SUPPLEMENTARY APPENDIX

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RNA Extraction

FFPE tissue blocks were cut into four 20μm sections and treated with 100% xylene (Fisher Scientific, Pittsburgh, PA) to deparaffinize. Samples were washed twice with 100% ethanol (Absolute Ethanol Molecular Biology Grade 200 proof, Fisher Scientific, Pittsburgh, PA) and dried via vacuum centrifugation at 40°C. Tissue was then incubated in Digestion Buffer and Protease (Ambion® RecoverAll, Life Technologies, Carlsbad, CA) at 50°C for 3 hours, followed by a 15-minute incubation at 80°C. RNA was separated using an Isolation Additive/Ethanol mixture (Ambion® RecoverAll, Life Technologies, Carlsbad, CA), and filtered by centrifugation at 10,000rpm. The sample was rinsed with Wash 1 and Wash 2 (Ambion® RecoverAll, Life Technologies, Carlsbad, CA), before and after incubation with DNase for 30 minutes at RT. RNA was eluted with 60μl of Elution Solution (Ambion® RecoverAll, Life Technologies, Carlsbad, CA) at RT.

Dermatopathology

Primary and recurrent melanomas were selected from the Tamtron PowerPath database at the Mount Sinai Medical Center (New York, NY), the Cerner CoPathPlus database at Geisinger Heath System (Danville, PA), and the Oracle Clinical RDC 4i database at NYU Medical Center (New York, NY). Selected slides and paraffin blocks were reviewed by two of the study authors (RGP and SS). Each sample was evaluated for histogenetic type, extent and type of inflammatory infiltrate, thickness, and ulceration.

High magnification images of H&E stained tumor specimens were evaluated for TILs and mitotic rate by a dermatopathologist. Tumor infiltrating lymphocytes (TILs) were defined as ones that percolated between and around tumor cells. (Rao *et al.*, 2010). Brisk refers to lymphocytes present throughout the substance or infiltrating the entire base of the vertical growth phase; non-brisk refers to lymphocytes in one focus or more of the vertical growth phase, either dispersed throughout or situated focally in the periphery; and absent if there were no lymphocytes or if they were present but did not infiltrate the melanoma.(Mandala *et al*, 2009) TILS were scored as 0 for absent, 1 for nonbrisk and 2 for brisk. Mitotic rate was defined as the number of mitosis per mm^2 and scored 1-7 based on number of mitosis per mm^2 (<1, <2, <5, <10, <15, <20 or >20, adapted from the AJCC update published by Balch and colleagues.(Balch *et al.*, 2011)). Scoring for TILS and mitotic rate was used for subsequent cox and multivariable analysis.

NanoString

Gene Expression Analysis

446 candidate genes were selected based on a PubMed literature search using the reference terms: melanoma, biomarker, immune, and gene signature (See Table S2). The nCounter® platform (NanoString Technologies, Seattle, WA), was used to quantify relative gene expression in a multiplex reaction. A custom CodeSet, designated MtSinai0511, was synthesized by NanoString for the 446 selected genes as well as 17 housekeeping genes and 14 controls in a 477-plex reaction (listed in the supplemental reference file). Hybridizations were carried out according to the supplier protocols.[3] In a total reaction volume of 30µl, 100ng of each RNA sample in 5µl H_2O was mixed with 10µl nCounter Reporter probes, 10µl

hybridization buffer (1x hybridization buffer = 5x SSPE, 0.1% Tween-20), and 5µl of nCounter Capture probes. Hybridizations were incubated at 65°C for approximately 16-20 hours. Following hybridization, the samples were processed in a PrepStation and counted in a DigitalAnalyzer (NanoString Technologies) according to standard protocol recommended by NanoString Technologies.

Normalization of Data

Calculated from the sum counts of reporters of 6 positive control RNA spikes, sample-specific normalization factors were used to normalize raw mRNA counts in order to account for slight differences in assay efficiency such as hybridization, purification, and binding. Concentrations of the control RNA spikes range from 0.125-128fM. Normalization for sample RNA quantity and quality differences were applied to the spike-normalized values using sample-specific normalization factors calculated from the geometric mean of the counts from reporters targeting the housekeeping genes. Housekeeping genes were discarded if spike-normalized counts showed significant ($p<0.05$) difference between progressors and non-progressors. The resulting normalized counts were used in downstream analyses. For the validation set, the 53 genes were measured in two batches, with some common samples between them (technical replicates). In order to account for batch effect, the ratio of probe counts between each of the replicate samples tested in both codesets. Standard ratios were then calculated for each probe and then used to adjust the two data sets so they could be analyzed together.

