EXTENDED DATA FIGURE LEGENDS.

Extended Data Figure 1. **Methodology and UVR spectrum.**

a. Schematic representation of experimental schedule, showing induction of ^{V600E}BRAF by tamoxifen at ~8 weeks of age followed by weekly exposure to UVR starting 4 weeks later, and for up to 6 months.

b. Graph showing spectral radiation distribution for the Waldmann UV6 lamp used in these studies. The UVA and UVB regions are indicated.

c. Photomicrograph of Trp53 staining in interfollicular and follicular keratinocytes (arrows) 24 hours after UVR exposure. *: hair follicles. Scale bar 50 μm .

Extended Data Figure 2. UVR induced melanocytic proliferation in ^{V600E}BRAF mice.

Photomicrographs showing DAPI, S100 and Ki67 immunofluorescence staining, together with a merged image in cloth-protected and UVR-exposed areas of the mid dermis from ^{V600E}BRAF mice 72 h after UVR exposure. Scale bar: 30 μm**.**

Extended Data Figure 3. UVR induces naevogenesis in ^{V600E}BRAF mice.

a. Schematic representation of experimental processing of mouse skin. Three skin sections (long rectangular boxes) were cut perpendicular to the longitudinal axis of the mice to span the UVR-exposed and protected areas (as marked by the dotted line) of the tamoxifen treated shaved area (pink).

b. Photomicrograph of hematoxylin and eosin stained representative skin from the protected and UVR-exposed skin of a tamoxifen treated ^{V600E}BRAF mouse subjected to UVR exposure and examined at 7 days. Dotted line: UVR treatment line demarcation. Scale bar 0.4 mm.

c. Photomicrograph of hematoxylin and eosin stained skin from the boxed black area in **b**, showing the cloth protected skin of a tamoxifen treated ^{V600E}BRAF mouse subjected to UVR exposure and examined at 7 days. Black boxes show individual naevi. Double-headed arrow shows example of maximum diameter of a single naevus. Scale bar 300μm.

d. Photomicrograph of hematoxylin and eosin stained skin from the dashed boxed black area in b, showing the UVR exposed skin of a tamoxifen treated ^{V600E}BRAF

mouse subjected to UVR exposure and examined at 7 days. Black boxes show individual naevi. Scale bar 300μm.

e. Photomicrograph of hematoxylin and eosin stained skin from the cloth-protected and UVR exposed skin of a tamoxifen treated CreERT2 control mouse subjected to weekly UVR exposure for 6 months. Scale bar 300μm.

f. Photograph showing macroscopic appearance of protected and UVR exposed skin from the tamoxifen treated CreERT2 control mouse shown in **a** above.

Extended Data Figure 4. **UVR-accelerated ^{V600E}BRAF-driven tumours present similar histology to ^{V600E}BRAF-driven tumours from non-UVR-exposed animals.**

a. Photomicrograph of an H&E stained tumour from a UVR treated ^{V600E}BRAF mouse highlighting the presence of atypical heterogeneous spindle dendritic and pigment producing cells (black asterisks and arrow respectively, left panel) and atypical plump spindle cells and mitotic figures (white asterisks and black arrowhead respectively, right panel). Scale bar 25μm.

b. Photomicrograph of an H&E stained tumour from a UVR treated ^{V600E}BRAF mouse highlighting a region of dermal ulceration (black arrow). Scale bar 0.5mm.

c. Photomicrograph of H&E stained tumours from non-UVR exposed (left panel) and UVR-exposed (right panel) ^{V600E}BRAF mice, showing the presence of nuclear pleomorphism (asterisks) in both tumours. Scale bar 10μm.

d. Photomicrograph of an S100 stained tumour from a UVR-exposed ^{V600E}BRAF mouse. Scale bar 100μm.

e. Photomicrograph of an Hmb45/MelanA stained tumour from a UVR-exposed ^{V600E}BRAF mouse. Scale bar 50μm.

f. Photomicrograph of a Ki67 stained tumour from a UVR-exposed ^{V600E}BRAF mouse. Scale bar 50μm.

Extended Data Figure 5. Sunscreen blocks the short-term effects of UVR exposure.

a. Photomicrograph showing lack of Trp53 staining in the cloth protected (Protected) and UVR-exposed, sunscreen-protected (UVR+SS) skin of a ^{V600E}BRAF mouse after 24 hours of UVR exposure (24h). Scale bar 40 μm.

b. Photomicrograph of H&E stained skin from the cloth protected (Protected) and UVR-exposed, sunscreen-protected (UVR+SS) regions of a ^{V600E}BRAF mouse after 24 hours of UVR exposure (24h). Scale bar 300 µm.

c. High magnification photomicrograph of H&E stained skin from the cloth protected (Protected) and UVR-exposed sunscreen-protected, (UVR+SS) regions of a ^{V600E}BRAF mouse after 24 hours of UVR exposure (24h) showing absence of apoptotic keratinocytes.

d. Photomicrograph of hematoxylin and eosin stained skin from a cloth-protected (Protected; left), UVA-exposed (UVA; centre), and UVA exposed, sunscreen protected (UVA+SS; right) skin of a mouse after 72 hours of UVR exposure (72 h) . Scale bar 300µm. The photomicrographs below the main images show areas of higher magnification of the images above. Asterisk: Epidermal hypertrophy, D: plump collagen bundles densely located in the dermis. Scale bar 150µm.

