**Supplementary Methods**

*RNF2 expression analysis*

Gene expression data were retrieved from original publication sources (Talantov et al. (1) and Kabbarah et al. (2)). Both microarray data were profiled by Affymetrix HG-U133A Gene Chip and processed by MAS 5.0 software. Expression values were logarithmically transformed and normalized using quantile method in R. Two sample t-tests and ANOVA test were applied to compare RNF2 expression levels among different sample groups using R statistical functions.

*Chromatin Immunoprecipitation*

Cells (5 million per antibody) were crosslinked using 1% paraformaldehyde for 10mins at 37$^{o}$C. Reaction was quenched by 0.125M glycine for 5mins, cells washed with PBS and stored at -80$^{o}$C. Next day cells were thawed on ice and lysed with RIPA buffer (10mM Tris-HCl pH 8.0, 1mM EDTA pH 8.0, 140mM NaCl, 1% Triton x-100, 0.2%SDS, 0.1% DOC) for 10min on ice. Sonication was performed using Branson Sonifier 250 to achieve shear length of 200-500bp. Antibodies [Rabbit IgG, V5 (abcam), H2AK119ub (Millipore)] were bound to dynabeads for 1 hr at 4$^{o}$C. Extracts were then incubated overnight with antibody-dynabead mixture Immunecomplexes were then washed 5 times with RIPA buffer, once with RIPA-500 (RIPA with 500mM NaCl) and once with LiCl wash buffer (10mM Tris-HCl pH 8.0, 1mM EDTA pH 8.0, 250mM LiCl, 0.5% NP-40, 0.5% DOC). Elution and decrosslinking was performed in direct elution buffer (10mM Tris-Cl pH 8.0, 5mM EDTA, 300mM NaCl, 0.5% SDS) by incubating immunecomplxes at 65$^{o}$C for 4-16hrs. Proteinase K and RNaseA treatment was performed and DNA cleaned up using SPRI beads (Beckman-Coulter).

RNF2 ChIP-Seq reads were aligned using Bowtie (version 0.12.2) (3) to human genome assembly NCBI Build 37 (UCSC hg19). Enriched regions were detected by

MACS version 1.4.0 (4) with a p-value cut-off of $1X10^{-5}$. PhastCons conservation scores for 44 vertebrates were downloaded from UCSC website (http://hgdownload.cse.ucsc.edu/goldenPath/hg18/phastCons44way/vertebrate/) and individual chromosome files were merged into a single wiggle file. Aggregate plots for conservation scores across enriched sites were generated using the Sitepro program under CEAS (5). Human RefSeq gene information was obtained from UCSC table browser (http://genome.ucsc.edu/cgi-bin/hgTables?command=start) and genes with a nearby peak in 5Kb up/down-stream of transcription start sites were designated as targets. We used DAVID (6) and Ingenuity Pathway Analysis tools to find significantly enriched biological pathways or processes in RNF2 target genes. Affymetrix U133 Plus2.0 microarrays were performed for each condition (HMEL-$BRAF^{V600E}$-GFP, HMEL-$BRAF^{V600E}$-$RNF2^{WT}$ cells, HMEL-$BRAF^{V600E}$-$RNF2^{WT}$ tumor) in duplicates. Robust multi-array average (RMA) method was used with default options (with background correction, quantile normalization, and log transformation) to normalize raw data from batches using R/Bioconductor's affy package (7). For genes, which were represented by multiple probes on the array, maximum expression value was retained for further analyses. A gene is called as differentially expressed if FDR corrected p-value is less than 0.05, which is calculated with empirical Bayes method by eBayes function in Bioconductor's 'limma' package. Differentially expressed genes in both sets (HMEL-$BRAF^{V600E}$-$RNF2^{WT}$ vs HMEL-$BRAF^{V600E}$-GFP cells and HMEL-$BRAF^{V600E}$-$RNF2^{WT}$ vs HMEL-$BRAF^{V600E}$-GFP tumor) were used in down-stream analyses.

*Plasmids*

For expression, wild type, I53S and R70C derivatives were cloned into pLenti6.3-DEST (for human cell lines) or pHAGE-EF1$\alpha$-Gateway-IRES-GFP (for mouse cell lines) using Gateway technology (Invitrogen). pDNR-RNF2 (human) was bought from Open

Biosystems. I53S and R70C derivatives were made in pDNR clone using site directed mutagenesis. Lentiviral pLKO.1 vector constructs were used for shRNA mediated knockdown (Open Biosystems). shRNA sequences are available on request.

