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Wnt Signaling Pathway Pharmacogenetics in Non-Small Cell Lung Cancer

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Abstract

Wnt/β-catenin pathway alterations in non-small cell lung cancer (NSCLC) are associated with poor prognosis and resistance. In 598 stage III-IV NSCLC patients receiving platinum-based chemotherapy at MD Anderson Cancer Center (MDACC), we correlated survival with 441 host SNPs in 50 Wnt pathway genes. We then assessed the most significant SNPs in 240 Mayo Clinic

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patients receiving platinum-based chemotherapy for advanced NSCLC, 127 MDACC patients receiving platinum-based adjuvant chemotherapy and 340 early stage MDACC patients undergoing surgery alone (cohorts 2–4). In multivariate analysis, survival correlates with SNPs for *AXIN2* (rs11868547 and rs4541111, of which rs11868547 was assessed in cohorts 2–4), *Wnt-5B* (rs12819505), *CXXC4* (rs4413407) and *WIF-1* (rs10878232). Median survival was 19.7, 15.6, and 10.7 months for patients with 1, 2, and 3–5 unfavorable genotypes, respectively ($p= 3.8\times10^{-9}$). Survival tree analysis classified patients into two groups (MST 11.3 vs 17.3 months, $p=4.7\times10^{-8}$). None of the SNPs achieved significance in cohorts 2–4; however, there was a trend in the same direction as cohort 1 for 3 of the SNPs. Using online databases, we found rs10878232 displayed expression quantitative trait loci (eQTL) correlation with the expression of *LEMD3*, a neighboring gene previously associated with NSCLC survival. In conclusion, results from cohort 1 provide further evidence for an important role for Wnt in NSCLC. Investigation of Wnt inhibitors in advanced NSCLC would be reasonable. Lack of a SNP association with outcome in cohorts 2–4 could be due to low statistical power, impact of patient heterogeneity, or false positive observations in cohort 1.

Keywords

Wnt; pharmacogenetics; NSCLC

Introduction

Lung cancer is the world's leading cause of cancer death,[1] and non-small cell lung cancer (NSCLC) accounts for 80–85% of lung cancer cases. Cisplatin- or carboplatin-based combinations are generally used in metastatic NSCLC,[2] and yield median survival times (MSTs) of 8–10 months.[3] Platinum-based regimens are combined with radiotherapy for inoperable stage IIIA and IIIB NSCLC,[4] with MSTs of 15–18 months,[5] and adjuvant platinum-based chemotherapy increases 5-year survival rates by approximately 5% in patients with resected NSCLC, with the major benefit being seen in stages II and III.[6]

The Wingless-type protein (Wnt) signaling pathway helps maintain cancer stem cells,[7] and signals through the major ("canonical") Wnt pathway via β-catenin and through various secondary ("non-canonical") pathways.[7,8] If Wnt is not present, β-catenin is phosphorylated by a complex consisting of Axis inhibition protein (AXIN), adenomatous polyposis coli (APC) and glycogen synthase kinase-3β (GSK-3β), and this phosphorylation results in its proteolytic degradation.[8] If Wnt is present, it complexes with members of the Frizzled (FZD) family of receptors, lipoprotein receptor-related protein (LRP), Disheveled (Dvl) and AXIN,[7,8] thereby inhibiting GSK-3β and preventing β-catenin destruction.[7,8] β-catenin then migrates to the nucleus and complexes with members of T-cell factor (TCF)/Lymphoid enhancer-binding factor (LEF) family of transcription factors,[8] and interacts with various transcriptional coactivators, such as cAMP response element-binding protein (CREB)-binding protein (CBP) or its homolog p300.[8] This ultimately leads to expression of cyclin D1,[7,9] c-Myc,[7] and other target genes.

There are also several Wnt inhibitors, including some members of the Wnt family itself (Wnt-5a and -5b),[10] secreted frizzled-related proteins (sFRPs) [7], Wnt inhibitory factor-1 (WIF-1),[7] Cerberus,[7] Disabled-2 (Dab2),[8] members of the Dickkopf (Dkk) family,[7] and the Dvl antagonists Idax (coded by the *CXXC4* gene[11]) and human homolog of Dapper (HDPR1).[12]

In NSCLC cell lines and/or xenografts, Wnt pathway activation, overexpression of various Wnt pathway components or aberrant methylation or down-regulation of expression of Wnt pathway inhibitors is associated with increased cell proliferation or xenograft growth and with increased cellular motility and invasion.[13] Similarly, in resected NSCLC tumor samples, Wnt pathway activation, overexpression of various Wnt pathway components or aberrant methylation or down-regulation of expression of Wnt pathway inhibitors is associated with poor prognosis.[13] Wnt signaling may also be associated with resistance to cisplatin, docetaxel and radiation.[13]

Cancers "inherit" genes from the host, and host genotype single nucleotide polymorphisms (SNPs) can thereby affect tumor behavior. Across a range of malignancies, various Wnt pathway component SNPs or SNP interactions have correlated with risk of cancer development,[14–16] or with tumor grade,[17] stage,[17] metastases,[14] or prognosis.[14,18,19] Exploration of the impact of Wnt pathway SNPs in NSCLC has to date been very limited.[20] Because the Wnt pathway appears to be very important in NSCLC, and because Wnt signaling is associated with resistance to platinums in cell lines, we hypothesized that Wnt signaling pathway SNPs would correlate with survival of platinum-treated patients with stage III–IV NSCLC.

Methods

Patients for this study were from the University of Texas MD Anderson Cancer Center (MDACC) and from the Mayo Clinic, recruited according to protocols approved by the Institutional Review Boards of the two institutions. All patients gave written informed consent. From each patient, blood was drawn into heparinized tubes, and clinical, demographic, therapy and follow-up data were recorded.

Cohort 1

We initially assessed 598 MDACC patients with inoperable stage III–IV NSCLC and no prior chemotherapy that were receiving platinum-based chemotherapy. Of these, 331 also received radiotherapy.

Cohorts 2–4

In secondary analyses to assess whether our initial observations could be extrapolated to other NSCLC populations, we assessed 240 consenting Mayo Clinic patients receiving first line platinum-based chemotherapy alone (100 patients) or combined with radiotherapy (140 patients) for inoperable stage III (106 patients) or IV (134 patients) NSCLC (cohort 2). We also assessed 127 MDACC patients with resected NSCLC who received adjuvant platinum-based chemotherapy (cohort 3) and 340 MDACC patients undergoing surgical resection alone for NSCLC (cohort 4). The Mayo Clinic cohort was most similar to our initial cohort

(metastatic NSCLC treated with platinum-based therapy). The adjuvant chemotherapy group was assessed based on the hypothesis that the impact of a specific SNP on chemotherapy efficacy or on prognosis might hold independent of tumor stage. The surgery alone group was assessed based on the hypothesis that if a SNP were a prognostic factor (linked to tumor aggressivenss) rather than a predictive factor (linked to chemotherapy sensitivity) then if might correlate with outcome even in patients who had not received any chemotherapy.

Polymorphism selection and genotyping

For cohort 1, we utilized Gene Oncology (http://www.geneontology.org) and performed a literature search of the National Center for Biotechnology Information (NCBI) PubMed (http://www.ncbi.nlm.nih.gov) database to identify a list of Wnt pathway-related genes. A priority score was assigned to each gene based on its importance and relevance to cancer and to the Wnt signaling pathway. For each gene, we selected haplotype tagging SNPs (htSNPs) located within 10 kb upstream of the transcriptional start site and 10 kb downstream of the transcriptional stop site based on data from the International HapMap Project (http://www.hapmap.org). Using the LD select program (http://droog.gs.washing.edu/ldSelect.html) and the UCSC Golden Path Gene Sorter program (http://genome.ucsc.edu), we further divided identified SNPs into bins based on an r^2 threshold of 0.8 and minor allele frequency (MAF) greater than 0.05 in Caucasians to select tagging SNPs. We also included potentially functional SNPs in the coding (synonymous SNPs, nonsynonymous SNPs) and regulatory regions (promoter, splicing site, 5-UTR, and 3-UTR). Selected SNPs were submitted to Illumina technical support for Infinium chemistry designability, beadtype analyses, and iSelect Infinium Beadchip synthesis. Due to limitation on the total number of SNPs that can be incorporated into the initial chip design, some genes of the Wnt pathway could not be included in this analysis (e.g. GSK3β, genes of noncanonical pathways, and downstream targets).

Genomic DNA was extracted from peripheral blood lymphocytes and stored at −80° C. Using the standard 3-day protocol for Illumina's Infinium iSelect HD Custom Genotyping BeadChip (Illumina, San Diego, CA) genotyping was successful in all 441 SNPs selected. BeadStudio software was used to autocall genotypes.

In cohorts 2–4, SNPs emerging as being most important in cohort 1 were then assessed using Taqman genotyping assay for Mayo Clinic patients and Illumina iSelect Infinium Beadchip for the MDACC adjuvant chemotherapy group and surgery alone group.

Statistical analysis

STATA software (version 10; STATA Corporation, College Station, TX) was used for statistical analyses. In cohort 1, Chi square test was used to assess differences between alive and dead patient groups for categorical variables in the host population. Cox's proportional hazards model was used to estimate Hazard Ratios (HRs) for the multivariate survival analyses, with adjustment for age, sex, ethnicity, smoking status, clinical stage, and performance status (PS). Kaplan-Meier curves were used to assess genotype effect on overall survival and log rank tests were used to assess survival differences across genotypes. The most common genotype served as the reference group. All statistical analyses were two

sided. $P<0.05$ was considered statistically significant. To correct for the effect of multiple comparisons, q values (false discovery rate adjusted *P*-values) were calculated by published methods[21] implemented in the R package. SNPs with $q<0.10$ were then used to assess the combined effects of unfavorable genotypes. Survival tree analysis was performed to assess higher-order gene-gene interactions using the STREE program (http://masal.med.yale.edu/stree/), which utilizes recursive-partitioning to identify subgroups of individuals with similar risk.

In cohorts 2–4, we assessed SNPs that were found to be important in cohort 1 and used multivariate Cox proportional hazards model to determine their association with outcome in each of cohorts 2–4 singly. Meta-analysis was conducted using HR and 95% CI derived from the Cox regression analysis in each of cohorts 2–4 to estimate the HR and 95% CI in cohorts 2–4 combined, and in the Mayo Clinic cohort (cohort 2) combined with the MDACC cohort that received adjuvant chemotherapy (cohort 3).

eQTL ANALYSIS

We checked for potential functional effects of identified SNPs on gene expression through the analysis of gene-SNP associations in expression quantitative trait loci (eQTL) studies compiled by the Genevar (GENe Expression VARiation) database (http://www.sanger.ac.uk/resources/software/genevar/)[22] using the HapMap3 dataset, the seeQTL database (http://www.bios.unc.edu/research/genomic_software/seeQTL/),[23] and the University of Chicago eQTL (http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/). All analyses were performed in the CEU population with MAF≥0.05.

Results

Characteristics of patients in cohort 1 are outlined in Table 1. Of the 441 SNPs assessed (Table 2), 57 were significantly associated with survival in multivariate analysis after adjusting for patients' age, ethnicity, pack-year smoking history, clinical stage, and performance status ($p<0.05$, Table 3), including SNPs in *AXIN2* (9 SNPs), *LRP 5* (7 SNPs), *Wnt-5A* (4 SNPs), *AXIN1*, *LRP6*, *WIF1*, *Wnt-2*, *Wnt-4*, *Wnt-3* and *Wnt-5B* (3 SNPs each), *CXXC4*, *Wnt-3A*, *Wnt-7A*, *Wnt-9A* and *TLE2* (2 SNPs each), and *DVL3*, *FRZB*, *FZD4*, *Wnt-6*, *Wnt-9B* and *Wnt-11* (1 SNP each). None of the 5 SNPs assessed from the gene for β-catenin (*CTNNB1)* correlated with patient survival.