Extended Data Figure 6. UVA-induced epidermal and dermal thickening following UVA radiation is abrogated by the use of sunscreen.

a. Photomicrographs of H&E stained epidermis from the cloth protected (Protected) and UVR-exposed, sunscreen-protected (UVR+SS) skin of a ^{V600E}BRAF mouse at 7 days (7d) after UVR exposure showing the similarity in the number and size of naevi in the two regions. Scale bar 300 um.

b. Photographs showing the macroscopic appearance of the cloth protected (Protected) and UVR-exposed, sunscreen-protected (UVR+SS) skin from a ^{V600E}BRAF mouse 5 months after UVR.

c. Photomicrographs of S100, Hmb45/MelanA and Ki67 stained tumours from UVR-exposed, sunscreen-protected (UVR+SS) mice. Scale bar 50µm.

Extended Data Figure 7. Tumours with a Trp53/TP53 mutation.

a. Boxplot graph showing median number of SNVs per MB (SNVs/MB) in UVR-exposed mutant *Trp53*, or UVR-exposed wild-type *Trp53* (WT-Trp53) tumours. ns: not significant (Mann-Whitney test).

b. Kaplan-Meier plot showing melanoma free survival in control mice (CreERT2; black line); ^{V600E}BRAF mice; (^{V600E}BRAF blue line); and ^{V600E}BRAF mice crossed with $^{flox/+}$PTEN mice (^{V600E}BRAF/$^{flox/+}$PTEN; orange line).

c. Photomicrographs of S100, Hmb45/MelanA and Ki67 stained tumour sections from a ^{V600E}Braf/$^{R172H/+}$Trp53 mouse. Scale bar 50µm.

d. Boxplot graph showing proportion of C>T (G>A) transitions in human primary melanomas from the TCGA dataset (left panel), human metastatic melanomas from the TCGA dataset (middle) and human metastatic melanomas from the Yale dataset (right) harbouring wild type *TP53* (*TP53* wt) or mutations in *TP53* (*TP53* Mut).; Wilcoxon Signed-Rank Test.

EXTENDED DATA TABLE LEGENDS.

Extended Data Table 1. UVR induces Trp53 and apoptosis in epidermal keratinocytes. The table shows quantification of Trp53 and apoptotic keratinocytes (sunburn cells) in keratinocytes from cloth-protected, UVR exposed and UVR-exposed sunscreen protected skin 24 hours after exposure. The data are presented as % of positive cells, with range in brackets and show cells presenting Trp53 positive nuclei (Trp53 positive) and average number of apoptotic keratinocytes (Apoptotic cells) in the interfollicular epidermis for each condition.

Extended Data Table 2: Quantification of naevi. Average number, with range in brackets of naevi present in 1.8 mm protected and 1.8 mm UVR-exposed skin of animals 7 days after UVR treatment. Naevi number quantification was performed by 2 independent observers (Obs1, Obs2). Average size of naevi (range; arbitrary units) observed in 10.8 mm protected and 10.8 mm UVR-exposed skin of animals 7 days after UVR treatment. *Wilcoxon Rank Sum Test, **U Mann-Whitney Test.

Extended Data Table 3. Summary of *Trp53* mutations in UVR-exposed ^{V600E}BRAF mouse tumours and the *TP53* mutation context in humans.

a. The table summarises the *Trp53* mutations in UVR-exposed mouse tumours, shows Sanger sequencing validation, the UVR-induced mutations, mutation context and records the intensity of Trp53 staining by immunohistochemistry. The table also show the corresponding human codon and the frequency of somatic mutations at those codons in human cancer (http://p53.iarc.fr/TP53GeneVariations.aspx) and if this codon is mutated in human melanoma. N.C.: not conserved between mouse and human. NA: not available.

b. The table shows the *Trp53* mutations in UVR-exposed ^{V600E}BRAF tumours, the corresponding human codon, the functional classification based on SIFT program (SIFT) and the promoter-specific transcriptional activity measured in yeast functional assays and expressed as percent of wild-type (WT) activity[13]. N.C.: not conserved between mouse and human

c. *TP53* mutations occurring at 3' end of pyrimidine dimers in human TCGA, Broad, and Yale databases. n= number of human samples with a *TP53* mutation (upper row) and *TP53* mutation at 3' end of pyrimidine dimers (lower row), %= column percentage.