Immunohistochemistry

Five micron sections of the same paraffin-embedded tissue samples analyzed by NanoString were prepared for immunophenotypic analysis. Immunohistochemistry (IHC) was performed using primary, pre-diluted anti-CD2 (MRQ-11, mouse anti-human, Ventana Medical Systems, Tucson, AZ). Sections were deparaffinized, stained according to standard protocol using a Ventana BenchMark XT immunostainer and manually counterstained.(Ventana, 2010) The immunohistochemical slides were evaluated and interpreted by two of the study authors (SGB & MMM) in a blinded manner without knowledge of corresponding clinical data. For each sample, cells with circumferential membrane staining were counted and averaged in 8 random HPFs using an ocular micrometer with a $1mm^2$ grid (Nikon Eclipse E400®).

Statistical Analysis

Computation Method for Co-expression Network Analysis

From the NIH GEO database, 46 samples of gene expression data identified based on origin in primary melanoma tissue and expression platform were colleted. Let N denote the total number of genes in the whole-genome. For an overlap of m genes between a module of size M and a panel of genes of size n, an enrichment fold was computed using the ratio of the proportion of panel genes contained in the module (m/n) to the proportion of whole genome genes contained in the module (M/N). That is, enrichment fold = (m/n)/(M/N). The p-value of this enrichment fold is calculated by using Fisher exact test.

Cross-validation

Please see Figure S1 for schema. We simulated 900 iterations of a 11-fold cross-validation on the training dataset with random sample reordering in each iteration to strengthen the robustness of our final classifier model. Four samples were removed at random. These sample sets were then used as training data to fit a statistical model. 10,000 model training tasks were performed. The trained model and gene predictors selected were recorded in each task yielding 10,000 models and 10,000 lists of gene predictors based on randomly sub-sampled training samples. For each model, we performed a classification for the entire training (40 samples) and test datasets (48 samples). To derive a robust list of gene hits by these models, the 10,000 gene lists were pooled and the statistical count of each gene (out of 446 genes) was selected by these models using the training cohort only. A higher count value for a given gene indicates that it is frequently selected as a predictor during the cross-validation process. Finally, all genes selected at least once in the 10,000 cross-validation were put into a final model training task to yield an optimal, compact predictor gene list of 53 genes.

Ensemble classification/regression method

We employed a two-step sequential ensemble classification scheme that sequentially concatenated two widely applied classifiers: random forest and elastic net. Random forest itself is an ensemble classifier consisting of many decision trees that generates the mode of individual classes yielded by independent trees. A powerful variable selector and classification/regression method, elastic net integrates a linear regression model with Lasso and Ridge regularization. Elastic net is particularly useful when there are many more

predictors than samples, serving to further exclude genes that are only correlated with, but not most predictive, of recurrence. We applied this two-step ensemble classification scheme to the cross-validated training data for the outer loop of the 900, 11-fold training cross-validation data points.

Random Forest

With 446 genes as an initial set of features and 40 samples from the cross-validation used as training data, a random forest model was fit. Initially, random forest was run without feature selection to determine the importance of all 446 genes based on various metrics in the RandomForest R package.(A., 2002) Next, an independent run was started that incorporated feature selection into random forest by sequentially reducing a certain number of predictors, ranked by variable importance, by employing a nested cross-validation procedure. In our simulation, a leave-one-out strategy was used. In each internal cross-validation, we removed (step=30%) the least important genes/features, ranked by variable importance, from the last cross-validation iteration. Next, we drew (Ntree=50k) bootstrap samples from the original data (40 samples). For each of the bootstrap samples, we generated an untrimmed classification/regression tree with randomly selected (mtry=22) genes from the pool of genes leftover following removal. Following cross-validation, we selected the number of genes that resulted in the lowest error rate among all the cross-validation runs. This number represents the number of genes (N_{RF}) selected by random forest after cross-validation. Next, we selected the top N_{RF} genes based on the averaged gene rank from the initial run without feature selection, yielding our final gene selections by random forest. The selected genes G_{RF} were used as input for an elastic net model in order to identify the constituents of a gene signature predictive of melanoma recurrence.

Elastic Net

A powerful variable selector and classification/regression method, elastic net integrates a linear regression model with Lasso and Ridge regularization (Zou, 2005). Elastic net is particularly useful when there are many more predictors than samples, serving to further exclude genes that are only correlated with, but not most predictive of recurrence. In each round of 11-fold cross-validation on the training data, there were 40 training samples. The number of genes selected by random forest varied from 50 to 446 depending on both the leave-one-out training data and randomized feature selection used during decision tree growth. Elastic net extends the basic form of linear/logistic regression via L1 and L2-regularization. λ controls the model complexity with higher values resulting in a less complex model (less number of genes). α controls the balance between two types of model complexity penalties, including the ridge-regression penalty (α =0) and the lasso penalty (α=1). The Ridge penalty is particularly useful when there are more genes and fewer samples. Ridge regression is known to shrink the coefficients of correlated predictors towards each other. In contrast, lasso tends to pick one out of an entire set and ignore the rest. In our study, we set α=0.2 and used an internal leave-one-out cross-validation to select an optimal value of λ(Friedman *et al.*, 2010). Our input training data was a subset of the original training data based on the gene lists G_{RF} determined by random forest. The output gene lists by elastic net with non-zero coefficients is our final gene list G_{EN} for the cross-validation run.