*iBIP mice development and characterization*

iBIP model is described in Kwong et al. (8). Briefly, iBIP mouse model was generated by intercrossing of the following alleles: 1. Ink/Arf null (9), 2. TetO:Braf$^{V600E}$ (10), 3. PTEN$^{L/L}$ (11) 4. Rosa26-LSL-Rtta (Jackson Laboratories), 5.Tyr-Cre$^{ERT2}$. The Braf$^{V600E}$ allele activation is achieved specifically in Tyrosinase expressing melanocytes by topical tamoxifen application along with doxycycline administration. PTEN deletion is achieved in tyrosinase expressing melanocytes by topical 4-hydroxytamoxifen (4-OHT) application.

*Generation of RNF2$^{L/L}$ allele and crossing with iBIP mice*

Rnf2 conditional knockout mice were generated via homologous recombination in mouse ES cells. Exon 2 is the first coding exon of the mouse Rnf2 gene. Homologous recombination was used to place a LoxP site 5' of exon 2 of the mouse *Rnf2* gene and a *frt-Neo-frt-LoxP* cassette 3' of Exon 2 (shown in Supplementary Figure 2D). A C57BL/6J mouse BAC clone RP23-41F24 was used as template for generation of target homology. Three fragment Multisite Gateway (Life Technologies/Invitrogen) was utilized to generate the final targeting construct. The left and right homology arms were PCR generated with appropriate Att sites and recombined into the appropriate Donor plasmids resulting in Entry clones for the left and right homology arms. The middle fragment containing exon 2 was PCR generated and blunt-end ligated into the Sal1 site of a pre-prepared Entry plasmid with the following configuration *LoxP-Sal1-Frt-Neo-Frt*. All three left, middle (*LoxP/Exon2/frt-Neo-frt-LoxP*), and right Entry fragments were recombined into a

Destination vector containing a Sfi1 restriction site for linearization and a DTA negative selection cassette. The final plasmid was linearized and utilized for electroporation. The targeting construct was electroporated into mouse ES cell line V6.5 selected in G418 and targeted ES cell clones were isolated.

*Co-immunoprecipitation*

HMEL-EV or HMEL-RNF2 cells were grown in a 15 cm plate to confluence. Cells were lysed in whole cell extract using NP-40 buffer (20 mMTris HCl pH 8.0, 150 mM NaCl, 1% Nonidet P-40 (NP-40), 2 mM EDTA, 1X Protease Inhibitor cocktails) and immunoprecipitation with V5 Antibody-Protein IgG Dynabead conjugates performed overnight. Immunecomplexes were washed three times in NP-40 buffer and immunoblotted for shown antibodies.

*Kinase Assay*

Recombinant MEK1 kinase (abcam) was incubated with V5-immunoprecipitated proteins from HMEL-EV, HMEL-RNF2$^{WT}$, HMEL-RNF2$^{S208A}$, HMEL-RNF2$^{S168A}$ and HMEL-RNF2$^{S41A}$ in Kinase buffer (25mM HEPES, pH7.4, 25mM MgCl2, 2mM DTT, 20uM ATP, 1X Protease Inhibitors cocktail,1X Phosphatase inhibitors cocktail) in the presence of $\gamma$-p32-ATP at 30$^{o}$C for 30mins. Reaction was stopped by adding SDS lysis buffer. Proteins were separated on a standard NuPAGE 4-12% gel, gel dried and exposed to a phosphorimager screen. Signal was detected in a typhoon imager.

**Supplementary Figure Legends**

**Supplementary Figure 1:** (A) Western blot showing RNF2 expression in different melanocytic and melanoma derived cell lines overexpressing GFP, $RNF2^{WT}$ or $RNF2^{I53S}$. (B) GFP, $RNF2^{WT}$ or $RNF2^{I53S}$ were overexpressed in HMEL-$BRAF^{V600E}$ (primary melanocytes), WM115 and 1205Lu cells and invasion capacity measured using Boyden Chamber matrigel-invasion assay. Count represents relative invasive cells obtained after dividing number of invaded cells by plating density approximated by absorbance at 600nm. (C) Western blot showing expression levels of RNF2 in 10 melanoma cell lines and HMEL-$BRAF^{V600E}$ cells. B-actin was used as a loading control. (D-E) 501Mel and HMEL-$BRAF^{V600E}$-shPTEN cells with stably integrated shGFP, shRNF2-1, shRNF2-2 were subjected to Boyden chamber matrigel invasion assay. (D) Graph showing relative invaded cell density. (E) Graph showing knockdown efficiency of RNF2 at mRNA levels in melanoma cells. (F) Graph showing percent of mice with lungs containing GFP positive nodule following intravenous injection of HMEL-$BRAF^{V600E}$-shPTEN cells corresponding to images in Figure 1E. (G) Graph showing knockdown efficiency of RNF2 at mRNA levels in B16-F10 cells with RNF2 shRNA. Across all panels "*" denotes significant change t-test $p < 0.05$ and "**" represents p value <0.01.