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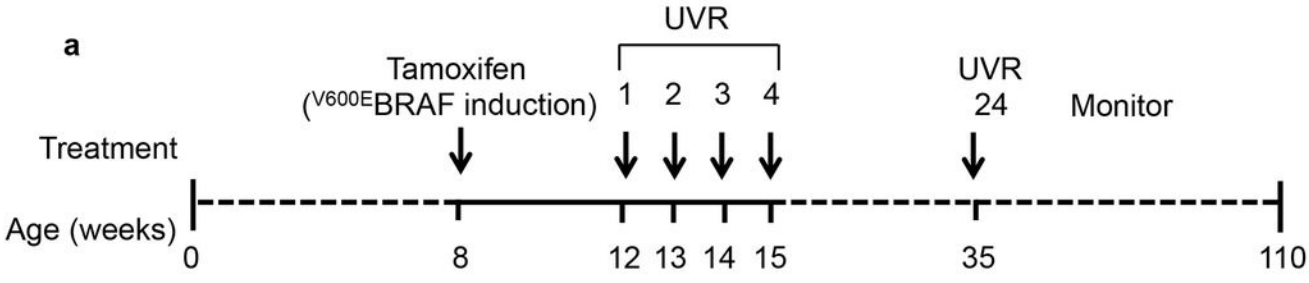
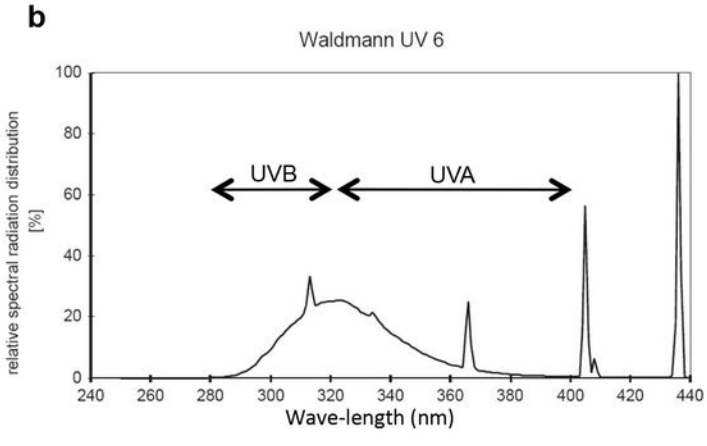
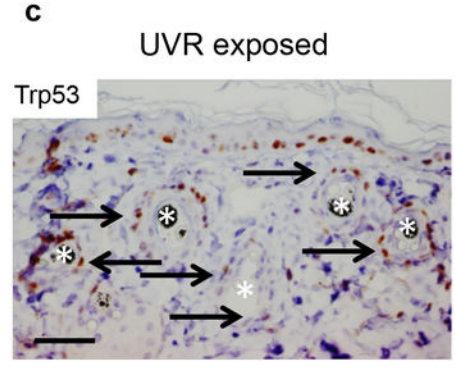

a
UVR
Tamoxifen
(V600EBRAF induction)
1 2 3 4
UVR
24
Monitor
Treatment
Age (weeks)
0
8
12 13 14 15
35
110


b
Waldmann UV 6
relative spectral radiation distribution [%]
UVB
UVA
Wave-length (nm)


c
UVR exposed
Trp53

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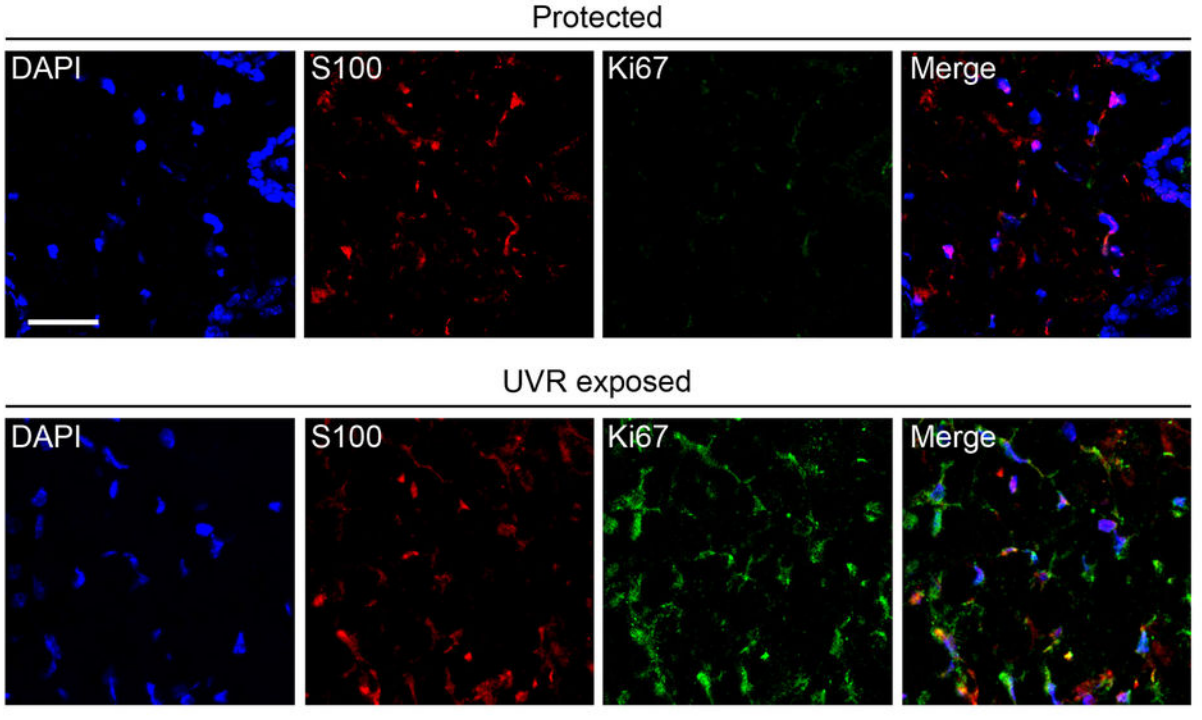
Protected
DAPI
S100
Ki67
Merge
UVR exposed
DAPI
S100
Ki67
Merge

