO** | CACCGCTTCTGAGGGAGTCTTCCGGG | AAACCCCGAAGACTCCCTCAGAAGC |
| **gRNA2\_AXIN1\_KO** | CACCGCCTTCGCTGTACCGTCTACTGG | AAACCCAGTAGACGGTACAGCGAAGGC |
| **gRNA\_AXIN1\_rs11648673\_check** | GCACTTACTGGCTACTGACC | CAGCCTGGTGAAGCATTTGT |
| **gRNA1\_AXIN1\_KO\_check** | TTGGAATATACGAGGACAGGCT | GTCGGACTCACCTGAACTCTCT |
| **gRNA2\_AXIN1\_KO\_check** | ATACCTGCCGACCTTAAATGAA | AGCTCTCGGAGGTGAGTACAGA |
| **AXIN1\_rs11648673\_ssDNAdonor** | TCCCACCCAGTCCCCTAACTAATGTGCAGGACACTTTGGTTGCTAGGCTGTAGTGAGGGCTTTCTGCATCATGTGCCTGGCCTCACCCAAGCACTGTTTGCTGAAATGCTCAGAAACTTTATAAAGA |

**Supplementary Table 2.** **Ten most statistically significant SNPs associated with OS in CALGB/SWOG 80405, adjusted for age (log10 transformed), sex, and tumor location (left vs. right/transverse).** Wald p-values are presented.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RSID** | **Chr** | **Gene** | **Alleles** | **Feature** | **MAF** | **HR** | **95% LCL** | **95% UCL** | **P-value** |
| rs7300446 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.15 | 1.45 | 1.20 | 1.76 | 1.62x10-4 |
| rs12426370 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.15 | 1.45 | 1.20 | 1.76 | 1.62x10-4 |
| rs10846370 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.15 | 1.41 | 1.17 | 1.68 | 2.00x10-4 |
| rs11644916 | 16 | *AXIN1* | G>A | Intronic | 0.30 | 1.32 | 1.14 | 1.53 | 1.80x10-4 |
| rs2461035 | 8 | *STMN2/HEY1* | A>G | Intergenic | 0.33 | 0.71 | 0.61 | 0.82 | 3.27x10-6 |
| rs16985284 | 2 | *KCNS3/RDH14* | A>C | Intergenic | 0.12 | 1.65 | 1.34 | 2.02 | 2.52x10-6 |
| rs11246159 | 11 | *ANO9* | A>G | Intronic | 0.17 | 1.45 | 1.21 | 1.73 | 6.92x10-5 |
| rs11649255 | 16 | *AXIN1* | A>G | Intronic | 0.29 | 1.31 | 1.14 | 1.52 | 2.51x10-4 |
| rs898838 | 2 | *MSGN1/KCNS3* | A>G | Intergenic | 0.45 | 0.72 | 0.63 | 0.83 | 5.33x10-6 |
| rs2467754 | 8 | *STMN2/HEY1* | A>G | Intergenic | 0.33 | 0.71 | 0.61 | 0.82 | 5.66x10-6 |

**Supplementary Table 3. SNPs from Supplementary Table 2 tested for associated with OS in CALGB/SWOG 80405, adjusted for age (log10 transformed), sex, *BRAF* V600E, MSI (MSI-H versus MSS), and CMS (1, 2, 3, 4).** MAF and statistical results are based on 289 patients with non-missing *BRAF* V600E, MSI, and CMS data. Wald p-values are presented.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RSID** | **Chr** | **Gene** | **Alleles** | **Feature** | **MAF** | **HR** | **95% LCL** | **95% UCL** | **P-value** |
| rs7300446 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.13 | 1.55 | 1.15 | 2.09 | 4.37x10-3 |
| rs12426370 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.13 | 1.55 | 1.15 | 2.09 | 4.37x10-3 |
| rs10846370 | 12 | *MGST1*/*LMO3* | A>G | Intergenic | 0.14 | 1.43 | 1.09 | 1.87 | 9.67x10-3 |
| rs11644916 | 16 | *AXIN1* | G>A | Intronic | 0.32 | 1.38 | 1.13 | 1.68 | 1.25x10-3 |
| rs2461035 | 8 | *STMN2/HEY1* | A>G | Intergenic | 0.34 | 0.70 | 0.57 | 0.86 | 7.44x10-4 |
| rs16985284 | 2 | *KCNS3/RDH14* | A>C | Intergenic | 0.12 | 1.74 | 1.29 | 2.35 | 2.97x10-4 |
| rs11246159 | 11 | *ANO9* | A>G | Intronic | 0.16 | 1.43 | 1.09 | 1.88 | 1.06x10-2 |
| rs11649255 | 16 | *AXIN1* | A>G | Intronic | 0.32 | 1.36 | 1.12 | 1.65 | 2.17x10-3 |
| rs898838 | 2 | *MSGN1/KCNS3* | A>G | Intergenic | 0.45 | 0.75 | 0.62 | 0.91 | 3.78x10-3 |
| rs2467754 | 8 | *STMN2/HEY1* | A>G | Intergenic | 0.34 | 0.71 | 0.58 | 0.88 | 1.35x10-3 |

**Supplementary Table 4. Bioinformatics analysis of SNPs associated with OS.** The linkage disequilibrium (LD) r2 reported for rs11648673 is in relation to rs11644916 in Europeans from the 1,000 Genomes Project. The SNP regions reported for rs11644916 and rs11648673 are relative to the *AXIN1* gene. The SNP in bold (rs11644916)is the variant in *AXIN1* that was associated with OS. The SNP in Italics is the one selected for the functional assays. RegulomeDB score represents the evidence that each SNP functions in a regulatory role (1-strong evidence, 6-weak evidence). ENCODE data includes experimental information for ChiP-seq and DNase I sensitivity, histone modifications, as well as transcription factor binding motifs that were identified using a combination of computational and experimental data. ND, not determined.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **LD (r2)**  | **Region** | **RegulomeDB score** |  |  **ENCODE data** |  |  |  |
|  |  |  |  | **ChIP-seq** | **Transcription factor binding motifs** | **DNase I sensitivity region** | **Histone modification** |  |
| **rs11644916** | - | Intronic | 3a | CTCF, RAD21 | RFX3 | No | None |  |
| *rs11648673* | 0.81 | Intronic | 1f | POLR2A | DBP, HNF4, TCF12 | ND | Enhancer |  |
| rs7300446 | ND | intergenic | 5 | SPI1 | ZBRK1 | ND | None |  |
| rs12426370 | ND | intergenic | 6 | ND | ND | ND | None |  |
| rs10846370 | ND | intergenic | No data | ND | ARNT, FOXD3, FOXL1, MYC | ND | None |  |

**Supplementary Table 5. *AXIN1* variants tested in this study: extent of LD between each other, and the association with OS, either in CALGB/SWOG 80405, TCGA, or both (when available).** The r2 indicates the LD according to the 1,000 Genomes Project in Europeans.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **RSID** | **Population** | **HR** | **95% LCL** | **95% UCL** | **P-value** | **r2** |
| **rs11644916** | **rs11649255** | **rs11648673** |
| rs11644916 | CALGB | 1.40 | 1.20 | 1.59 | 4.26x10-6 |  | 0.99 | 0.81 |
| rs11649255 | CALGB | 1.38 | 1.20 | 1.58 | 6.83x10-6 | 0.99 |  | 0.82 |
|  | TCGA | 2.24 | 1.20 | 4.19 | 0.0096 |  |  |  |
| rs11648673 | CALGB | 1.31 | 1.14 | 1.52 | 1.86x10-4 | 0.81 | 0.82 |  |