**Supplementary Figure 2:** (A-D) Graphs showing tumor volume from mice following intradermal injection of (A) HMEL-$BRAF^{V600E}$ cells, (B) WM115 cells, (C) 1205Lu cells and (D) pMEL-$NRAS^{G12D}$ overexpressing GFP, RNF2 wild type or catalytic mutant derivatives (R70C or I53S). For all plots shown in panels A-D, t-test $p<0.01$. (E) Graph showing relative expression of RNF2 to β-actin assessing knockdown in 501Mel and WM983B cells. Asterisk "*" denotes significant change t-test $p < 0.05$. (F-G) Graphs showing tumor volumes from mice following injection of (F) 501Mel cells and (G) WM983B cells expression shRNAs against GFP (shGFP) or RNF2 (shRNF2).

Significance t-test $p < 0.001$. (H-J) Proliferation curve for 501Mel (H), B16-F10 (I) and HMEL-BRAF$^{V600E}$-shPTEN (J) cells stably expressing control (shSCR) or two RNF2 shRNAs (shRNF2-1 and shRNF2-2). Y-axis represents cell density and x-axis represents hours post plating.

**Supplementary Figure 3:** (A) RNF2 expression in the melanoma expression data for normal skin, nevi and primary tumors (ANOVA $p < .0104$). (B) RNF2 expression in primary and metastatic melanoma samples (t-test $p < 0.00766$). (C) Immunohistochemistry for RNF2 in a tissue microarray containing progression melanoma tumors. Pictures show representative intensities and counts. (D) Proliferation curve of HMEL-BRAF$^{V600E}$ cells overexpressing GFP, RNF2$^{WT}$ or RNF2$^{I53S}$. Y-axis represents cell density and x-axis represents hours post plating. (E) Western blot showing expression levels of RNF2$^{WT}$ and RNF2$^{I53S}$ in WM983B cells. (F) Schematic of targeting vector used to generate RNF2 null mice. (G) Kaplan-Meier curve showing tumor free survival after doxycycline (2mg/ml) administration and treatment with 4-hydroxytamoxifen (1 μM) in iBIP mice with iBIP;RNF2$^{+/+}$ or iBIP;RNF2$^{L/L}$ genotype.

**Supplementary Figure 4:** (A) Heat map showing clustering of top 10% deregulated genes in duplicates of expression data from RNF2$^{WT}$ overexpressing compared to GFP overexpressing HMEL-BRAF$^{V600E}$ cells. (B) ChIP-Seq profiles for RNF2 in RNF2$^{WT}$ overexpressing HMEL-BRAF$^{V600E}$ cells and in HMEL-BRAF$^{V600E}$-RNF2$^{WT}$ driven tumor cells. (C) Plot showing PhastCons score predicting evolutionary conservation of RNF2 occupied DNA binding site across genomes of 45 species. (D-E) Circle diagram showing distribution of RNF2 binding sites relative to distance from nearest TSS in (D) HMEL-BRAF$^{V600E}$-RNF2$^{WT}$ cells and (E) HMEL-BRAF$^{V600E}$-RNF2$^{WT}$ tumor cells. (F-G) Top five GO enrichment categories in (F) upregulated-occupied and (G) downregulated-occupied

genes. (H) Western blot showing expression of GFP, $RNF2^{WT}$ or $RNF2^{R70C}$ or $RNF2^{I53S}$ in HEK293 cells. (I) Western blot showing expression pattern of TGFβ target genes ID1, ID2 and ID3 in HMEL-$BRAF^{V600E}$ cells overexpressing GFP, $RNF2^{WT}$ or $RNF2^{I53S}$. (J) Graph showing relative expression of LTBP2 in HMEL-$BRAF^{V600E}$ and WM115 cells infected with shGFP, shLTBP2-1 or shLTBP2-2. Asterisk "*" denotes significant change t-test $p < 0.05$.

**Supplementary Figure 5: Chromatin state analysis on HMEL-$BRAF^{V600E}$ cells.** (A) Transition parameters for the 45-state model predicted by ChromHMM. (B) Overlap of different genomic features (CpG island, RefSeq TSS, RefSeq TES, laminB lads and zinc finger motifs with chromatin state calls in HMEL-$BRAF^{V600E}$ cells.

**Supplementary Table Legends**

**Supplementary Table 1:** Binding sites for RNF2 in HMEL-$RNF2^{WT}$ cells.

**Supplementary Table 2:** Genes that are occupied by RNF2 and show changed expression in HMEL-$RNF2^{WT}$ cells.

**Supplementary Table 3:** Description of states in 45-state chromatin state model.

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