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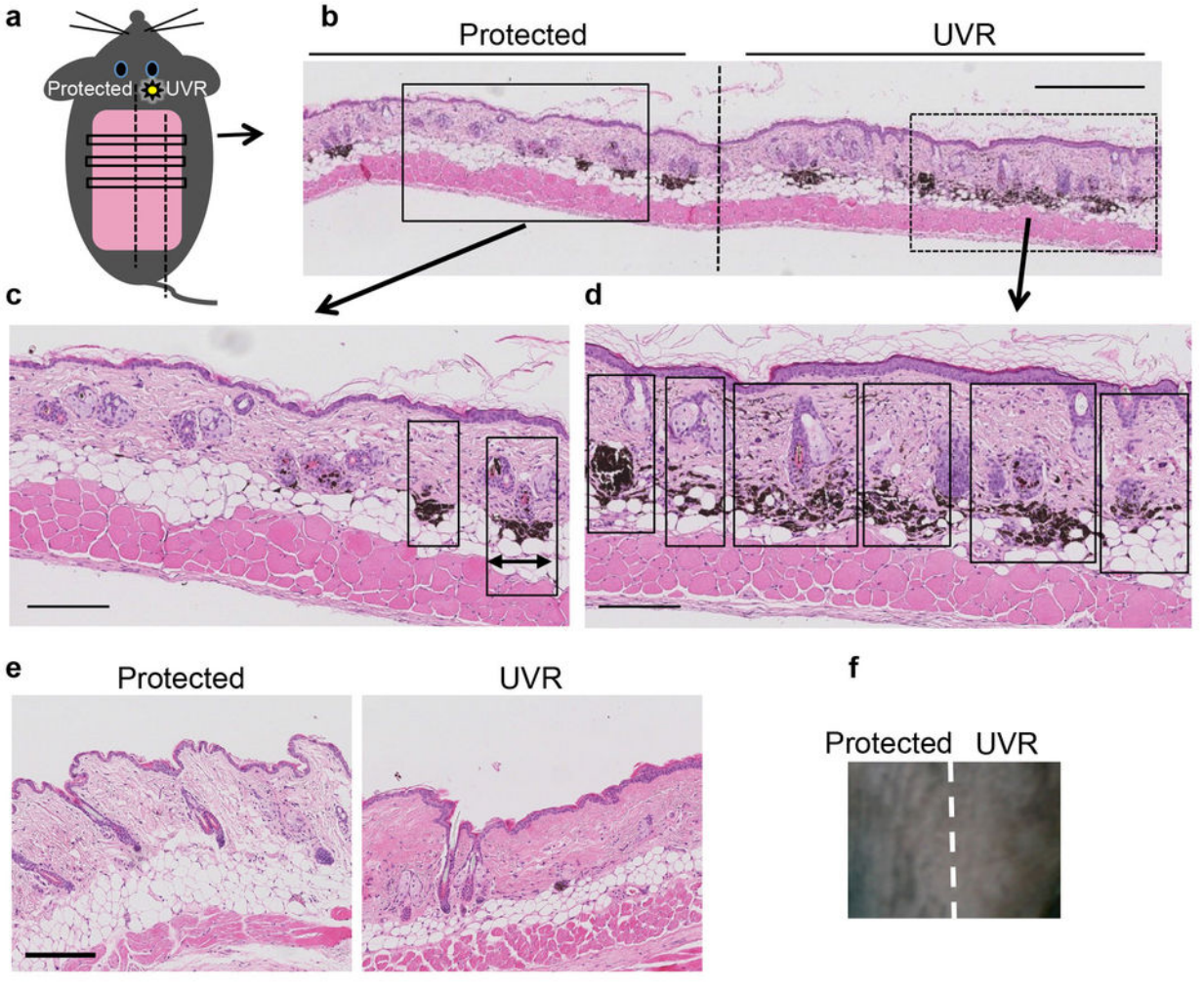
a
Protected
UVR
b
Protected
UVR
c
d
e
Protected
UVR
f
Protected
UVR