Network Analysis

Constructing the 53-gene and 446-gene induced networks in VisAnt

To identify a biologically relevant neighborhood of genes surrounding the 53-gene panel, a physical gene interaction network was constructed using the knowledgebase network tool VisAnt 4.0. (Hu *et al.*, 2013; Hu *et al.*, 2004) A reference network was similarly constructed using the original 446-gene panel.

Filters were used to constrain the interactions to the following tissues/cells: epidermis, immune cells, immune cell lines, or melanoma cell lines. Furthermore, filters were used to constrain interactions to those that were observed in cancer, immunological diseases, or without any disease association. Each VisAnt network (53-gene panel network and 446-gene panel network) was obtained in the following two steps. After uploading a gene panel into VisAnt, a search was made for all first neighbor interactions within the gene panel or between a panel gene and a new gene. All interactions were obtained from the Predictome. (Mellor *et al.*, 2002) database that is now housed within VisAnt. Any interaction that was based on prediction/inference (Dataset S5) was removed. To reduce the possible number of false positive interactions, interactions that were supported by one reference/evidence were also removed. Second, with the new list of genes induced by the gene panel, an internal query for interactions among new first neighbor genes was also made. Therefore, the resulting induced networks represented all possible interactions among panel genes and their first neighbors. The gene lists from each of these networks were then used to construct Bayesian networks using the melanoma gene expression dataset (GSE15605).

Constructing the 53-gene and 446-gene Bayesian Networks

As the interactions in VisAnt were only weakly related to Melanoma, the *interactions* modeling the specific immune response to melanoma were identified via a Bayesian network (BN) on the VisAnt node list using the same melanoma gene expression dataset as the co-expression analysis (GSE15605). If a panel gene or a gene identified in VisAnt was not in the gene expression data set, it was dropped from the Bayesian network. A reference Bayesian network was similarly constructed for the 446-gene panel and its neighborhood set. For the Bayesian network inference, a Markov Chain Monte Carlo Markov Chain (MCMC) method was used for sampling from the posterior distribution of network structures. As an input data for the Bayesian network inference, each variable (gene expression) is discretized into three groups by equal quantiles. On a high-performance computing facility, the gene set of g53 was run for MCMC of 30 chains from an empty network for 48 hours and the gene set of g463 was run for MCMC of 97 chains from an empty network for 120 hours. During 48 hours, the MCMC chains for g53 gene list were run for 7×10^7 iterations on average and every 5000 iteration was taken as posterior samples of networks after removing the first 5×10^7 iterations for burn-ins. The posterior samples from each chain were aggregated into one set of posterior samples. For g463 gene list, during 120 hours, the MCMC chains were run for 7.5×10^6 iterations on average and every 5000 iteration was taken as posterior samples of networks after removing the first 5×10^7 iterations for burn-ins. The posterior samples of 97 chains were aggregated into one set of posterior samples. A Bayesian model selection was conducted on the posterior samples of Bayesian network structures. The posterior probability of the presence of each directed edge is calculated and the edges of top 1% posterior probability were selected to be included in the final network structure. These two network structures (g53 and g463) were drawn with

Cytoscape. The graphs were laid out by spring-embedded algorithm. Edge transparencies were in proportion to the posterior probability and node sizes were in proportion to the out-degree of the node.

LEGEND FOR SUPPLEMENTAL FIGURES

Figure S1. A flowchart illustrates the cross validation process on the training set to strengthen the robustness of our model. Dashed box shows the ensemble classification algorithm for gene selection. Data bootstrap is performed by resampling the data samples with replacement (n=10,000). The final gene panel is a combination of gene lists.

Figure S2. Mean ROC curves with cross-validation and distributions of AUC values of the 42 genes in the 53-gene panel for the training set (**a**) and the test set (**b**) are shown. Training: mean AUC=0.910, $p<0.001$. Test: mean AUC=0.744, $p<0.001$. In (**c**), distribution of AUC values using a leave-8-out cross-validation with bootstrapping test is shown.