Of the 57 SNPs with $p<0.05$, 5 had $q<0.10$ after correction for multiple comparisons (Table 4). Compared to the reference genotypes, variants for rs11868547 and rs4541111 (both in *AXIN2*) were associated with improved survival, while variants for rs12819505 (*WNT5B*), rs4413407 (*CXXC4*) and rs10878232 (*WIF1*) were associated with worse survival after adjusting for clinical variables, as outlined above. MSTs were 19.7 months for patients with just one of these 5 unfavorable SNPs vs. 15.6 months for patients with 2 unfavorable SNPs and 10.7 months for patients with 3–5 unfavorable SNPs (p for trend 3.8×10^{-9}, log rank $p=1.86 \times 10^{-7}$, Table 5, Figure 1). Each of these SNPs remained significantly ($p<0.005$) associated with survival after adjusting for agents (taxane vs other) given concurrently with

cisplatin or carboplatin (data not shown). MAF of these SNPs by race is presented in Table 6.

For these 5 most significant SNPs, recursive partitioning STREE analysis (Figure 2) indicated high order gene-gene interaction and divided patients into 5 distinct "nodes" with significant survival differences. These nodes could be further classified into two groups of low and high risk. Nodes 1 and 2 combined had significantly better survival than nodes 3, 4 and 5 combined (17.3 vs 11.3 months, log rank $p=4.7 \times 10^{-8}$, Wilcoxon $p=1.0 \times 10^{-8}$) (Table 7 and Fig 3). The 75^{th} percentile, 50^{th} percentile and 25^{th} percentile survival times were 7.4 months (95% CI 6.5–8.8 months), 16.2 (13.8–18.0) months and 32.2 (26.8–41.3) months, respectively, in the combined Nodes 1 and 2 group, and were 5.9 (4.6–7.1) months, 11.1 (9.6–11.9) months and 22.2 (18.4–26.3) months, respectively, in the combined Nodes 3, 4 and 5 group (log rank $p=1.04 \times 10^{-4}$, Wilcoxon $p=5.87 \times 10^{-5}$).

Characteristics of patients in Cohorts 2, 3 and 4 are presented in Table 8. Since there was high linkage disequilibrium between the two *AXIN2* SNPs s4341111 and rs11868547 ($R^2>0.80$), we only considered the one with the more significant p-value rs11868547 in the secondary analysis involving cohorts 2–4. None of the 4 SNPs assessed correlated significantly with survival in any of cohorts 2–4 assessed individually, nor in meta-analyses combining cohorts 2–4 together, nor in the meta-analysis combining cohort 2 (Mayo Clinic patients) with cohort 3 (MDACC adjuvant chemotherapy patients) (Table 9). However, for rs11868547, the hazard ratios for each of cohorts 2–4 and for the 2 meta-analyses was in the same direction as in cohort 1. For rs12819707, the hazard ratio for cohort 2 (the Mayo Clinic group), cohort 4 (the surgery alone group) and the overall meta-analysis of cohorts 2–4 was in the same direction as in cohort 1, and for rs10878232, the hazard ratio for two of the 3 secondary analysis cohorts and for both meta-analyses secondary analysis groupings was in the same direction as in cohort 1.

In assessing correlation of these SNPs with NSCLC stage across all 4 cohorts, we found that none of the SNPs were significantly associated with stage except for rs10878232 in cohort 4 (the surgery alone group) ($p<0.05$).

To explore whether any of the 4 SNPs have functional relevance, we conducted expression quantitative trait loci (eQTL) analysis. We checked 3 databases including Genevar, seeQTL, and University of Chicago eQTL. Among candidate SNPs, a highly significant correlation was consistently shown for rs10878232 and *LEMD3*. Genevar analysis showed that the C allele was consistently correlated with higher expression of *LEMD3* in adipose tissues, lymphoblastoid cell lines and skin tissues obtained from healthy female twins (Figure 4). All p-values are less than 10^{-6} for Spearman's correlation and $<10^{-4}$ for permutation test. Similar results were obtained by exploring the seeQTL and University of Chicago eQTL. rs10878232 is located in the 5′ flanking region between *WIF1* and *LEMD3*. No cis-eQTL correlation was found for the other SNPs.

Discussion

Results from our initial cohort suggested that selected host genotype Wnt pathway SNPs may affect outcome in platinum-treated patients with stage III–IV NSCLC: 57 SNPs in 21 different Wnt pathway components correlated with survival. Of these, 5 SNPs in 4 pathway genes remained significant in multivariate analysis after correcting for the effect of multiple comparisons and after adjusting for other clinical factors. Survival worsened as the number of unfavorable genotypes increased, revealing the joint effect of these SNPs. Survival tree analysis revealed potential higher order gene-gene interactions.

In our follow-up studies exploring impact of these SNPs in other patient groups, cohort 2 (from the Mayo Clinic) was most similar to our initial cohort (platinum-based chemotherapy +/− radiotherapy for stage III–IV NSCLC), although the Mayo Clinic patient population was smaller (only 240 patients). As with cohort 1, rs11868547 G to C allelic change in Mayo Clinic patients was associated with improved survival and rs12819505 A to G allelic change was associated with worse survival. This suggests that these associations in particular warrant further assessment, although these associations did not achieve statistical significance in the Mayo Clinic patients. The lack of statistical significance in the Mayo Clinic patients (and outcomes for rs4413407 and rs10878232) may have been due to a true lack of biological importance of these SNPs (with the association in cohort 1 being due to chance alone), or could instead have been related to low statistical power (due to relatively small patient numbers in the Mayo Clinic cohort) or impact of unappreciated differences in the patient populations or therapy details. It would also be worthwhile assessing whether these differences might be related to differences in second or third line therapy between the 2 groups. We did not have data available on therapy received following first line platinum-based regimens, and so cannot directly test this here, but it is possible that an association of the SNPs with survival could have been impacted by specific therapies received.

None of the SNPs correlated significantly with outcome in cohort 3 (the MDACC postoperative adjuvant chemotherapy NSCLC group) nor in cohort 4 (the MDACC surgery alone NSCLC group), indicating that we cannot extrapolate from our advanced disease patients to our early stage patients. Again, this may have been due to patient numbers/low statistical power or it could have been due to the differences that existed between the patient groups or to actual lack of biological importance of the SNPs identified in cohort 1.

When we did a meta-analysis adding cohorts 2–4 together, the direction of association (decreased risk for rs11868547 G to C allelic change and increased risk for rs12819505 A to G allelic change and rs10878232 A to C allelic change) was the same in the meta-analysis as in cohort 1, supporting further assessment of these SNPs, although the associations were again not statistically significant.

With respect to the SNPs that emerged as being most important in our initial cohort, each of *AXIN2*, *CXX4* and *WIF1* are potentially important in NSCLC as Wnt pathway inhibitors. *AXIN2* allelic loss is common in NSCLC,[20] hypermethylation of *AXIN* is often seen in resected NSCLC tumor samples,[24] risk of developing lung adenocarcinoma varies with the

host genotype for codon 50 of *AXIN2*,[20] and lung cancer cell line transfection with *AXIN* increased apoptosis, inhibited cell line proliferation, and decreased cell invasiveness.[25]

While *Wnt-5a* appears to be important in NSCLC, there is less information available on *Wnt-5b*, although *Wnt-5b* expression is upregulated by exposure of bronchial epithelium to cigarette smoke extract.[26] Both Wnt-5a and Wnt-5b are non-canonical Wnts and may inhibit canonical Wnt signaling.[10]

The *CXXC4* gene codes for the Disheveled (Dvl) inhibitor Idax.[11] While little is known about the role of *CXXC4* or Idax in NSCLC, Dvl is probably important. Dvl is frequently expressed in NSCLC tumor samples,[27] and expression is associated with poor prognosis.[28] In NSCLC cell lines, exogenous Dvl enhanced tumor cell invasiveness,[27] and inhibition of Dvl inhibited growth.[29]

The Wnt pathway inhibitor *WIF-1* is frequently hypermethylated and/or down-regulated in NSCLC tumor samples and cell lines,[30–32] particularly in squamous cell lung carcinomas[31] and in patients with COPD,[32] and promoter hypermethylation of *WIF-1* was associated with poor prognosis in NSCLC patients.[32,33] In lung cancer cell lines, methylation inhibitors[34] or transfection with *WIF-1*[35] demethylated *WIF-1*,[34] increased *WIF-1* expression,[34] inhibited the canonical Wnt pathway,[34] inhibited cell line proliferation,[35] and induced apoptosis.[34,35]

Little is known regarding the functional impact of the SNPs observed. Further assessment of the functional impact would be useful in better understanding how these SNPs may have contributed to patient outcome and for validation in a larger independent cohort. None of the 5 most significant SNPs were in gene coding or promoter regions. While little is known about how these specific SNPs could affect gene/gene product functions, there are several possibilities. For example, SNPs in flanking regions may be in transcriptional enhancers that affect nearby gene expression,[36] SNPs in the 3′ untranslated region (UTR) may affect microRNA binding[37] and mRNA stability,[38] nuclear transport,[39] polyadenylation status[39] and subcellular targeting,[39] and intronic SNPs may affect alternative splicing[40] and gene product function.[41]

To check for functional relevance for the identified SNPs from cohort 1, we carried out eQTL analysis using Genevar database (a public resource containing four eQTL studies[42–45]), and found highly significant correlation between rs10878232 and *LEMD3* expression. The rs10878232 data are available in the MuTHER pilot study implemented in Genevar. *LEMD3* (also known as *MAN1*) encodes a LEM domain-containing gene that serves to antagonize transforming growth factor beta signaling at the inner nuclear membrane.[46] Mutations of this gene have been found in osteopoikilosis, Buscheke-Ollendorff syndrome, and melorheostosis.[47] Interestingly, the expression level of *LEMD3* correlated with two loci associated with overall survival in never smokers with NSCLC in a previous study from our group.[48] Although our current dataset of late-stage NSCLC patient is too small for stratified analysis by smoking status, we found a stronger association of rs10878232 with survival in never smokers while weak or no significant association was found in ever smokers, suggesting a potential interaction of this SNP with smoking status. In light of the known association of negative smoking history with epidermal growth factor

(EGFR) mutations, one might question whether there might be an interaction of rs10878232 with EGFR mutation status, but this cannot be addressed in our study since EGFR mutation status was not known for most patients. Further study in a larger population of NSCLC patients is necessary to verify our findings and to assess any potential interaction with EGFR mutation status.

In summary, the pharmacogenetic data from our initial patient cohort suggest that host genotype SNPs may modulate the impact of the Wnt pathway on outcome of patients with advanced NSCLC, although SNP associations with outcome in secondary analyses using cohorts 2–4 were much weaker. Overall, available evidence from cell lines and resected tumors suggests that Wnt pathway signaling is important in NSCLC tumorigenesis, patient prognosis and resistance to therapy.[13] Targeting of the Wnt pathway (through Wnt antagonists, demethylating agents, and other steps to restore function of silenced Wnt inhibitors) warrants assessment in the treatment of NSCLC.