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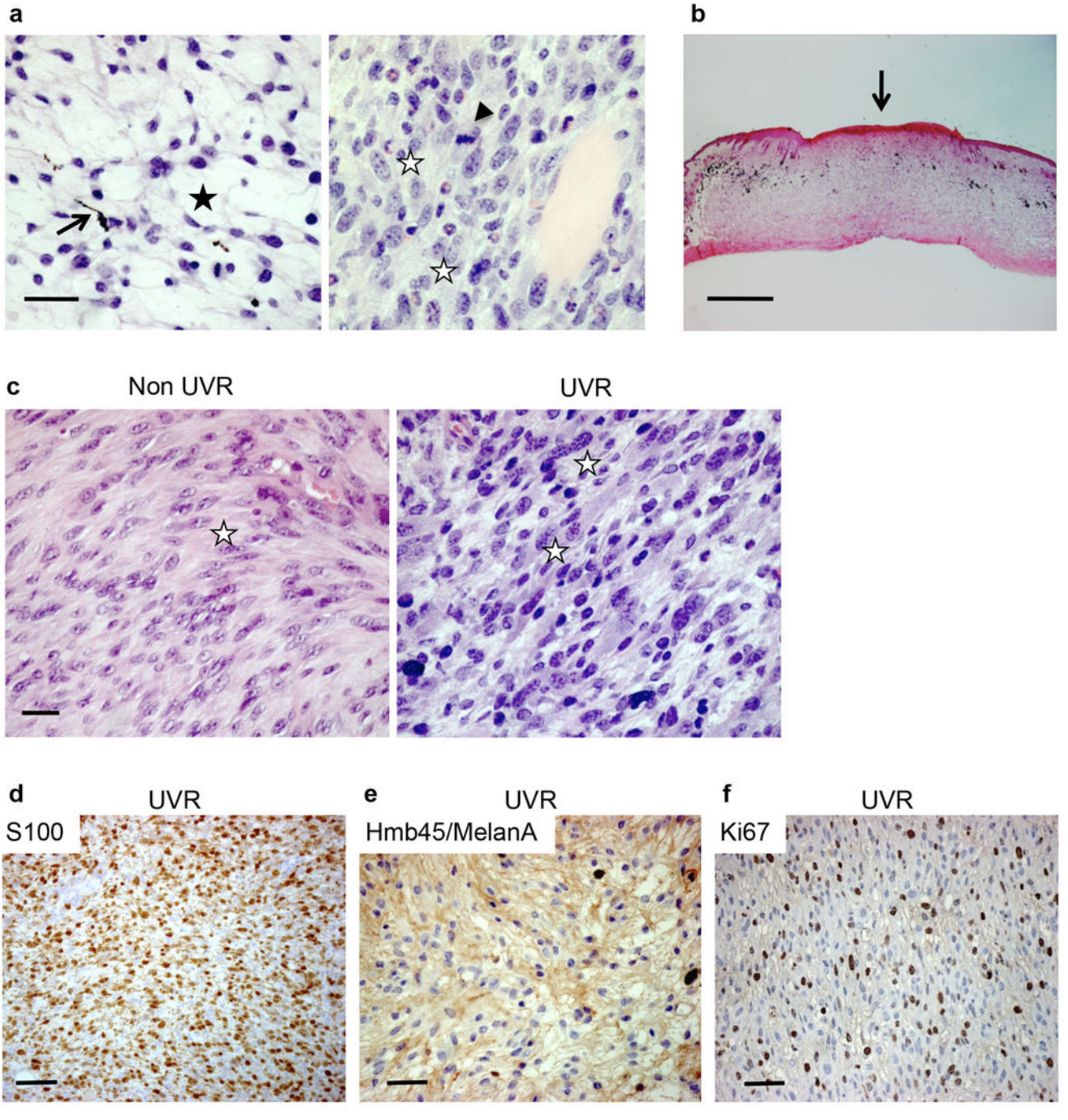
a
b
c
Non UVR
UVR
d
UVR
S100
e
UVR
Hmb45/MelanA
f
UVR
Ki67