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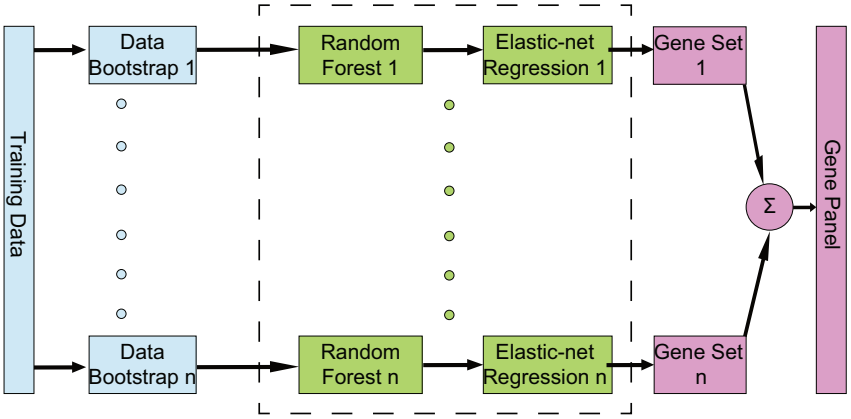

Figure S1 A flowchart illustrating the cross validation process for selection of the 53 gene panel.

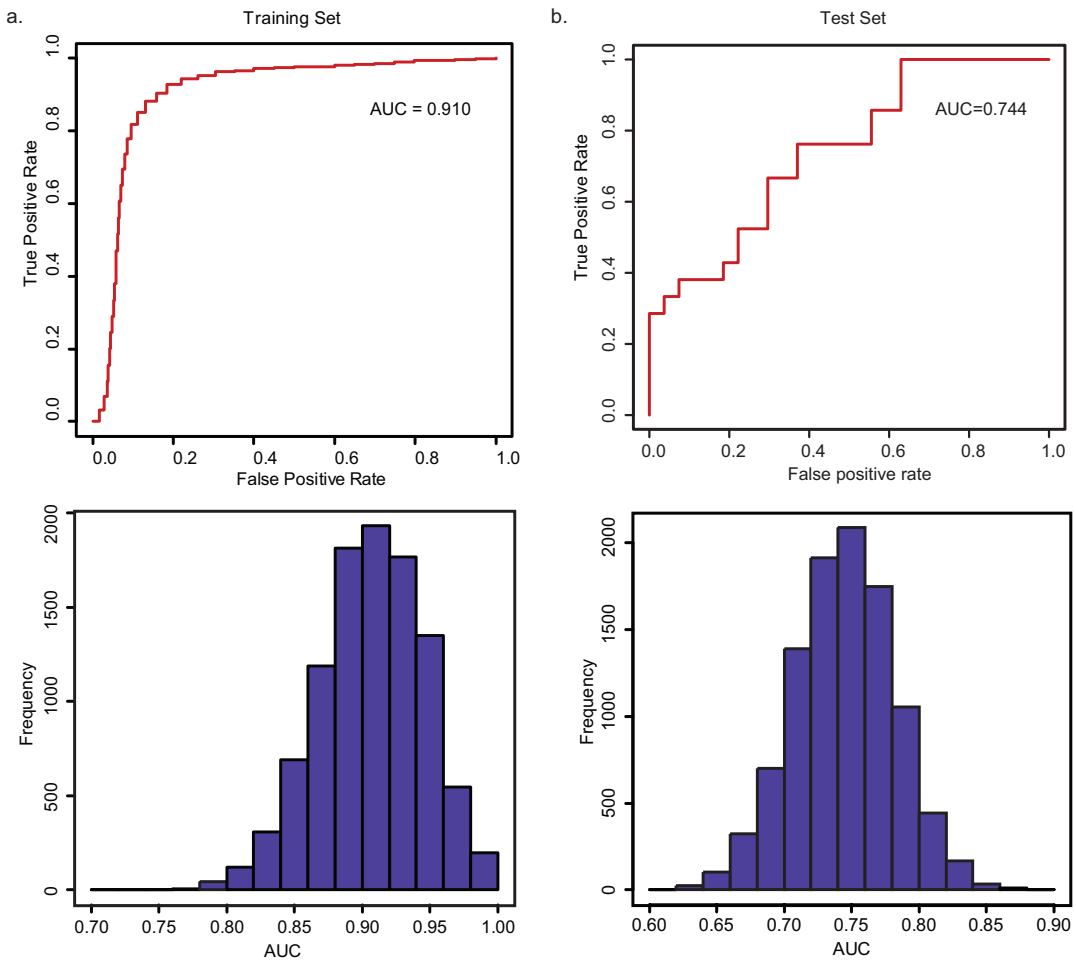

Figure S2 A mean ROC curve of the cross validation of the 42 overlap genes between the 53-gene panel and the 758-gene GEO module and its AUC distribution

Table S1. Official names of all 446 genes selected for NanoString analysis in Training Set.