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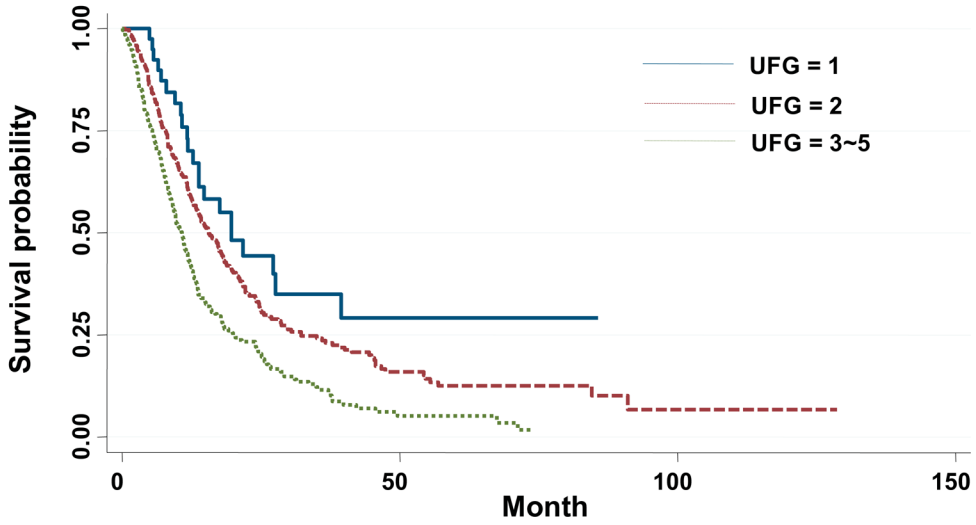

Figure 1.

Kaplan Meier survival estimates for patients with 1 (blue line) vs 2 (red line) vs 3–5 (green line) unfavorable genotypes (UFGs) in our initial cohort (median survival times 19.7 vs 15.7 vs 10.7 months, p for trend = 3.8×10^{-9}, log rank p = 1.9×10^{-7})

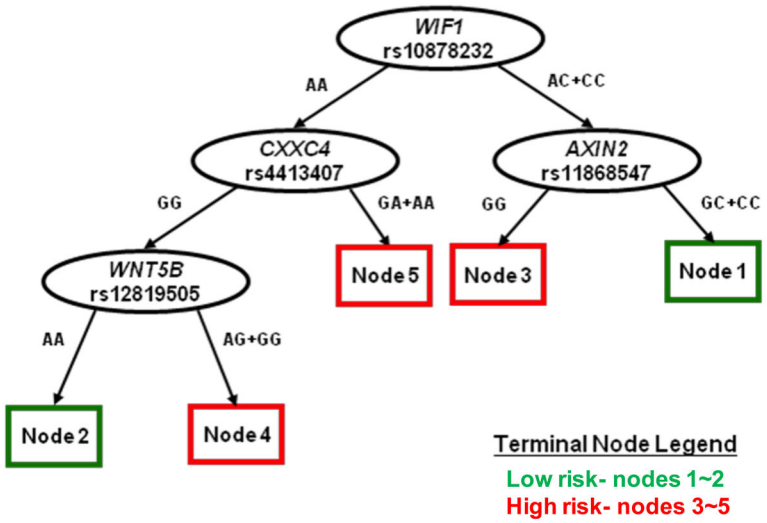

Figure 2.

Survival tree analysis of significant SNPs associated with NSCLC survival identified from the single SNP analysis (q<0.10) in our initial cohort. Five terminal nodes were identified, which could be classified into two groups of low and high risk.

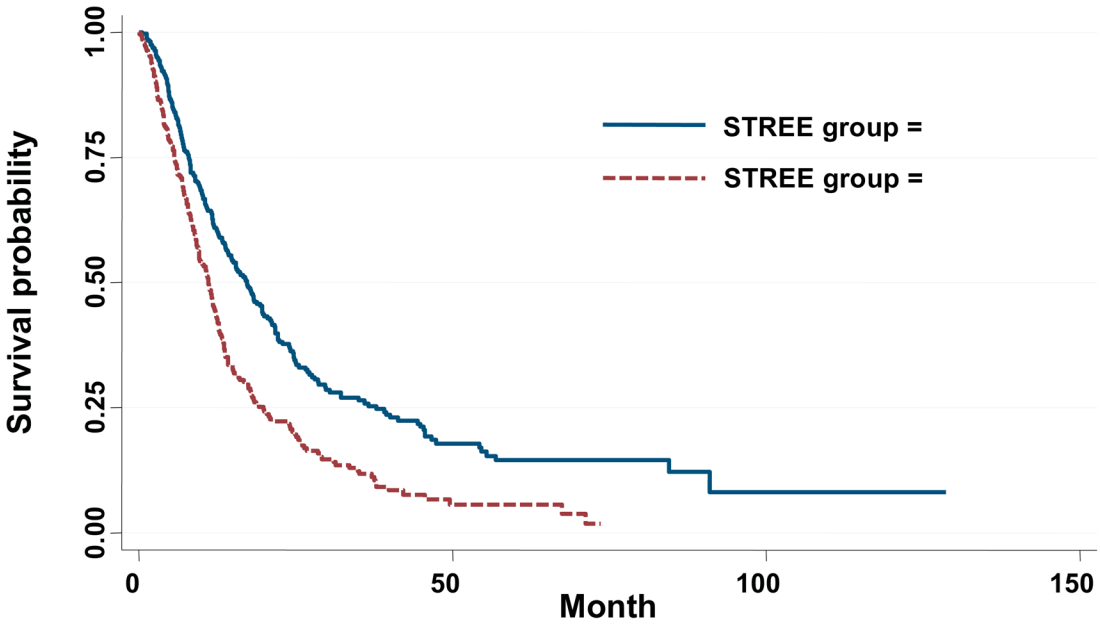

Figure 3.

Kaplan Meier survival estimates for the two risk groups identified from the survival tree analysis of our initial cohort. Survival of NSCLC patients in STREE groups 1 (49 patients) and 2 (275 patients) (blue line) was significantly better than for groups 3 (198 patients), 4 (45 patients) and 5 (31 patients) combined (red line) (17.3 vs 11.1 months, Wilcoxon p=1.0 $\times 10^{-8}$, log rank p = 4.66 $\times 10^{-8}$).

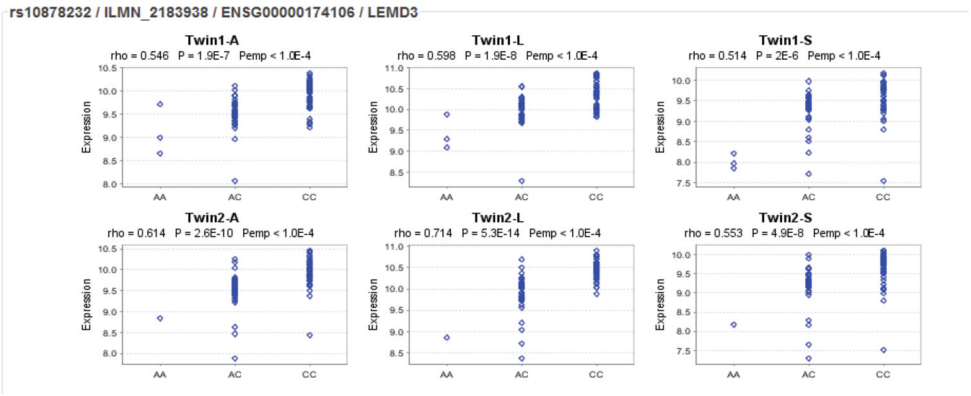

Figure 4.

Rs10878232 genotypes and *LEMD3* gene expression in cell lines and tissues from healthy female twins based on eQTL analysis in Genevar database of SNP-gene associations. Twin2-A, adipose tissue; Twin2-L, lymphoblastoid cell lines; Twin2-S, skin tissue. Rho, correlation value; Pemp, non-parametric permutation p value for 10,000 reiterations.

Table 1

Characteristics of 598 patients assessed in cohort 1

Variable	No. Patients (%)
Median survival, months	12.9
Median age (range), years	61 (28–81)
Pack year, mean (SD)	45 (27.8)
Survival status at last follow-up	
Alive	142 (23.7)
Dead	456 (76.3)
Sex	
Male	323 (54.0)
Female	275 (46.0)
Clinical stage	
Stage IIIA	82 (13.7)
Stage IIIB	
No malignant effusion	142 (23.7)
Malignant effusion*	39 (6.5)
Stage IV	335 (56.0)
Smoking status	
Never	112 (18.7)
Former	243 (40.6)
Current & Recently Quit (<1 year)	243 (40.6)
ECOG Performance status	
0	143 (23.9)
1	334 (55.9)
2–4	74 (12.4)
Unspecified	47 (7.9)
Differentiation	
Well	27 (4.5)
Moderate	61 (10.2)
Poor and undifferentiated	299 (50.0)
Unspecified	211 (35.3)
Weight loss	
Weight gain or stable	295 (49.3)
0–5%	80 (13.4)
5–10%	88 (14.7)
>10%	63 (10.5)
Unknown	72 (12.0)
Race	
White	470 (78.6)
Black	95 (15.9)
Others	33 (5.5)

Variable	No. Patients (%)
First line chemo agents (331 also received radiotherapy)	
Platinum (cisplatin or carboplatin) only	11 (1.8)
Platinum + pemetrexed	21 (3.5)
Platinum + etoposide +/− targretin	88 (14.7)
Platinum + gemcitabine +/− other agent	25 (4.2)
Platinum + taxane	283 (47.3)
Platinum + taxane + other agents	138 (23.1)
Platinum + other agents	32 (5.4)

*Now considered stage IV per recent revisions to staging systems[49]

SD- standard deviation

Table 2

Wnt pathway SNPs that were assessed in cohort 1

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs1882619	2.69E-01	0.85(0.64–1.13)	*APC*	5	112106681	0.307820239
rs2439595	2.21E-01	1.23(0.88–1.72)	*APC*	5	112146237	0.290363518
rs2431507	2.32E-01	0.86(0.67–1.10)	*APC*	5	112174080	0.296677764
rs2707761	6.88E-01	0.96(0.77–1.19)	*APC*	5	112177826	0.424838822
rs13167522	8.11E-01	1.03(0.78–1.36)	*APC*	5	112195207	0.447606546
rs42427	2.35E-01	1.18(0.90–1.55)	*APC*	5	112204224	0.298902339
rs459552	7.19E-02	1.49(0.96–2.31)	*APC*	5	112204655	0.222980247
rs2229995	8.78E-01	0.95(0.52–1.75)	*APC*	5	112206694	0.468410227
rs41116	8.13E-01	0.97(0.78–1.21)	*APC*	5	112208820	0.447606546
rs382427	7.86E-01	1.03(0.82–1.30)	*APC*	5	112215335	0.443413702
rs4807928	9.96E-02	1.18(0.97–1.43)	*APC2*	19	1399180	0.247221759
rs12005	3.11E-01	0.87(0.67–1.14)	*APC2*	19	1408875	0.315893774
rs11668593	6.94E-01	1.04(0.84–1.29)	*APC2*	19	1411473	0.424838822
rs265274	2.13E-01	1.20(0.90–1.61)	*APC2*	19	1423007	0.284945038
rs2456163	9.50E-02	1.29(0.96–1.75)	*APC2*	19	1427432	0.246983910
rs2238371	1.09E-01	0.66(0.40–1.10)	*AXIN1*	16	268917	0.247221759
rs373271	7.52E-01	0.95(0.72–1.27)	*AXIN1*	16	269672	0.437337077
rs421195	5.30E-01	0.92(0.71–1.19)	*AXIN1*	16	273147	0.379736909
rs419949	2.74E-01	1.12(0.91–1.37)	*AXIN1*	16	274891	0.308381238
rs2685127	4.14E-01	1.10(0.88–1.37)	*AXIN1*	16	275374	0.354708008
rs400037	2.15E-01	0.78(0.52–1.16)	*AXIN1*	16	276397	0.284945038
rs1048786	5.99E-02	1.25(0.99–1.59)	*AXIN1*	16	276917	0.205417788
rs394128	2.99E-01	0.82(0.56–1.19)	*AXIN1*	16	277872	0.315893774
rs214247	2.12E-01	1.14(0.93–1.42)	*AXIN1*	16	289222	0.284945038
rs214246	4.03E-02	0.77(0.61–0.99)	*AXIN1*	16	289294	0.186192568
rs1204042	1.48E-01	0.73(0.47–1.12)	*AXIN1*	16	292737	0.270394908
rs1981492	1.06E-01	1.19(0.96–1.47)	*AXIN1*	16	296690	0.247221759
rs11644916	6.02E-01	1.05(0.87–1.28)	*AXIN1*	16	299568	0.401557037