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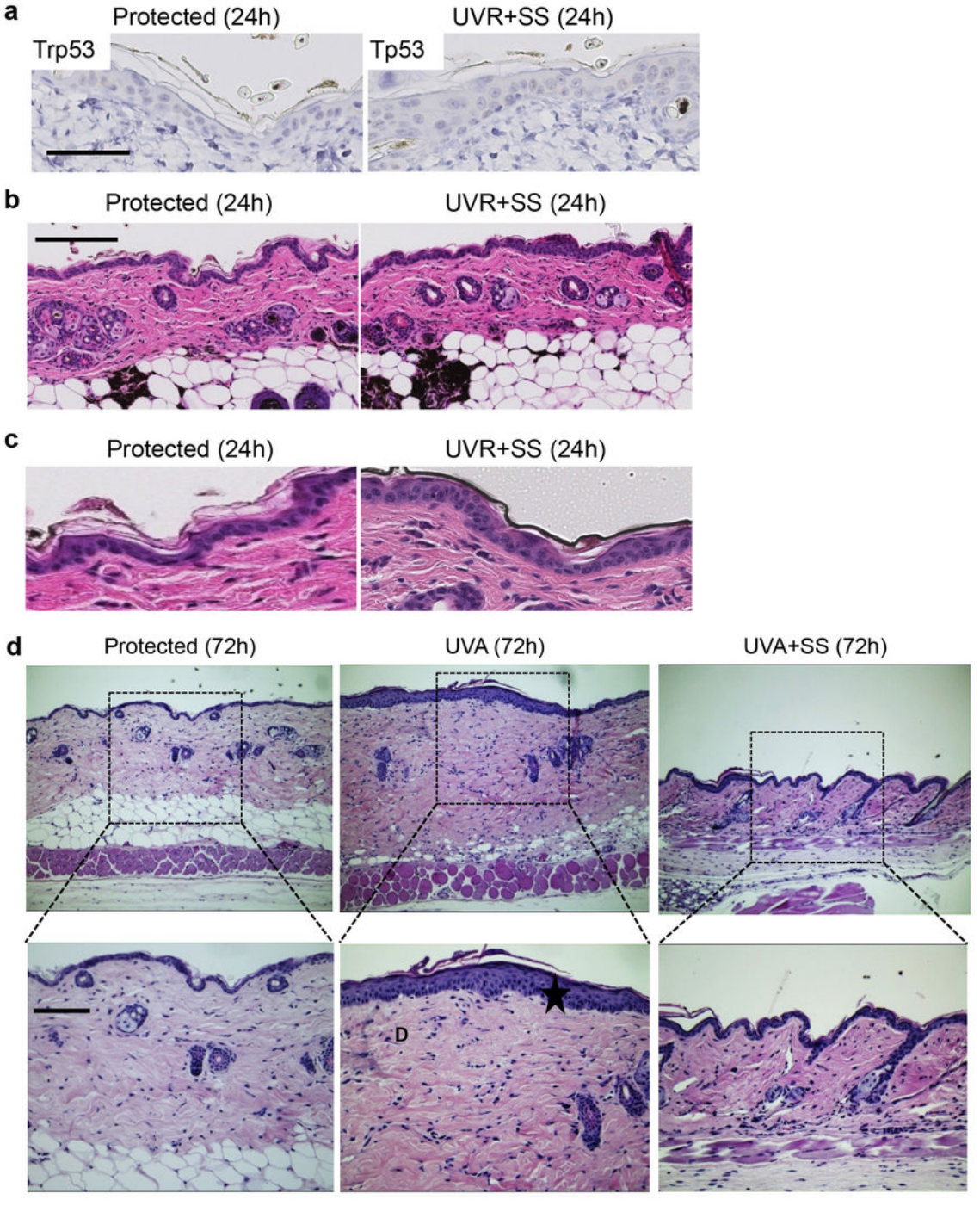
a
Protected (24h)
UVR+SS (24h)
Trp53
Tp53
b
Protected (24h)
UVR+SS (24h)
c
Protected (24h)
UVR+SS (24h)
d
Protected (72h)
UVA (72h)
UVA+SS (72h)
D