A2M	CCL24	CD207	CMKLR1	ENG	HLAE	IGHG2	IL1RAPL2	IRF7
ALCAM	CCL25	CD209	COLEC12	F13A1	HLAF	IGHG3	IL1RL1	IRF8
ALOX5	CCL26	CD24	CREB1	FAS	HLAG	IGHG4	IL1RL2	IRF9
AMICA1	CCL27	CD27	CRP	FCAMR	HMGB1	IGHM	IL1RN	ISG15
ANGPTL4	CCL28	CD36	CSF1	FCER1A	ICAM1	IGKC	IL2	ISG20
ANXA1	CCL3	CD37	CSF1R	FCER2	ICOS	IGLL1	IL21	ITGA1
ANXA11	CCL3L1	CD38	CSF2	FCGR1A	ICOSLG	IGSF4	IL22RA1	ITGA2
B2M	CCL4	CD3E	CSF2RA	FCGR2A	IFI27	IGSF9	IL23A	ITGA4
BCL10	CCL5	CD4	CSF2RB	FCGR3A	IFI35	IKBKG	IL23R	ITGA5
BCL2A1	CCL7	CD40	CSF3	FCGR3B	IFI44	IKZF1	IL24	ITGA6
BCL3	CCL8	CD40LG	CSF3R	FCGRT	IFI6	IKZF5	IL25	ITGA9
BCL6	CCR1	CD47	CTLA4	FLT3	IFIH1	IL10	IL27	ITGAL
BDCA3	CCR10	CD48	CTSS	FN1	IFIT1	IL10RA	IL28A	ITGAM
BIK	CCR2	CD5	CX3CL1	Foxp3	IFIT2	IL11	IL28RA	ITGB1
BIRC5	CCR3	CD53	CX3CR1	FPR1	IFITM1	IL12A	IL2R	ITGB2
CXCR5	CCR4	CD55	CXCL1	FYN	IFITM2	IL12B	IL33	ITGB3
BTK	CCR5	CD58	CXCL10	GATA3	IFNA1	IL12RB1	IL34	ITGB4
C1QA	CCR6	CD63	CXCL11	GBP1	IFNA14	IL12RB2	IL37	ITK
C3	CCR7	CD68	CXCL12	GBP2	IFNA2	IL13	IL3RA	JAK1
C3AR1	CCR8	CD70	CXCL13	GHR	IFNA21	IL13RA1	IL4	KCNIP2
CASP1	CCR9	CD74	CXCL14	GPR44	IFNA4	IL13RA2	IL4R	KLF6
CCBP2	CCRL1	CD79A	CXCL16	GZMK	IFNA5	IL15	IL5	KLRD1
CCL1	CCRL2	CD79B	CXCL2	HIF1A	IFNA6	IL15RA	IL6	KLRK1
CCL11	CD101	CD80	CXCL3	HLAA	IFNA8	IL17D	IL6R	LAMP1
CCL13	CD14	CD83	CXCL5	HLAB	IFNAR1	IL17F	IL7	LAMP2
CCL14	CD163	CD86	CXCL6	HLAC	IFNAR2	IL17RA	IL8	LAMP3
CCL15	CD164	CD8A	CXCL7	HLA-DMA	IFNE1	IL17RB	CXCR2	LAT2
CCL16	CD180	CDC42	CXCL9	HLA-DOB	IFNG	IL18	INHBA	LAX1
CCL17	CD19	CEACAM1	CXCR3	HLA-DPA1	IFNGR1	IL18RAP	IRAK1	LCK
CCL18	CD1A	CEBPA	CXCR4	HLA-DPB1	IFNGR2	IL19	IRAK2	LEPR
CCL19	CD1B	CHST4	CXCR6	HLA DQA1	IFNK	IL1A	IRF1	LGMN
CCL2	CD1C	CISH3	CYBB	HLA-DQA2	IFRG28	IL1B	IRF2	LRP1
CCL20	CD1D	CKLF	CYFIP2	HLA-DQB1	IGCL2	IL1F10	IRF3	LSP1
CCL21	CD2	CLEC2A	DUSP1	HLA-DRB1	IGF1R	IL1R1	IRF4	LTA
CCL22	CD20	CLEC4C	DUSP5	HLA-DRB3	IGHA1	IL1R2	IRF5	LTB
CCL23	CD200	CLECL1	EHD1	HLA-DRB4	IGHG1	IL1RAP	IRF6	LTBR