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs2301522	1.32E-01	0.77(0.55–1.08)	*AXIN1*	16	299954	0.263342145
rs17136060	8.74E-02	1.22(0.97–1.52)	*AXIN1*	16	302460	0.244482539
rs7359414	3.73E-02	0.78(0.61–0.99)	*AXIN1*	16	302639	0.186192568
rs3916990	2.89E-01	1.11(0.91–1.36)	*AXIN1*	16	312598	0.314961177
rs9921222	9.50E-01	1.00(0.87–1.14)	*AXIN1*	16	315783	0.481138076
rs12719801	7.19E-01	1.04(0.85–1.27)	*AXIN1*	16	321142	0.426451944
rs370681	7.03E-01	1.04(0.84–1.30)	*AXIN1*	16	332462	0.426046532
rs395901	5.33E-02	0.77(0.59–1.00)	*AXIN1*	16	333343	0.196213611
rs2885415	3.12E-01	1.11(0.91–1.35)	*AXIN1*	16	335397	0.315893774
rs758033	2.00E-01	1.14(0.93–1.39)	*AXIN1*	16	337045	0.284431004
rs12599449	6.14E-02	1.26(0.99–1.60)	*AXIN1*	16	337270	0.205417788
rs11645554	7.90E-02	0.71(0.49–1.04)	*AXIN1*	16	340246	0.235767882
rs17136255	1.99E-01	1.15(0.93–1.43)	*AXIN1*	16	340476	0.284431004
rs11860497	7.27E-02	1.21(0.98–1.49)	*AXIN1*	16	345417	0.222980247
rs9888749	3.11E-02	0.76(0.60–0.98)	*AXIN1*	16	348373	0.185653186
rs4340364	5.00E-01	1.08(0.86–1.37)	*AXIN2*	17	60946245	0.377760052
rs8068404	8.90E-02	0.61(0.34–1.08)	*AXIN2*	17	60946802	0.245844226
rs12452196	8.52E-01	0.98(0.78–1.23)	*AXIN2*	17	60951241	0.458967631
rs11868547	6.10E-04	0.77(0.66–0.89)	*AXIN2*	17	60954065	0.095030240
rs7591	6.14E-03	1.23(1.06–1.44)	*AXIN2*	17	60955544	0.135500153
rs4074947	4.68E-02	1.23(1.00–1.51)	*AXIN2*	17	60957682	0.186667333
rs7224837	3.44E-02	1.28(1.02–1.62)	*AXIN2*	17	60958585	0.186192568
rs11655966	1.48E-02	1.21(1.04–1.41)	*AXIN2*	17	60960112	0.144627899
rs4541111	1.53E-03	0.79(0.68–0.91)	*AXIN2*	17	60965000	0.095030240
rs11079571	1.62E-02	1.29(1.05–1.59)	*AXIN2*	17	60979143	0.144627899
rs3923087	5.29E-02	1.24(1.00–1.53)	*AXIN2*	17	60979723	0.196213611
rs3923086	1.06E-01	1.13(0.97–1.32)	*AXIN2*	17	60979950	0.247221759
rs757558	3.67E-01	1.11(0.88–1.40)	*AXIN2*	17	60992054	0.331747799
rs740026	4.46E-01	0.94(0.81–1.10)	*AXIN2*	17	60992143	0.359705483
rs12943295	4.39E-01	1.09(0.88–1.36)	*AXIN2*	17	60994967	0.359395383
rs1548581	3.65E-02	1.29(1.02–1.64)	*AXIN2*	17	60995973	0.186192568

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs1544427	3.39E-01	1.11(0.89–1.39)	*AXIN2*	17	60996130	0.328827360
rs2158520	9.29E-01	1.02(0.68–1.52)	*AXIN2*	17	60996372	0.478174891
rs12942924	1.57E-02	1.18(1.03–1.36)	*AXIN2*	17	60996861	0.144627899
rs9675157	6.67E-01	0.94(0.69–1.26)	*AXIN2*	17	60997479	0.422148501
rs2007085	8.21E-01	1.03(0.80–1.33)	*AXIN2*	17	60997824	0.449815441
rs17207681	4.58E-01	0.90(0.69–1.18)	*CTN1*	5	138196426	0.359705483
rs11744283	5.42E-01	1.13(0.76–1.70)	*CTN1*	5	138237303	0.379736909
rs288030	3.79E-01	1.09(0.90–1.33)	*CTN1*	5	138244182	0.336074710
rs288029	6.80E-01	1.04(0.86–1.27)	*CTN1*	5	138245204	0.424838822
rs10515503	7.80E-01	0.96(0.73–1.27)	*CTN1*	5	138246077	0.443413702
rs288027	6.15E-01	1.06(0.85–1.33)	*CTN1*	5	138250229	0.407840284
rs17031	6.17E-01	1.09(0.77–1.55)	*CTN1*	5	138298441	0.407981867
rs9872276	2.10E-01	0.86(0.68–1.09)	*CTNNB1*	3	41206972	0.284945038
rs1722846	1.39E-01	0.90(0.79–1.03)	*CTNNB1*	3	41208893	0.265029247
rs11564445	7.73E-01	1.06(0.73–1.52)	*CTNNB1*	3	41242756	0.443413702
rs11564447	1.04E-01	1.33(0.94–1.89)	*CTNNB1*	3	41243358	0.247221759
rs4135385	9.28E-01	1.01(0.82–1.24)	*CTNNB1*	3	41254444	0.478174891
rs4413407	1.72E-03	1.28(1.10–1.50)	*CXXC4*	4	105612810	0.095030240
rs4698921	4.04E-02	1.16(1.01–1.34)	*CXXC4*	4	105633671	0.186192568
rs10891310	2.49E-01	1.13(0.92–1.38)	*DIXDC1*	11	111397269	0.301906315
rs7100461	9.92E-02	0.77(0.56–1.05)	*DKK1*	10	53735827	0.247221759
rs1896368	3.19E-01	1.08(0.93–1.25)	*DKK1*	10	53738910	0.317400735
rs1528877	4.64E-01	1.09(0.87–1.37)	*DKK1*	10	53741348	0.359830407
rs3763511	5.40E-01	0.92(0.69–1.21)	*DKK4*	8	42355015	0.379736909
rs222850	2.78E-01	1.18(0.88–1.58)	*DVL2*	17	7078674	0.310012797
rs11919795	1.75E-02	0.67(0.48–0.93)	*DVL3*	3	185373562	0.144627899
rs4666865	5.64E-01	1.09(0.81–1.46)	*FRZB*	2	183406336	0.388647584
rs7775	8.96E-01	1.02(0.79–1.31)	*FRZB*	2	183407829	0.474806202
rs288326	8.17E-01	1.03(0.81–1.31)	*FRZB*	2	183411581	0.448878241
rs12469777	1.44E-02	0.85(0.74–0.97)	*FRZB*	2	183440609	0.144627899
rs506197	4.59E-01	0.95(0.83–1.09)	*FSHB*	11	30212399	0.359705483

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs506306	4.59E-01	0.95(0.83–1.09)	*FSHB*	11	30212443	0.359705483
rs676349	4.59E-01	0.95(0.83–1.09)	*FSHB*	11	30212558	0.359705483
rs560078	5.44E-01	0.96(0.83–1.10)	*FSHB*	11	30213698	0.379736909
rs12577729	2.10E-01	1.14(0.93–1.41)	*FSHB*	11	30213953	0.284945038
rs626869	4.59E-01	0.95(0.83–1.09)	*FSHB*	11	30215346	0.359705483
rs12537425	7.40E-01	1.03(0.88–1.20)	*FZD1*	7	90726006	0.433519176
rs6977978	9.40E-01	1.01(0.81–1.25)	*FZD1*	7	90726349	0.478174891
rs3750145	6.09E-01	0.94(0.75–1.18)	*FZD1*	7	90734767	0.405077519
rs10252817	4.56E-01	0.92(0.74–1.14)	*FZD1*	7	90742874	0.359705483
rs17163759	1.56E-01	0.81(0.61–1.08)	*FZD1*	7	90744979	0.270394908
rs4792948	1.61E-01	0.84(0.66–1.07)	*FZD2*	17	39993014	0.271874053
rs4793121	7.20E-01	0.96(0.75–1.22)	*FZD2*	17	39993435	0.426451944
rs7501777	2.43E-01	0.88(0.72–1.09)	*FZD2*	17	39994203	0.301906315
rs1946583	5.10E-01	1.08(0.87–1.34)	*FZD3*	8	28406672	0.377760052
rs352222	5.12E-01	1.07(0.87–1.32)	*FZD3*	8	28477700	0.377760052
rs4732863	4.32E-01	0.91(0.72–1.15)	*FZD3*	8	28478407	0.359395383
rs713065	1.99E-02	0.79(0.64–0.96)	*FZD4*	11	86335168	0.146727575
rs10898563	1.96E-01	1.22(0.90–1.67)	*FZD4*	11	86336861	0.284431004
rs13020497	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202605764	0.328827360
rs12994568	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202605821	0.328827360
rs13034206	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202609480	0.328827360
rs13034579	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202609524	0.328827360
rs4673222	3.39E-01	0.88(0.68–1.14)	*FZD7*	2	202610155	0.328827360
rs12474408	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202612051	0.328827360
rs12478708	3.57E-01	0.84(0.59–1.21)	*FZD7*	2	202612343	0.328827360
rs7583130	2.26E-01	0.85(0.66–1.10)	*FZD7*	2	202613333	0.295085709
rs1178947	2.83E-01	0.90(0.73–1.10)	*FZD9*	7	72488114	0.312911216
rs1046890	9.10E-01	0.99(0.81–1.21)	*FZD10*	12	129215723	0.475872051
rs3741568	7.88E-01	1.03(0.84–1.26)	*FZD10*	12	129215915	0.443413702
rs1046895	8.96E-01	0.99(0.80–1.22)	*FZD10*	12	129215994	0.474806202
rs11060753	7.88E-01	1.03(0.84–1.26)	*FZD10*	12	129216375	0.443413702