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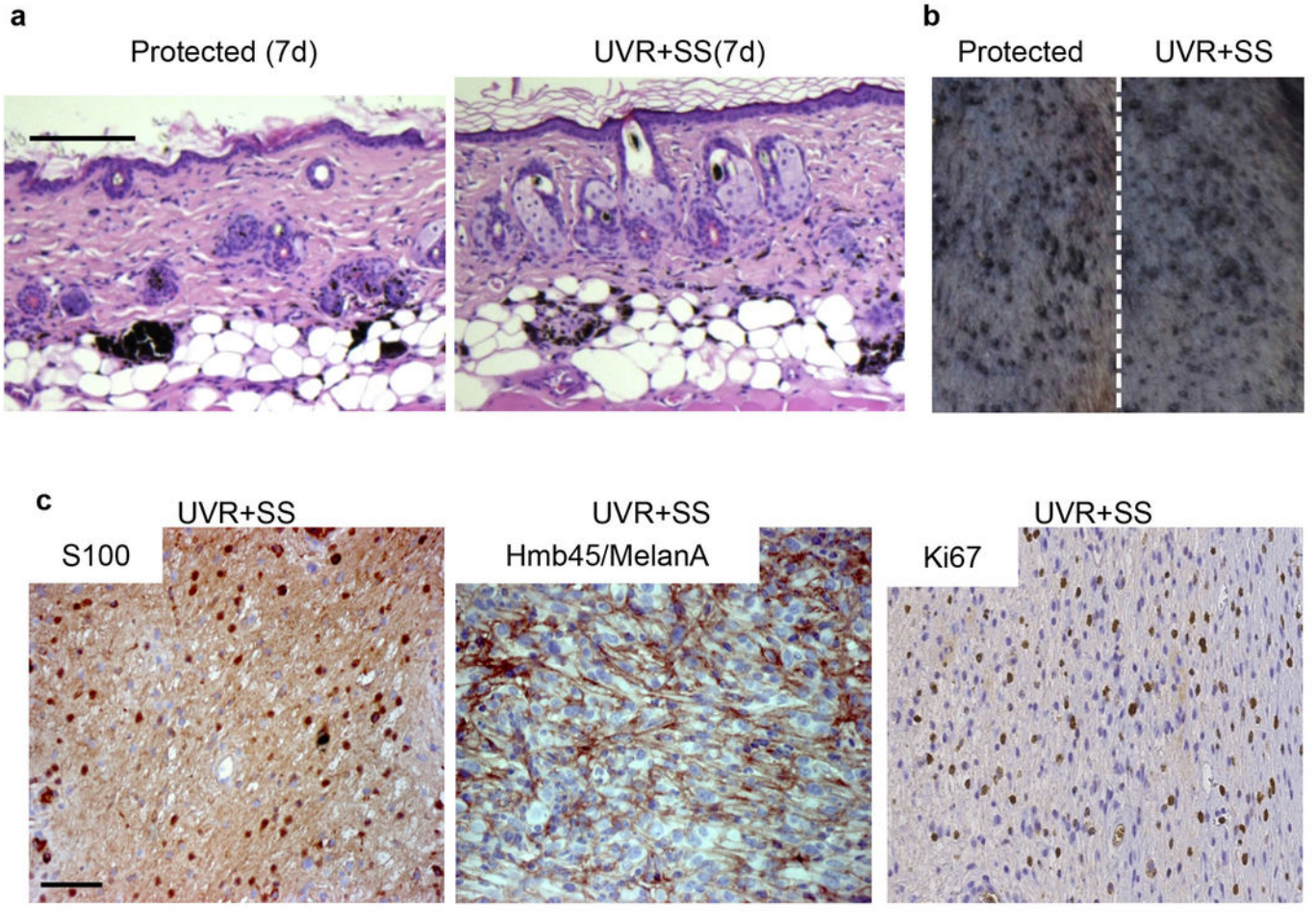
a
Protected (7d)
UVR+SS(7d)
b
Protected
UVR+SS
c
UVR+SS
S100
UVR+SS
Hmb45/MelanA
UVR+SS
Ki67