LY9	MMP9	NLRC5	REL	STAT1	TIRAP	TNFAIP3	TNFRSF25	TRAF2
LY96	MRC1	NOS2A	RELA	STAT2	TLR1	TNFAIP6	TNFRSF4	TRAF3
LYVE1	MSR1	OAS1	RELB	STAT3	TLR10	TNFRSF10B	TNFRSF8	TRAF6
MAL2	MST1R	OPTN	RIPK2	SYK	TLR2	TNFRSF11A	TNFRSF9	TRAT1
MALT1	MX1	OSM	Runx1	TAP1	TLR3	TNFRSF11B	TNFSF10	TSLP
MAP3K7	MYADM	PDCD1	S100A12	TAP2	TLR4	TNFRSF12A	TNFSF11	TXK
MAPK1	MYD88	PDL1	SAA1	TARP	TLR5	TNFRSF13B	TNFSF12	VCAM1
MCAM	NFAM1	PILRA	SERPINB2	TBX21	TLR6	TNFRSF13C	TNFSF13	VEGFC
MDK	NFATC3	PILRB	SIGIRR	TCL1A	TLR7	TNFRSF14	TNFSF13B	XCL1
MERTK	NFKB1	PLCG2	SIGLEC1	THBS1	TLR8	TNFRSF17	TNFSF14	XCL2
MFGE8	NFKB2	PPARG	SKAP1	TIA1	TLR9	TNFRSF18	TNFSF18	XCR1
MGLL	NFKBIA	PRG1	SOCS1	TICAM1	TNF	TNFRSF19L	TNFSF4	ZAP70
MIF	NFKBIZ	PTGS2	SP110	TICAM2	TNFAIP3	TNFRSF1A	TNFSF9	
MITF	NLRC3	PTPRC	SPP1	TIMP3	TNFAIP6	TNFRSF21	TRAF1	

Table S2. Supplemental references used for gene selection and annotation.

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Table S3. The Proposed functions* of the 25 genes with the highest out-degree in the 53-gene panel Bayesian network.

Gene	Out-Degree	Log2 Fold Change	T-Statistic	p value	FDR	Proposed Function
CCR5	12	-0.5754	1.9699	0.0593	0.1598	Expressed on Th1 CD4 T cells (Loetscher *et al*, 1998) sand regulates functions of macrophages, NK cells and T cells
CD8A	12	-0.9392	2.5076	0.0182	0.1021	Co-receptor with the T-cell receptor on cytotoxic T lymphocytes to recognize antigens in the context of class I MHC molecules.
CD3D	11	NT*	NT	NT	NT	Part of the T-cell receptor complex, involved in T-cell development and signal transduction.
CD8B	11	NT	NT	NT	NT	Similar function to CD8A with which it forms a heterodimer
IKZF1	11	-0.5553	2.3094	0.0265	0.1044	Transcription factor associated with chromatin remodeling, functions as a regulator of lymphocyte differentiation.
BTK	10	-0.4292	2.3713	0.0234	0.1044	Expressed by B cells and crucial for their development
LCK	10	-0.9079	2.9279	0.0063	0.1021	Key signaling molecule in the selection and maturation of developing T-cells.
CD3E	9	-0.6031	2.192	0.0357	0.1205	Part of the T cell receptor complex, couples antigen recognition to signal-transduction pathways.
CD53	9	-0.5731	2.425	0.0222	0.1044	Contributes to the transduction of CD2-generated signals in T cells and natural killer cells.
COPS2	9	NT	NT	NT	NT	Essential component of the COP9 signalosome complex (CSN), a complex involved in multiple cellular processes and implicated in interferon related signaling.(Cohen *et al*, 2000)
CXCL9	9	-0.7667	1.9471	0.0592	0.1589	Chemokine implicated in T cell trafficking.
EGFR	9	NT	NT	NT	NT	Receptor for members of the epidermal growth factor family.
EPS8L1	9	NT	NT	NT	NT	A substrate for the epidermal growth factor receptor.
FGFR3	9	NT	NT	NT	NT	The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation.
GPS1	9	NT	NT	NT	NT	Suppresses G-protein and mitogen-activated signal transduction in mammalian cells.
MS4A1	9	NT	NT	NT	NT	B-lymphocyte surface molecule, plays a role in the development and differentiation of B-cells into plasma cells.
PPP3CB	9	NT	NT	NT	NT	Acalcium-dependent, calmodulin-stimulated protein phosphatase. This subunit may have a role in the calmodulin activation of calcineurin.
CD1A	8	-0.1511	0.5498	0.5857	0.6981	structurally related to the major histocompatibility complex (MHC) proteins and form heterodimers with beta-2-microglobulin.
CD2	8	-0.9678	3.4058	0.0020	0.0852	A surface antigen of the human T-lymphocyte lineage that is expressed on all peripheral blood T cells.
CD58	8	-0.0554	0.3335	0.7406	0.8211	A ligand of the T lymphocyte CD2 protein of the immunoglobulin superfamily, functions in adhesion and activation of T lymphocytes.
CD81	8	NT	NT	NT	NT	A cell-surface protein that co-ordinates special localization of transmembraine proteins and can module leucocyte activation and signaling. Also proposed tumor suppressor. (Mattila *et al*, 2013)
IL2RB	8	NT	NT	NT	NT	Subunit of the interleukin 2 receptor, involved in receptor-mediated endocytosis and transduction of mitogenic signals from interleukin 2.