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs1463865	3.43E-01	0.83(0.57–1.22)	*FZD10*	12	129217207	0.328827360
rs11725638	3.18E-01	0.84(0.59–1.18)	*LEF1*	4	109185967	0.317400735
rs4245927	3.71E-01	1.22(0.79–1.86)	*LEF1*	4	109189039	0.333220288
rs17439845	9.12E-01	1.01(0.78–1.32)	*LEF1*	4	109213028	0.475872051
rs1291490	7.12E-01	0.96(0.76–1.21)	*LEF1*	4	109213461	0.426046532
rs4956157	7.09E-02	1.40(0.97–2.02)	*LEF1*	4	109218815	0.222980247
rs6533348	5.71E-02	1.34(0.99–1.81)	*LEF1*	4	109236385	0.203076161
rs749414	4.98E-01	0.94(0.80–1.12)	*LEF1*	4	109247362	0.377760052
rs7698367	1.35E-01	0.85(0.70–1.05)	*LEF1*	4	109249931	0.263342145
rs10022956	1.25E-01	0.86(0.70–1.04)	*LEF1*	4	109253428	0.258797750
rs10516550	5.68E-01	0.92(0.69–1.22)	*LEF1*	4	109255277	0.388647584
rs17038617	2.49E-01	0.88(0.70–1.10)	*LEF1*	4	109266333	0.301906315
rs12503104	4.62E-01	1.08(0.88–1.34)	*LEF1*	4	109281959	0.359830407
rs922163	6.86E-01	0.94(0.71–1.25)	*LEF1*	4	109285815	0.424838822
rs64388	3.31E-02	1.25(1.02–1.52)	*LRP5*	11	67830957	0.186192568
rs312009	1.12E-01	1.18(0.96–1.45)	*LRP5*	11	67833814	0.247221759
rs682429	1.13E-01	1.18(0.96–1.44)	*LRP5*	11	67835895	0.247221759
rs11228202	9.82E-01	1.00(0.79–1.28)	*LRP5*	11	67840804	0.494069355
rs4988331	2.40E-01	0.84(0.63–1.12)	*LRP5*	11	67841909	0.301281403
rs4988300	9.77E-03	0.74(0.58–0.93)	*LRP5*	11	67845407	0.135500153
rs2508836	1.03E-02	0.81(0.68–0.95)	*LRP5*	11	67847841	0.135500153
rs3781600	9.41E-01	0.99(0.76–1.28)	*LRP5*	11	67849913	0.478174891
rs606989	5.71E-01	1.08(0.82–1.42)	*LRP5*	11	67858576	0.389104323
rs312778	6.07E-02	0.78(0.59–1.01)	*LRP5*	11	67864908	0.205417788
rs314756	1.97E-02	0.69(0.51–0.94)	*LRP5*	11	67868248	0.146727575
rs729635	3.14E-01	0.87(0.67–1.14)	*LRP5*	11	67868336	0.316902816
rs312786	3.81E-02	0.66(0.45–0.98)	*LRP5*	11	67876553	0.186192568
rs624947	7.84E-01	1.02(0.88–1.19)	*LRP5*	11	67897358	0.443413702
rs638051	3.03E-01	1.14(0.89–1.46)	*LRP5*	11	67897990	0.315893774
rs11826287	4.64E-01	1.08(0.88–1.33)	*LRP5*	11	67903237	0.359830407
rs671191	3.61E-01	1.14(0.86–1.51)	*LRP5*	11	67906557	0.328827360

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs4930573	3.19E-01	0.84(0.59–1.19)	*LRP5*	11	67920032	0.317400735
rs545382	2.06E-01	0.85(0.67–1.09)	*LRP5*	11	67927589	0.284431004
rs2277268	4.67E-01	0.90(0.68–1.20)	*LRP5*	11	67930698	0.360602406
rs640569	4.14E-01	0.86(0.61–1.23)	*LRP5*	11	67941396	0.354708008
rs608343	9.14E-01	1.01(0.83–1.24)	*LRP5*	11	67953406	0.475872051
rs3781586	4.47E-02	1.26(1.01–1.57)	*LRP5*	11	67955969	0.186200636
rs12417014	5.18E-01	0.92(0.70–1.20)	*LRP5*	11	67957583	0.379094638
rs2242340	5.10E-01	0.92(0.71–1.19)	*LRP5*	11	67970695	0.377760052
rs676318	4.18E-02	0.75(0.57–0.99)	*LRP5*	11	67973996	0.186192568
rs2302684	1.14E-01	0.84(0.68–1.04)	*LRP6*	12	12169735	0.247221759
rs1012672	1.09E-02	1.47(1.09–1.97)	*LRP6*	12	12176182	0.135500153
rs11054704	9.12E-01	0.99(0.78–1.25)	*LRP6*	12	12191036	0.475872051
rs2302685	5.05E-01	0.93(0.75–1.15)	*LRP6*	12	12193165	0.377760052
rs11054709	2.00E-01	0.84(0.65–1.10)	*LRP6*	12	12193689	0.284431004
rs7301012	3.00E-01	1.12(0.90–1.39)	*LRP6*	12	12198911	0.315893774
rs12310020	1.58E-01	0.83(0.64–1.08)	*LRP6*	12	12212448	0.270394908
rs12833575	7.44E-01	0.95(0.68–1.32)	*LRP6*	12	12216108	0.434472104
rs11054721	1.37E-01	1.19(0.95–1.49)	*LRP6*	12	12222594	0.263578639
rs10845493	4.39E-01	1.09(0.87–1.37)	*LRP6*	12	12223463	0.359395383
rs10492120	6.94E-01	1.04(0.85–1.28)	*LRP6*	12	12224619	0.424838822
rs10845498	7.58E-01	0.97(0.78–1.20)	*LRP6*	12	12285841	0.437484457
rs12823867	7.93E-01	1.03(0.83–1.27)	*LRP6*	12	12287397	0.443989861
rs10743980	5.74E-02	1.15(1.00–1.32)	*LRP6*	12	12304062	0.203076161
rs12309338	6.00E-01	0.93(0.71–1.22)	*LRP6*	12	12312326	0.401557037
rs7136900	5.61E-01	1.04(0.90–1.21)	*LRP6*	12	12314360	0.388164447
rs12816278	9.69E-01	1.00(0.80–1.25)	*LRP6*	12	12317344	0.488452597
rs7296283	2.57E-01	1.10(0.93–1.31)	*LRP6*	12	12319275	0.302073322
rs11054760	1.67E-02	1.53(1.08–2.17)	*LRP6*	12	12320749	0.144627899
rs10431302	4.21E-02	0.80(0.65–0.99)	*LRP6*	12	12320918	0.186192568
rs10491321	9.39E-01	1.01(0.82–1.24)	*PPP2CA*	5	133555489	0.478174891
rs4246019	6.39E-01	0.94(0.74–1.20)	*PPP2CA*	5	133593991	0.414986215

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs254057	5.79E-02	1.26(0.99–1.60)	*PPP2CA*	5	133599755	0.203076161
rs6993129	6.45E-01	0.95(0.77–1.18)	*PPP2CB*	8	30753679	0.415574805
rs7017734	6.45E-01	0.95(0.77–1.18)	*PPP2CB*	8	30754985	0.415574805
rs11780378	6.93E-01	1.06(0.80–1.39)	*PPP2CB*	8	30760201	0.424838822
rs4733509	8.33E-01	1.04(0.74–1.46)	*PPP2CB*	8	30761490	0.452520518
rs13268487	9.84E-01	1.00(0.73–1.38)	*PPP2CB*	8	30766081	0.494172410
rs1116003	9.46E-02	1.39(0.94–2.04)	*PPP2CB*	8	30774905	0.246983910
rs4733200	5.92E-01	1.08(0.81–1.45)	*PPP2CB*	8	30784198	0.397139194
rs4733518	5.92E-01	1.08(0.81–1.45)	*PPP2CB*	8	30793453	0.397139194
rs2248033	5.18E-02	0.82(0.67–1.00)	*PYGO1*	15	53619722	0.196213611
rs1624779	6.98E-02	0.83(0.68–1.01)	*PYGO1*	15	53620813	0.222980247
rs16976371	9.05E-01	1.02(0.79–1.30)	*PYGO1*	15	53624141	0.475872051
rs11071189	1.98E-01	1.16(0.93–1.45)	*PYGO1*	15	53624380	0.284431004
rs11858624	6.54E-01	0.93(0.67–1.28)	*PYGO1*	15	53625877	0.418665386
rs7183943	7.79E-02	0.84(0.69–1.02)	*PYGO1*	15	53662358	0.235608553
rs7181481	4.50E-01	1.10(0.86–1.41)	*PYGO1*	15	53674236	0.359705483
rs7181496	7.52E-01	0.97(0.79–1.18)	*PYGO1*	15	53674260	0.437337077
rs12898968	5.39E-01	0.93(0.73–1.18)	*PYGO1*	15	53674548	0.379736909
rs2917844	7.31E-01	0.96(0.75–1.22)	*PYGO1*	15	53675019	0.431489740
rs552292	6.84E-01	0.97(0.84–1.12)	*PYGO1*	15	53676324	0.424838822
rs6474328	2.94E-01	1.11(0.91–1.36)	*SFRP1*	8	41236656	0.315417003
rs3242	3.12E-01	1.08(0.93–1.26)	*SFRP1*	8	41238711	0.315893774
rs12914	3.10E-01	1.11(0.91–1.36)	*SFRP1*	8	41239309	0.315893774
rs1127379	2.93E-01	1.14(0.89–1.46)	*SFRP1*	8	41240437	0.315417003
rs12639885	6.31E-01	1.05(0.86–1.29)	*SFRP2*	4	154919824	0.413471411
rs10014299	6.37E-01	1.05(0.85–1.29)	*SFRP2*	4	154920308	0.414986215
rs2039826	7.59E-01	0.95(0.70–1.30)	*SFRP5*	10	99516658	0.437484457
rs7478323	7.57E-01	0.95(0.70–1.30)	*SFRP5*	10	99516933	0.437484457
rs4919139	5.02E-01	1.07(0.87–1.32)	*SFRP5*	10	99522850	0.377760052
rs168649	5.66E-01	1.07(0.86–1.32)	*TCF7*	5	133472819	0.388647584
rs244952	4.18E-01	0.89(0.66–1.19)	*TCF7*	5	133474171	0.354708008

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs2436323	4.18E-01	0.89(0.66–1.19)	*TCF7*	5	133474960	0.354708008
rs151822	6.55E-01	1.05(0.85–1.29)	*TCF7*	5	133483860	0.418665386
rs152402	1.92E-01	1.15(0.93–1.43)	*TCF7*	5	133506240	0.284431004
rs30489	8.72E-01	0.98(0.75–1.28)	*TCF7*	5	133509366	0.466081299
rs4958216	1.13E-01	1.19(0.96–1.48)	*TCF7*	5	133514162	0.247221759
rs390258	4.64E-03	1.64(1.16–2.30)	*TLE2*	19	2947339	0.128006452
rs423232	2.21E-02	0.74(0.57–0.96)	*TLE2*	19	2947483	0.152312051
rs4806893	1.04E-01	0.81(0.63–1.04)	*TLE2*	19	2947889	0.247221759
rs14089	7.35E-01	0.96(0.75–1.22)	*TLE2*	19	2948790	0.432545906
rs1688128	7.36E-01	1.04(0.83–1.30)	*TLE2*	19	2981168	0.432545906
rs3743309	1.72E-01	1.19(0.93–1.51)	*TLE3*	15	68127565	0.277576313
rs2807304	4.23E-01	0.94(0.79–1.10)	*TLE4*	9	81375174	0.357966724
rs4355856	9.34E-01	1.01(0.82–1.24)	*TLE4*	9	81532323	0.478174891
rs4285553	9.34E-01	1.01(0.82–1.24)	*TLE4*	9	81532471	0.478174891
rs11667371	4.00E-01	0.83(0.54–1.28)	*TLE6*	19	2927724	0.349296428
rs17681742	4.11E-01	1.10(0.88–1.37)	*TLE6*	19	2928599	0.354708008
rs1446527	2.87E-01	0.87(0.68–1.12)	*WIF1*	12	63733304	0.313365199
rs3782497	6.73E-01	0.93(0.68–1.28)	*WIF1*	12	63746341	0.423223626
rs3782499	3.07E-01	1.16(0.87–1.55)	*WIF1*	12	63752919	0.315893774
rs6581606	1.24E-01	1.12(0.97–1.30)	*WIF1*	12	63753893	0.258519177
rs12818732	3.02E-01	1.21(0.84–1.73)	*WIF1*	12	63755986	0.315893774
rs7397906	1.48E-01	0.90(0.78–1.04)	*WIF1*	12	63769889	0.270394908
rs7309476	1.43E-01	1.11(0.96–1.29)	*WIF1*	12	63773962	0.270394908
rs1466828	1.59E-01	0.79(0.56–1.10)	*WIF1*	12	63790221	0.270394908
rs17101044	5.78E-01	1.08(0.82–1.42)	*WIF1*	12	63791366	0.392545122
rs7301320	2.72E-03	1.35(1.11–1.65)	*WIF1*	12	63800533	0.100176561
rs17101051	4.36E-01	0.91(0.72–1.15)	*WIF1*	12	63803872	0.359395383
rs2336434	5.44E-01	0.87(0.55–1.37)	*WIF1*	12	63805533	0.379736909
rs17101056	5.14E-01	0.92(0.72–1.18)	*WIF1*	12	63806743	0.377760052
rs7304867	6.68E-02	0.61(0.36–1.03)	*WIF1*	12	63806806	0.217115370
rs10878232	2.16E-03	1.36(1.12–1.66)	*WIF1*	12	63808914	0.095602299