NCOR2	8	NT	NT	NT	NT	Part of a multisubunit complex which includes histone deacetylases to modify chromatin structure that prevents basal transcriptional activity of target genes. Aberrant expression is associated with certain cancers.
PRKD2	8	NT	NT	NT	NT	Belongs to the protein kinase D (PKD) family of serine/threonine protein kinases. Binds to diacylglycerol (DAG) in the trans-Golgi network (TGN) and may regulate basolateral membrane protein exit from TGN.
TNFRSF1B	8	NT	NT	NT	NT	Signaling through this receptor modulates apoptosis as well as tumor necrosis factor (TNF) signaling.

*Based on Pubgene and references as indicated by footnotes

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Table S4. Top 10 enriched KEGG and GO terms (using DAVID) in the 53-gene, 446-gene, and 758-gene modules relative to the whole genome.

Module	Category	Term	p value	Fold Enrichment	Bonferroni	Benjamini	FDR
53-gene	GOTERM_BP_FAT	GO:0006955~immune response	2.34E-57	5.987716412	5.76E-54	5.76E-54	4.12E-54
	GOTERM_BP_FAT	GO:0002684~positive regulation of immune system process	1.48E-42	9.524596866	3.65E-39	1.82E-39	2.61E-39
	GOTERM_BP_FAT	GO:0048584~positive regulation of response to stimulus	9.87E-33	8.210994045	2.43E-29	8.11E-30	1.74E-29
	GOTERM_BP_FAT	GO:0045321~leukocyte activation	4.12E-31	7.856332365	1.02E-27	2.54E-28	7.26E-28
	GOTERM_BP_FAT	GO:0050778~positive regulation of immune response	1.39E-30	10.59041938	3.43E-27	6.86E-28	2.45E-27
	GOTERM_BP_FAT	GO:0001775~cell activation	2.75E-30	7.006686129	6.79E-27	1.13E-27	4.85E-27
	GOTERM_BP_FAT	GO:0046649~lymphocyte activation	6.60E-29	8.451555073	1.63E-25	2.32E-26	1.16E-25
	KEGG_PATHWAY	hsa04650:Natural killer cell mediated cytotoxicity	1.68E-28	7.031371532	1.78E-26	1.78E-26	1.88E-25
	GOTERM_BP_FAT	GO:0042110~T cell activation	2.44E-28	11.02668383	6.01E-25	7.51E-26	4.29E-25
	KEGG_PATHWAY	hsa04660:T cell receptor signaling pathway	1.91E-27	7.757024266	2.02E-25	1.01E-25	2.14E-24
446-gene	GOTERM_BP_FAT	GO:0006955~immune response	2.92E-104	3.130862049	1.44E-100	1.44E-100	5.55E-101
	GOTERM_BP_FAT	GO:0010941~regulation of cell death	3.14E-85	2.726186103	1.55E-81	7.73E-82	5.96E-82
	GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	4.09E-85	2.728678557	2.01E-81	6.71E-82	7.77E-82
	KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	1.05E-84	3.192464986	1.72E-82	1.72E-82	1.28E-81
	GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	3.02E-83	2.717554176	1.49E-79	3.72E-80	5.74E-80
	GOTERM_BP_FAT	GO:0006952~defense response	1.35E-74	2.892202076	6.63E-71	1.33E-71	2.56E-71
	GOTERM_BP_FAT	GO:0010604~positive regulation of macromolecule metabolic process	1.87E-73	2.542309068	9.19E-70	1.53E-70	3.55E-70
	GOTERM_BP_FAT	GO:0009611~response to wounding	1.49E-69	2.984442117	7.36E-66	1.05E-66	2.84E-66
	GOTERM_BP_FAT	GO:0007243~protein kinase cascade	4.28E-67	3.393394486	2.11E-63	2.63E-64	8.13E-64
	GOTERM_BP_FAT	GO:0002684~positive regulation of immune system process	1.50324E-66	4.06002401	7.40198E-63	8.22442E-64	2.85615E-63
758-gene	GOTERM_BP_FAT	GO:0006955~immune response	2.92E-104	3.130862049	1.44E-100	1.44E-100	5.55E-101
	GOTERM_BP_FAT	GO:0010941~regulation of cell death	3.14E-85	2.726186103	1.55E-81	7.73E-82	5.96E-82
	GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	4.09E-85	2.728678557	2.01E-81	6.71E-82	7.77E-82
	KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	1.05E-84	3.192464986	1.72E-82	1.72E-82	1.28E-81
	GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	3.02E-83	2.717554176	1.49E-79	3.72E-80	5.74E-80
	GOTERM_BP_FAT	GO:0006952~defense response	1.35E-74	2.892202076	6.63E-71	1.33E-71	2.56E-71
	GOTERM_BP_FAT	GO:0010604~positive regulation of macromolecule metabolic process	1.87E-73	2.542309068	9.19E-70	1.53E-70	3.55E-70
	GOTERM_BP_FAT	GO:0009611~response to wounding	1.49E-69	2.984442117	7.36E-66	1.05E-66	2.84E-66
	GOTERM_BP_FAT	GO:0007243~protein kinase cascade	4.28E-67	3.393394486	2.11E-63	2.63E-64	8.13E-64
	GOTERM_BP_FAT	GO:0002684~positive regulation of immune system process	1.50E-66	4.06002401	7.40E-63	8.22E-64	2.86E-63

Table S5: Comparison of the clinical-pathologic features of training set and test set.

Parameter	p value*
Gender	0.6043
Age	0.5305
Location	0.9176
Depth	0.8780
Ulceration	0.9150
TILs	0.0383
Mitosis	0.0020
Stage	0.9642
Disease progression	0.9698
Died from Melanoma	0.8736

*p values are shown without correction for multiple comparisons. Student T test was used for continuous variables and Fisher Exact Test for categorical variables.

Table S6. Gene expression data from primary melanoma tumors GEO (GSE15605).

GEO sample	Phenotype
GSM390224	Primary_melanoma MEL101
GSM390225	Primary_melanoma MEL128
GSM390226	Primary_melanoma MEL131
GSM390227	Primary_melanoma MEL135
GSM390228	Primary_melanoma MEL142
GSM390229	Primary_melanoma MEL145
GSM390230	Primary_melanoma MEL157
GSM390231	Primary_melanoma MEL173
GSM390232	Primary_melanoma MEL176
GSM390233	Primary_melanoma MEL185
GSM390234	Primary_melanoma MEL190
GSM390235	Primary_melanoma MEL197
GSM390236	Primary_melanoma MEL209
GSM390237	Primary_melanoma MEL213
GSM390238	Primary_melanoma MEL233
GSM390239	Primary_melanoma MEL236
GSM390240	Primary_melanoma MEL243
GSM390241	Primary_melanoma MEL244
GSM390242	Primary_melanoma MEL250
GSM390243	Primary_melanoma MEL257
GSM390244	Primary_melanoma MEL258
GSM390245	Primary_melanoma MEL272
GSM390246	Primary_melanoma MEL275
GSM390247	Primary_melanoma MEL276
GSM390248	Primary_melanoma MEL280
GSM390249	Primary_melanoma MEL282
GSM390250	Primary_melanoma MEL283
GSM390251	Primary_melanoma MEL287
GSM390252	Primary_melanoma MEL290
GSM390253	Primary_melanoma MEL294
GSM390254	Primary_melanoma MEL298
GSM390255	Primary_melanoma MEL307
GSM390256	Primary_melanoma MEL310
GSM390257	Primary_melanoma MEL326
GSM390258	Primary_melanoma MEL339
GSM390259	Primary_melanoma MEL340
GSM390260	Primary_melanoma MEL356
GSM390261	Primary_melanoma MEL362

GSM390262	Primary_melanoma MEL364
GSM390263	Primary_melanoma MEL375
GSM390264	Primary_melanoma MEL380
GSM390265	Primary_melanoma MEL385
GSM390266	Primary_melanoma MEL395
GSM390267	Primary_melanoma MEL420
GSM390268	Primary_melanoma MEL429
GSM390269	Primary_melanoma MEL430

Table S7. Clinical characteristics of patients with primary melanoma in extracted vs. non-extracted samples

Characteristics	Training Set			Test Set		
	Extracted (N=40)	Non-extracted (N=7)	p value	Extracted (N=48)	Non-extracted (N=9)	p value
Clinical characteristics						
Sex						
Male -- no.(%)	28 (70)	6 (86)	0.655	26 (54)	5 (56)	1.000
Female -- no.(%)	12 (30)	1 (14)		22 (46)	4 (44)	
Age						
Median (range) --no.	67 (29-87)	73 (54-77)	0.423	65 (27-90)	55 (46-88)	0.415
Location of Tumor						
Trunk -- no.(%)	24 (60)	5 (71)	0.692	25 (52)	7 (78)	0.273
Extremity -- no.(%)	16 (40)	2 (29)		23 (48)	2 (22)	
Stage						
II -- no. (%)	18 (45)	3 (43)	0.731	25 (52)	4 (44)	0.730
III -- no. (%)	22 (55)	4 (57)		23 (48)	5 (56)	
Pathological characteristics						
Depth (mm) – median (range)	2.65 (1.2-13)	2.18 (1.30-2.95)	0.166	3.47 (1-30)	3.90 (1-8)	0.655
Ulceration						
Absent -- no.(%)	21 (52)	4 (57)	0.701	20 (42)	6 (67)	0.275
Present -- no.(%)	19 (48)	3 (43)		28 (58)	3 (33)	
Disease progression	21 (52)	2 (29)	0.416	22 (46)	2 (22)	0.278