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs1155722	6.21E-03	1.32(1.08–1.61)	*WIF1*	12	63809424	0.135500153
rs12318130	3.98E-01	1.12(0.86–1.47)	*WIF1*	12	63810846	0.349296428
rs6946781	2.87E-02	0.63(0.42–0.95)	*WNT2*	7	116694979	0.176207503
rs887574	3.59E-01	1.08(0.92–1.27)	*WNT2*	7	116703248	0.328827360
rs887575	1.59E-01	0.91(0.79–1.04)	*WNT2*	7	116703464	0.270394908
rs4730775	8.60E-02	1.23(0.97–1.56)	*WNT2*	7	116704354	0.244482539
rs2228946	6.25E-01	0.95(0.78–1.16)	*WNT2*	7	116705321	0.410945313
rs733153	8.63E-01	1.02(0.80–1.31)	*WNT2*	7	116706028	0.463958815
rs2896218	2.29E-01	0.88(0.72–1.08)	*WNT2*	7	116707214	0.296677764
rs3779548	5.15E-01	1.05(0.91–1.20)	*WNT2*	7	116718131	0.377760052
rs17139625	6.60E-01	0.94(0.73–1.22)	*WNT2*	7	116722714	0.420006663
rs39306	2.32E-01	0.89(0.73–1.08)	*WNT2*	7	116728472	0.296677764
rs6947329	4.41E-02	1.29(1.01–1.65)	*WNT2*	7	116730371	0.186200636
rs1989836	1.87E-01	0.87(0.72–1.07)	*WNT2*	7	116734432	0.284431004
rs2285545	3.44E-02	0.87(0.76–0.99)	*WNT2*	7	116735407	0.186192568
rs2239956	9.43E-02	1.26(0.96–1.64)	*WNT2*	7	116736522	0.246983910
rs739517	1.85E-01	0.83(0.63–1.09)	*WNT2*	7	116742935	0.284431004
rs39315	1.71E-01	0.90(0.78–1.04)	*WNT2*	7	116750798	0.277576313
rs254536	1.65E-01	0.87(0.71–1.06)	*WNT2*	7	116757818	0.274758970
rs6961545	8.37E-01	0.97(0.74–1.28)	*WNT2*	7	116759067	0.452937961
rs254538	2.56E-01	0.89(0.74–1.08)	*WNT2*	7	116760524	0.302008524
rs3795821	1.84E-01	0.87(0.71–1.07)	*WNT2B*	1	112802088	0.284431004
rs2488787	2.02E-01	0.91(0.78–1.05)	*WNT2B*	1	112807331	0.284431004
rs1175649	8.69E-01	0.98(0.75–1.27)	*WNT2B*	1	112820800	0.465726073
rs1175650	1.10E-01	0.83(0.67–1.04)	*WNT2B*	1	112821097	0.247221759
rs10776751	7.01E-01	1.06(0.80–1.39)	*WNT2B*	1	112821821	0.426046532
rs1620668	8.45E-01	1.02(0.83–1.26)	*WNT2B*	1	112825503	0.456546450
rs974442	4.02E-01	0.90(0.72–1.14)	*WNT2B*	1	112829794	0.349296428
rs351359	6.62E-01	1.05(0.85–1.29)	*WNT2B*	1	112841800	0.420006663
rs351360	1.58E-01	0.83(0.64–1.08)	*WNT2B*	1	112841944	0.270394908
rs11807828	4.69E-01	1.11(0.84–1.47)	*WNT2B*	1	112844072	0.360602406

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs351361	9.30E-01	0.99(0.81–1.22)	*WNT2B*	1	112844081	0.478174891
rs351364	5.23E-01	1.12(0.79–1.59)	*WNT2B*	1	112846584	0.379736909
rs3790604	1.59E-01	0.81(0.60–1.09)	*WNT2B*	1	112848402	0.270394908
rs3790606	3.47E-01	0.91(0.74–1.11)	*WNT2B*	1	112853709	0.328827360
rs351370	5.38E-01	1.08(0.84–1.38)	*WNT2B*	1	112856182	0.379736909
rs3790609	3.51E-01	1.11(0.89–1.37)	*WNT2B*	1	112858513	0.328827360
rs2273368	2.62E-01	1.13(0.91–1.39)	*WNT2B*	1	112865294	0.306380050
rs3790611	1.58E-01	0.89(0.75–1.05)	*WNT2B*	1	112869315	0.270394908
rs3809857	3.48E-02	0.80(0.65–0.98)	*WNT3*	17	42203482	0.186192568
rs199506	9.52E-01	0.99(0.81–1.23)	*WNT3*	17	42214192	0.481138076
rs199500	6.37E-01	0.95(0.77–1.17)	*WNT3*	17	42218572	0.414986215
rs2074404	2.46E-01	1.28(0.84–1.94)	*WNT3*	17	42220599	0.301906315
rs2074405	2.55E-01	1.10(0.93–1.31)	*WNT3*	17	42221161	0.302008524
rs199497	7.89E-01	1.03(0.82–1.29)	*WNT3*	17	42221762	0.443413702
rs199496	3.51E-01	1.12(0.89–1.41)	*WNT3*	17	42221887	0.328827360
rs11658976	1.22E-02	1.45(1.08–1.94)	*WNT3*	17	42221965	0.142078914
rs12452064	1.98E-01	1.17(0.92–1.50)	*WNT3*	17	42223353	0.284431004
rs199494	2.77E-01	1.15(0.89–1.47)	*WNT3*	17	42224229	0.310012797
rs7218567	4.29E-03	1.68(1.18–2.40)	*WNT3*	17	42225421	0.128006452
rs8080199	1.92E-01	1.17(0.93–1.47)	*WNT3*	17	42228781	0.284431004
rs11650531	1.21E-01	0.87(0.74–1.04)	*WNT3*	17	42229159	0.254403903
rs1563304	8.83E-01	1.02(0.81–1.28)	*WNT3*	17	42229617	0.469718466
rs7207916	2.06E-01	0.83(0.62–1.11)	*WNT3*	17	42234514	0.284431004
rs3933652	5.34E-01	1.07(0.86–1.34)	*WNT3*	17	42243714	0.379736909
rs3933653	3.68E-01	0.82(0.54–1.26)	*WNT3*	17	42243741	0.331747799
rs3916033	7.70E-01	1.03(0.84–1.27)	*WNT3*	17	42244702	0.442803211
rs11079738	3.37E-01	0.90(0.73–1.11)	*WNT3*	17	42259048	0.328827360
rs708108	1.05E-01	1.18(0.97–1.45)	*WNT3A*	1	226256478	0.247221759
rs708110	2.73E-02	1.26(1.03–1.55)	*WNT3A*	1	226257428	0.175417920
rs708122	4.29E-01	0.92(0.75–1.13)	*WNT3A*	1	226283620	0.359395383
rs10916258	1.74E-01	0.87(0.71–1.06)	*WNT3A*	1	226286505	0.278295542

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs3121309	7.14E-01	1.08(0.72–1.61)	*WNT3A*	1	226289659	0.426046532
rs3121310	1.47E-02	1.39(1.07–1.82)	*WNT3A*	1	226291447	0.144627899
rs7412010	3.83E-01	1.11(0.88–1.40)	*WNT4*	1	22309033	0.338387524
rs4654783	1.77E-02	1.58(1.08–2.31)	*WNT4*	1	22312107	0.144627899
rs3765351	1.82E-01	1.19(0.92–1.52)	*WNT4*	1	22318578	0.284431004
rs12131703	7.04E-01	0.96(0.77–1.20)	*WNT4*	1	22320804	0.426046532
rs7526484	4.59E-01	0.93(0.76–1.14)	*WNT4*	1	22324432	0.359705483
rs10917155	7.32E-03	1.54(1.12–2.11)	*WNT4*	1	22324553	0.135500153
rs2235525	5.44E-01	0.93(0.75–1.16)	*WNT4*	1	22326912	0.379736909
rs10917158	5.44E-01	0.93(0.75–1.16)	*WNT4*	1	22326960	0.379736909
rs2865174	9.04E-01	0.98(0.71–1.35)	*WNT4*	1	22337747	0.475872051
rs7515106	2.09E-02	1.61(1.07–2.42)	*WNT4*	1	22345997	0.149155672
rs7521775	9.31E-02	1.24(0.96–1.60)	*WNT4*	1	22348236	0.246983910
rs7542242	2.66E-01	1.12(0.92–1.37)	*WNT4*	1	22350080	0.307524913
rs7548239	8.34E-01	1.05(0.68–1.60)	*WNT4*	1	22351780	0.452520518
rs1499890	9.62E-02	0.89(0.78–1.02)	*WNT5A*	3	55464838	0.247172881
rs629537	1.95E-02	1.29(1.04–1.60)	*WNT5A*	3	55466053	0.146727575
rs503022	3.62E-02	1.26(1.01–1.56)	*WNT5A*	3	55466476	0.186192568
rs508407	1.08E-01	1.22(0.96–1.57)	*WNT5A*	3	55467460	0.247221759
rs476986	8.01E-01	0.94(0.60–1.49)	*WNT5A*	3	55468554	0.445017693
rs11706227	7.94E-01	1.03(0.82–1.31)	*WNT5A*	3	55471300	0.443989861
rs597437	2.72E-02	1.43(1.04–1.95)	*WNT5A*	3	55471449	0.175417920
rs11710229	6.22E-01	1.06(0.84–1.34)	*WNT5A*	3	55472993	0.410413148
rs590386	9.43E-02	1.22(0.97–1.54)	*WNT5A*	3	55474447	0.246983910
rs1047898	8.53E-02	0.89(0.78–1.02)	*WNT5A*	3	55474821	0.244482539
rs1829556	1.33E-01	0.90(0.79–1.03)	*WNT5A*	3	55476215	0.263342145
rs7622120	6.52E-02	0.79(0.61–1.02)	*WNT5A*	3	55479770	0.214878269
rs11918967	4.30E-01	1.10(0.87–1.40)	*WNT5A*	3	55480430	0.359395383
rs648872	1.93E-01	1.15(0.93–1.42)	*WNT5A*	3	55494897	0.284431004
rs566926	2.11E-01	0.90(0.77–1.06)	*WNT5A*	3	55495818	0.284945038
rs557077	4.73E-02	1.40(1.00–1.96)	*WNT5A*	3	55506307	0.186667333

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs4765829	1.55E-01	0.87(0.71–1.06)	*WNT5B*	12	1591055	0.270394908
rs10773974	2.69E-01	0.90(0.74–1.09)	*WNT5B*	12	1619633	0.307820239
rs2270038	1.69E-01	0.90(0.78–1.05)	*WNT5B*	12	1620166	0.277576313
rs2240509	2.84E-01	0.88(0.70–1.11)	*WNT5B*	12	1620858	0.312911216
rs2240510	2.85E-01	0.83(0.59–1.17)	*WNT5B*	12	1623486	0.312911216
rs2240511	1.77E-01	0.86(0.69–1.07)	*WNT5B*	12	1623551	0.279313968
rs7132752	8.10E-01	0.96(0.69–1.34)	*WNT5B*	12	1623995	0.447606546
rs3803164	1.76E-01	0.87(0.72–1.06)	*WNT5B*	12	1625915	0.279313968
rs3803163	2.72E-01	0.83(0.60–1.15)	*WNT5B*	12	1626221	0.308376026
rs12819505	1.37E-03	1.58(1.19–2.09)	*WNT5B*	12	1626926	0.095030240
rs1003939	9.87E-03	0.56(0.36–0.87)	*WNT5B*	12	1626939	0.135500153
rs6489314	8.65E-02	0.82(0.66–1.03)	*WNT5B*	12	1627431	0.244482539
rs4766403	1.03E-02	1.21(1.05–1.39)	*WNT5B*	12	1630739	0.135500153
rs4766408	3.50E-01	0.91(0.74–1.11)	*WNT5B*	12	1634790	0.328827360
rs7296858	1.71E-01	1.21(0.92–1.59)	*WNT5B*	12	1636194	0.277576313
rs7596898	4.86E-02	0.80(0.64–1.00)	*WNT6*	2	219427976	0.188401227
rs940469	2.50E-01	1.13(0.92–1.39)	*WNT6*	2	219428221	0.301906315
rs751135	6.56E-01	1.04(0.88–1.22)	*WNT6*	2	219428593	0.418665386
rs690877	3.43E-01	1.10(0.90–1.35)	*WNT6*	2	219430908	0.328827360
rs2053101	6.88E-01	0.92(0.62–1.38)	*WNT7A*	3	13825667	0.424838822
rs9864832	9.03E-03	1.52(1.11–2.08)	*WNT7A*	3	13827744	0.135500153
rs11712819	3.55E-01	0.91(0.75–1.11)	*WNT7A*	3	13830800	0.328827360
rs2163910	7.99E-01	1.03(0.81–1.31)	*WNT7A*	3	13832893	0.445017693
rs1124480	5.25E-01	0.93(0.73–1.17)	*WNT7A*	3	13832970	0.379736909
rs1946620	1.10E-02	1.32(1.07–1.63)	*WNT7A*	3	13833800	0.135500153
rs3796316	5.08E-01	1.09(0.85–1.39)	*WNT7A*	3	13834174	0.377760052
rs3796314	3.09E-01	1.12(0.90–1.38)	*WNT7A*	3	13834333	0.315893774
rs9840696	3.33E-01	0.90(0.73–1.11)	*WNT7A*	3	13840076	0.328827360
rs12492620	4.02E-01	0.92(0.75–1.13)	*WNT7A*	3	13842256	0.349296428
rs867606	5.24E-01	1.07(0.86–1.33)	*WNT7A*	3	13844302	0.379736909
rs934453	6.91E-01	0.95(0.75–1.21)	*WNT7A*	3	13845053	0.424838822

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs12634816	1.37E-01	1.29(0.92–1.81)	*WNT7A*	3	13847271	0.263578639
rs11711182	1.21E-01	1.19(0.95–1.49)	*WNT7A*	3	13851910	0.254403903
rs12634112	4.59E-01	0.92(0.73–1.15)	*WNT7A*	3	13853890	0.359705483
rs11922919	5.87E-01	1.06(0.86–1.30)	*WNT7A*	3	13854617	0.396598092
rs9863149	2.71E-01	1.18(0.88–1.58)	*WNT7A*	3	13858361	0.308376026
rs4257529	5.13E-01	1.07(0.87–1.32)	*WNT7A*	3	13869117	0.377760052
rs3762721	5.52E-01	0.93(0.73–1.18)	*WNT7A*	3	13870807	0.383590947
rs12639607	3.62E-01	1.11(0.89–1.38)	*WNT7A*	3	13871285	0.328827360
rs9819887	4.33E-01	1.06(0.91–1.24)	*WNT7A*	3	13873619	0.359395383
rs13069140	1.98E-01	0.84(0.64–1.10)	*WNT7A*	3	13878304	0.284431004
rs6442416	1.34E-01	0.90(0.78–1.03)	*WNT7A*	3	13882101	0.263342145
rs9864031	2.02E-01	0.87(0.71–1.08)	*WNT7A*	3	13883072	0.284431004
rs12632968	2.51E-01	0.92(0.80–1.06)	*WNT7A*	3	13887198	0.301906315
rs4685048	4.71E-01	0.95(0.82–1.09)	*WNT7A*	3	13897736	0.360699651
rs1077524	6.70E-01	0.96(0.79–1.17)	*WNT7A*	3	13905134	0.422621937
rs6768050	8.13E-02	1.29(0.97–1.72)	*WNT7A*	3	13905491	0.239365623
rs217259	4.45E-01	1.14(0.82–1.58)	*WNT8A*	5	137440862	0.359705483
rs10440755	2.94E-01	0.88(0.70–1.11)	*WNT8A*	5	137442365	0.315417003
rs4835761	6.94E-01	1.05(0.82–1.34)	*WNT8A*	5	137445768	0.424838822
rs10036244	5.82E-01	0.94(0.77–1.16)	*WNT8A*	5	137447624	0.394635311
rs2040862	3.75E-01	1.10(0.89–1.35)	*WNT8A*	5	137447888	0.333860360
rs4919464	1.49E-01	0.89(0.75–1.04)	*WNT8B*	10	102211185	0.270394908
rs3793771	1.15E-01	0.88(0.74–1.03)	*WNT8B*	10	102212947	0.247366510
rs12762598	8.24E-01	1.02(0.87–1.20)	*WNT8B*	10	102217746	0.450428119
rs7552818	9.03E-01	1.01(0.82–1.25)	*WNT9A*	1	226167514	0.475872051
rs10916243	2.01E-01	1.10(0.95–1.28)	*WNT9A*	1	226167742	0.284431004
rs1009658	1.10E-01	0.84(0.68–1.04)	*WNT9A*	1	226170404	0.247221759
rs12748472	2.78E-02	1.18(1.02–1.38)	*WNT9A*	1	226170998	0.175417920
rs8192633	9.90E-01	1.00(0.62–1.59)	*WNT9A*	1	226176094	0.495714725
rs10127943	1.27E-01	1.17(0.96–1.43)	*WNT9A*	1	226176687	0.259279357
rs12046421	7.15E-01	0.96(0.79–1.18)	*WNT9A*	1	226177357	0.426046532

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs680997	1.48E-01	0.79(0.57–1.09)	*WNT9A*	1	226193850	0.270394908
rs680148	4.05E-02	1.25(1.01–1.54)	*WNT9A*	1	226194014	0.186192568
rs681239	5.30E-01	0.89(0.61–1.29)	*WNT9A*	1	226206295	0.379736909
rs6665129	2.53E-01	0.87(0.69–1.10)	*WNT9A*	1	226207083	0.301906315
rs2083798	9.16E-01	0.99(0.81–1.21)	*WNT9B*	17	42276896	0.475872051
rs2083797	4.03E-01	1.14(0.84–1.54)	*WNT9B*	17	42276928	0.349470404
rs4968275	9.42E-01	1.01(0.81–1.25)	*WNT9B*	17	42279659	0.478174891
rs7212246	9.42E-01	1.01(0.81–1.25)	*WNT9B*	17	42280490	0.478174891
rs12150651	7.07E-01	0.96(0.77–1.19)	*WNT9B*	17	42288568	0.426046532
rs2165846	2.48E-01	1.15(0.91–1.47)	*WNT9B*	17	42296365	0.301906315
rs12952746	4.35E-01	1.10(0.87–1.39)	*WNT9B*	17	42298412	0.359395383
rs6504591	3.06E-01	0.93(0.81–1.07)	*WNT9B*	17	42299827	0.315893774
rs4968281	4.42E-01	1.16(0.79–1.71)	*WNT9B*	17	42305121	0.359705483
rs1530364	4.45E-02	0.67(0.45–0.99)	*WNT9B*	17	42306776	0.186200636
rs754474	2.52E-01	1.24(0.86–1.78)	*WNT9B*	17	42308855	0.301906315
rs17603901	8.32E-01	1.03(0.79–1.34)	*WNT9B*	17	42313021	0.452520518
rs10177996	7.78E-01	1.03(0.83–1.28)	*WNT10A*	2	219454805	0.443413702
rs4574113	7.12E-01	1.04(0.84–1.30)	*WNT10A*	2	219470906	0.426046532
rs833839	4.98E-01	1.08(0.86–1.35)	*WNT10B*	12	47653157	0.377760052
rs7311091	4.72E-01	1.11(0.84–1.46)	*WNT10B*	12	47669474	0.360699651
rs664499	3.06E-01	0.86(0.65–1.15)	*WNT11*	11	75565334	0.315893774
rs626207	2.39E-01	1.13(0.92–1.38)	*WNT11*	11	75565460	0.301281403
rs4944091	8.02E-01	0.97(0.78–1.21)	*WNT11*	11	75566622	0.445017693
rs647159	2.64E-01	1.18(0.88–1.57)	*WNT11*	11	75570389	0.307231178
rs11236644	3.62E-01	0.94(0.81–1.08)	*WNT11*	11	75572655	0.328827360
rs581794	6.45E-01	0.95(0.75–1.19)	*WNT11*	11	75572939	0.415574805
rs12277860	4.39E-01	0.91(0.73–1.15)	*WNT11*	11	75574295	0.359395383
rs17749202	4.67E-02	1.39(1.00–1.92)	*WNT11*	11	75575022	0.186667333
rs7936750	2.15E-01	0.81(0.57–1.13)	*WNT11*	11	75577055	0.284945038
rs10899175	1.02E-01	1.20(0.96–1.50)	*WNT11*	11	75577129	0.247221759
rs882151	7.14E-01	0.96(0.78–1.18)	*WNT11*	11	75581785	0.426046532

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs3781730	5.45E-01	1.07(0.86–1.33)	*WNT11*	11	75585731	0.379736909
rs689095	1.63E-01	0.87(0.71–1.06)	*WNT11*	11	75591735	0.273188390
rs663907	2.31E-01	0.84(0.63–1.12)	*WNT11*	11	75600717	0.296677764
rs689419	7.88E-01	0.97(0.79–1.19)	*WNT11*	11	75604615	0.443413702
rs12416814	3.74E-01	1.23(0.78–1.92)	*WNT11*	11	75605089	0.333860360
rs3757552	5.68E-01	0.93(0.72–1.20)	*WNT16*	7	120751201	0.388647584
rs3801387	1.52E-01	1.15(0.95–1.40)	*WNT16*	7	120762001	0.270394908
rs3801385	7.16E-01	1.05(0.80–1.37)	*WNT16*	7	120764779	0.426046532
rs2707461	2.06E-01	0.77(0.51–1.16)	*WNT16*	7	120774586	0.284431004
rs2536182	1.30E-01	0.90(0.78–1.03)	*WNT16*	7	120778073	0.263051430

Table 3

Wnt pathway SNPs associated with survival in multivariate analysis in cohort 1 (P<0.05)*

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs11868547	0.0006	0.77 (0.66–0.89)	*AXIN2*	17	60954065	0.095030240
rs12819505	0.0014	1.58 (1.19–2.09)	*WNT5B*	12	1626926	0.095030240
rs4541111	0.0015	0.79 (0.68–0.91)	*AXIN2*	17	60965000	0.095030240
rs4413407	0.0017	1.28 (1.10–1.50)	*CXXC4*	4	105612810	0.095030240
rs10878232	0.0022	1.36 (1.12–1.66)	*WIF1*	12	63808914	0.095602299
rs7301320	0.0027	1.35 (1.11–1.65)	*WIF1*	12	63800533	0.100176561
rs7218567	0.0043	1.68 (1.18–2.40)	*WNT3*	17	42225421	0.128006452
rs390258	0.0046	1.64 (1.16–2.30)	*TLE2*	19	2947339	0.128006452
rs7591	0.0061	1.23 (1.06–1.44)	*AXIN2*	17	60955544	0.135500153
rs1155722	0.0062	1.32 (1.08–1.61)	*WIF1*	12	63809424	0.135500153
rs10917155	0.0073	1.54 (1.12–2.11)	*WNT4*	1	22324553	0.135500153
rs9864832	0.0090	1.52 (1.11–2.08)	*WNT7A*	3	13827744	0.135500153
rs4988300	0.0098	0.74 (0.58–0.93)	*LRP5*	11	67845407	0.135500153
rs1003939	0.0099	0.56 (0.36–0.87)	*WNT5B*	12	1626939	0.135500153
rs4766403	0.010	1.21 (1.05–1.39)	*WNT5B*	12	1630739	0.135500153
rs2508836	0.010	0.81 (0.68–0.95)	*LRP5*	11	67847841	0.135500153
rs1012672	0.011	1.47 (1.09–1.97)	*LRP6*	12	12176182	0.135500153
rs1946620	0.011	1.32 (1.07–1.63)	*WNT7A*	3	13833800	0.135500153
rs11658976	0.012	1.45 (1.08–1.94)	*WNT3*	17	42221965	0.142078914
rs12469777	0.014	0.85 (0.74–0.97)	*FRZB*	2	183440609	0.144627899
rs3121310	0.015	1.39 (1.07–1.82)	*WNT3A*	1	226291447	0.144627899
rs11655966	0.015	1.21 (1.04–1.41)	*AXIN2*	17	60960112	0.144627899
rs12942924	0.016	1.18 (1.03–1.36)	*AXIN2*	17	60996861	0.144627899
rs11079571	0.016	1.29 (1.05–1.59)	*AXIN2*	17	60979143	0.144627899
rs11054760	0.017	1.53 (1.08–2.17)	*LRP6*	12	12320749	0.144627899
rs11919795	0.018	0.67 (0.48–0.93)	*DVL3*	3	185373562	0.144627899
rs4654783	0.018	1.58 (1.08–2.31)	*WNT4*	1	22312107	0.144627899
rs629537	0.020	1.29 (1.04–1.60)	*WNT5A*	3	55466053	0.146727575

SNP	*P* value	Hazard Ratio (95% CI)	Gene	Chromo-some	Position	Q value
rs314756	0.020	0.69 (0.51–0.94)	*LRP5*	11	67868248	0.146727575
rs713065	0.020	0.79 (0.64–0.96)	*FZD4*	11	86335168	0.146727575
rs7515106	0.021	1.61 (1.07–2.42)	*WNT4*	1	22345997	0.149155672
rs423232	0.022	0.74 (0.57–0.96)	*TLE2*	19	2947483	0.152312051
rs597437	0.027	1.43 (1.04–1.95)	*WNT5A*	3	55471449	0.17541792
rs708110	0.027	1.26 (1.03–1.55)	*WNT3A*	1	226257428	0.17541792
rs12748472	0.028	1.18 (1.02–1.38)	*WNT9A*	1	226170998	0.17541792
rs6946781	0.029	0.63 (0.42–0.95)	*WNT2*	7	116694979	0.176207503
rs9888749	0.031	0.76 (0.60–0.98)	*AXIN1*	16	348373	0.185653186
rs64388	0.033	1.25 (1.02–1.52)	*LRP5*	11	67830957	0.186192568
rs7224837	0.034	1.28 (1.02–1.62)	*AXIN2*	17	60958585	0.186192568
rs2285545	0.034	0.87 (0.76–0.99)	*WNT2*	7	116735407	0.186192568
rs3809857	0.035	0.80 (0.65–0.98)	*WNT3*	17	42203482	0.186192568
rs503022	0.036	1.26 (1.01–1.56)	*WNT5A*	3	55466476	0.186192568
rs1548581	0.037	1.29 (1.02–1.64)	*AXIN2*	17	60995973	0.186192568
rs7359414	0.037	0.78 (0.61–0.99)	*AXIN1*	16	302639	0.186192568
rs312786	0.038	0.66 (0.45–0.98)	*LRP5*	11	67876553	0.186192568
rs214246	0.040	0.77 (0.61–0.99)	*AXIN1*	16	289294	0.186192568
rs4698921	0.040	1.16 (1.01–1.34)	*CXXC4*	4	105633671	0.186192568
rs680148	0.041	1.25 (1.01–1.54)	*WNT9A*	1	226194014	0.186192568
rs676318	0.042	0.75 (0.57–0.99)	*LRP5*	11	67973996	0.186192568
rs10431302	0.042	0.80 (0.65–0.99)	*LRP6*	12	12320918	0.186192568
rs6947329	0.044	1.29 (1.01–1.65)	*WNT2*	7	116730371	0.186200636
rs1530364	0.045	0.67 (0.45–0.99)	*WNT9B*	17	42306776	0.186200636
rs3781586	0.045	1.26 (1.01–1.57)	*LRP5*	11	67955969	0.186200636
rs17749202	0.047	1.39 (1.00–1.92)	*WNT11*	11	75575022	0.186667333
rs4074947	0.047	1.23 (1.00–1.51)	*AXIN2*	17	60957682	0.186667333
rs557077	0.047	1.40 (1.00–1.96)	*WNT5A*	3	55506307	0.186667333
rs7596898	0.049	0.80 (0.64–1.00)	*WNT6*	2	219427976	0.188401227

*Adjusted for age, race, sex, pack-year smoking, clinical stage, and performance status

Table 4

Wnt pathway SNPs with q<0.10 in cohort 1

SNP	Gene	Location	Allelic change	Minor Allele Frequency	Model	Hazard Ratio* (95% CI)	*P* value	q value
rs11868547	*AXIN2*	3′ flanking	G>C	0.421	Additive	0.77 (0.66–0.89)	6.10E-04	0.09503
rs12819505	*WNT5B*	3′ flanking	A>G	0.07	Dominant	1.58 (1.19–2.09)	1.37E-03	0.09503
rs4541111	*AXIN2*	Intron	C>A	0.456	Additive	0.79 (0.68–0.91)	1.53E-03	0.09503
rs4413407	*CXXC4*	3′ UTR	G>A	0.299	Additive	1.28 (1.10–1.50)	1.72E-03	0.09503
rs10878232	*WIF1*	5′ flanking	A>C	0.242	Dominant	1.36 (1.12–1.66)	2.16E-03	0.09560

*Adjusted for age, race, sex, pack-year smoking, clinical stage, and performance status

Table 5

Impact of number of unfavorable genotypes on survival in cohort 1

No. unfavorable genotypes	No. (%) alive	No. (%) dead	Hazard ratio (95% CI) (1 SNP = reference)	*P* value	Median Survival Time (mo.)	Log-rank p value
1	19 (46.3)	22 (53.7)			19.67	
2	83 (26.9)	226 (73.1)	1.53 (0.97–2.41)	6.8×10^{-2}	15.56	
3–5	40 (16.1)	208 (83.9)	2.61 (1.65–4.12)	4.3×10^{-5}	10.72	1.9×10^{-7}
trend				3.8×10^{-9}		

Table 6

Minor Allele Frequency by race for SNPs significantly associated with patient survival

SNP	All	White	Black	Other
rs11868547	0.44	0.45	0.20	0.56
rs12819505	0.07	0.08	0.01	0.04
rs4541111	0.47	0.49	0.20	0.54
rs4413407	0.30	0.32	0.05	0.33
rs10878232	0.28	0.28	0.33	0.27

Table 7

Hazard ratios and median survival times for different recursive partitioning nodes in cohort 1

STREE Nodes	Dead N (%)	Alive N (%)	Adjusted Hazard Ratio (95% CI)	*P* value	Median Survival (months)	Log Rank Test
1	34 (69.39)	15 (30.61)	1.00 (reference)	18.82		
2	192 (69.82)	83 (30.18)	1.09 (0.73–1.62)	0.067	17.27	
3	163 (82.32)	35 (17.68)	1.93 (1.30–2.89)	0.001	10.07	
4	39 (86.67)	6 (13.33)	1.79 (1.08–2.96)	0.024	13.52	
5	28 (90.32)	3(9.68)	1.98 (1.17–3.37)	0.011	11.94	2.68×10^{-6}
STREE Group						
Nodes 1~2	226 (69.75)	98 (30.25)	1.00 (reference)	17.27		
Nodes 3~5	230 (83.94)	44 (16.06)	1.78 (1.46–2.17)	1×10^{-8}	11.09	4.66×10^{-8}

Table 8

Characteristics of patients assessed in cohorts 2, 3 and 4

Variable	Cohort 2 No. Patients (%)	Cohort 3 No. Patients (%)	Cohort 4 No. Patients (%)
Median survival, months	21.09	118.3	86.05
Median age (range), years	64.02*	63 (29–83)	67 (34–86)
Pack year, median (range)**	40.48*	40 (0.1–159)	45 (0.2–256)
Survival status at last follow-up			
Alive	49	88	210
Dead	191	39	130
Sex			
Male	142	68	166
Female	98	59	174
Clinical stage			
Stage IA		23	181
Stage IB		55	113
Stage IIA		14	10
Stage IIB		35	36
Stage III	106		
Stage IV	134		
Smoking status			
Never	14	16	48
Former	150	67	168
Current & Recently Quit (<1 year)	76	44	124
ECOG Performance status			
0	64		
1	120		
2–4	13		
Tumor Type			
Adenocarcinoma		74	213
Squamous		34	87
NSCLC not otherwise specified		7	11
Other		12	29
Race			
White		109	305
Black		10	25
Others		8	10
Treatment			
Chemotherapy (platinum regimen) only	100		
Platinum regimen + radiotherapy	140		
Surgery + adjuvant platinum regimen		127	
Surgery alone			340

* mean instead of median; range not available

** among ever smokers

Table 9

Assessment of SNPs in secondary analyses (cohorts 2–4)

	Mayo Clinic (Cohort 2)†		MDACC Adjuvant Chemo (Cohort 3)‡		MDACC Surgery Alone (Cohort 4)‡		Mayo + Adjuvant (Cohorts 2 + 3)			Mayo + Adjuvant + Surgery (Cohorts 2 + 3 + 4)		
SNP	**HR(95% CI)**	***P***	**HR(95% CI)**	***P***	**HR(95% CI)**	***P***	**HR(95% CI)**	***P***	**P-H***	**HR(95% CI)**	***P***	**P-H***
rs11868547	0.94(0.75–1.18)	0.58	0.89(0.55–1.45)	0.65	0.96(0.74–1.24)	0.75	0.93(0.76–1.14)	0.48	0.85	0.94(0.80–1.11)	0.46	0.96
rs12819505	1.30(0.85–1.99)	0.23	0.40(0.14–1.18)	0.10	1.12(0.67–1.86)	0.68	0.80(0.26–2.50)	0.70	0.04	1.11(0.81–1.52)	0.51	0.13
rs4413407	0.88(0.69–1.13)	0.32	1.10(0.61–2.01)	0.75	0.99(0.76–1.30)	0.96	0.91(0.72–1.15)	0.43	0.50	0.94(0.79–1.13)	0.52	0.72
rs10878232	1.00(0.77–1.28)	0.98	1.80(0.91–3.56)	0.09	1.05(0.79–1.41)	0.73	1.07(0.85–1.36)	0.58	0.11	1.06(0.88–1.28)	0.52	0.28

* P-H: *P* value for heterogeneity

† Advanced stage patients

‡ Early stage patients