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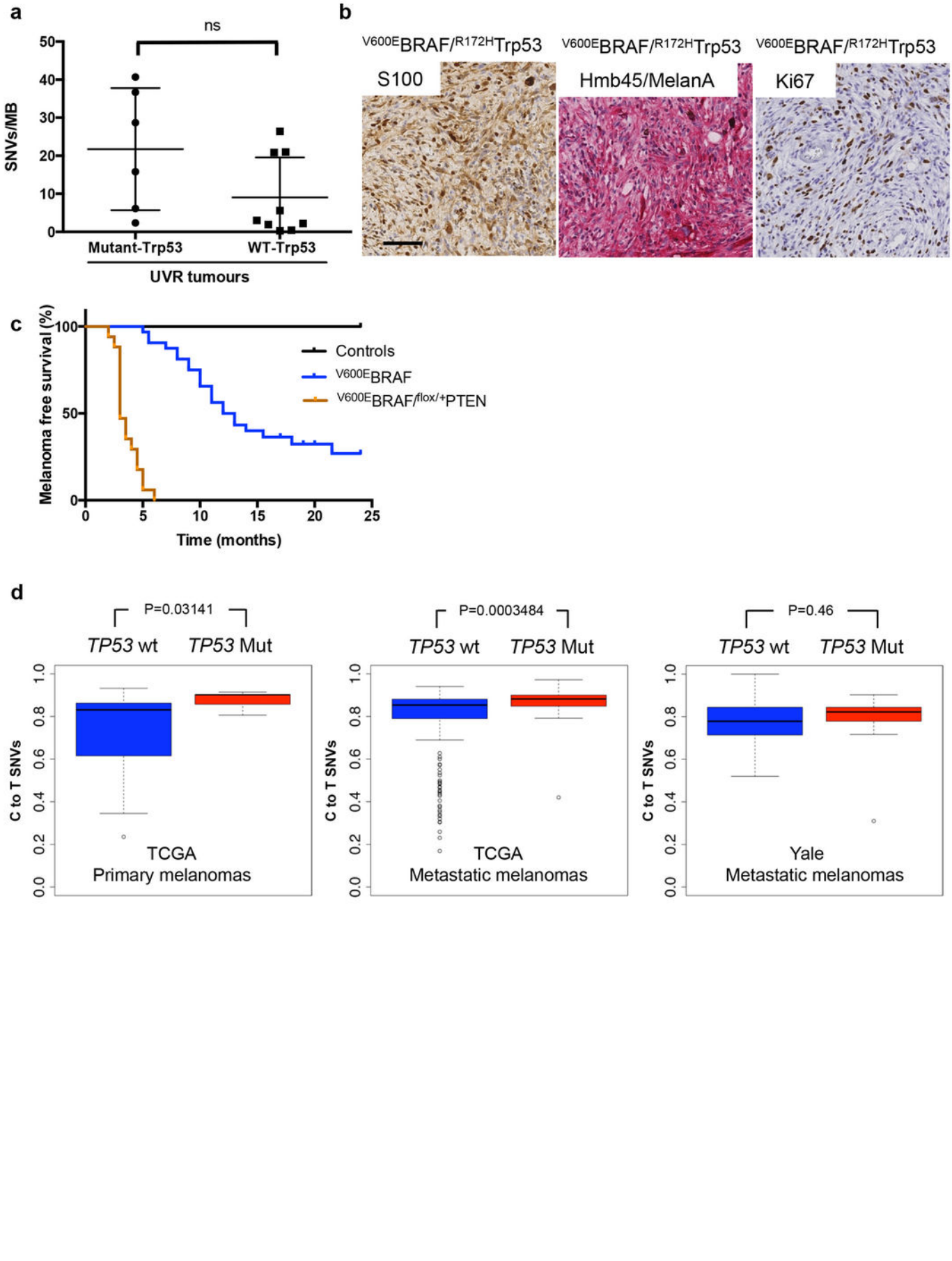
a
ns
SNVs/MB
Mutant-Trp53
WT-Trp53
UVR tumours
b
V600EBRAF/R172HTrp53
S100
Hmb45/MelanA
Ki67
c
Melanoma free survival (%)
Time (months)
Controls
V600EBRAF
V600EBRAF/flox/+PTEN
d
P=0.03141
P=0.0003484
P=0.46
TP53 wt
TP53 Mut
C to T SNVs
TCGA
Primary melanomas
TCGA
Metastatic melanomas
Yale
Metastatic melanomas

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	Protected	UVR exposed	UVR exposed + sunscreen
Trp53 positive	0	41(35-60)%	0
Apoptotic cells	0	17(9-27)/mm	0

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	Protected	UVR	p value
Naevi Number Obs 1	7(2-10)	11(6-14)	0.003*
Naevi Number Obs 2	5(3-7)	9(6-11)	0.0001*
Naevi Size Obs 1	0.9(0.2-1.5)	1.3(0.4-2.3)	0.0002**

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a

Tumour	Mouse	Sanger validation	UV induced mutation	Mutation context	IHC	Human	Human somatic mutation frequency	Mutated in human melanoma
UVR 1	R245C	Yes	C/T	AC**C**GC	Nuclear 3+	R248	1887	Yes
UVR 2	H39Y	Yes	C/T	CT**C**AC	Nuclear 3+	Q38	4	Not found
UVR 5	R270C	Yes	C/T	TT**C**GT	Nuclear 3+	R273	1790	Yes
UVR 6	C272G	Yes	T/G	TT**T**GT	Nuclear 2+	C275	175	Yes
UVR 12	S124F	Yes	C/T	CT**C**TC	Nuclear 3+	S127	64	Yes
UVR 15	R245C	Yes	C/T	AC**C**GC	Nuclear 3+	R248	1887	Yes
UVR SS 8	R270C	Yes	C/T	TT**C**GT	NA	R273	1790	Yes
^{V600E}**BRAF**/ ^{R172H}**TP53**	R172H	NA	NA	NA	Nuclear 2+	R175H	1303	Yes

b

		Ability to transactivate (% of WT activity)		
Human mutation	**SIFT**	**WAF1/p21**	**MDM2**	**BAX1**
S127F	Deleterious	20.6	20.1	14.3
R248C	Deleterious	0	0.6	0
R273C	Deleterious	1.5	0	2.7
C275G	Deleterious	1	0	0
R175H	Deleterious	20.5	17.6	10.5

c

	TCGA n (%)	**Broad n (%)**	**Yale n (%)**	**Total n (%)**
Total *TP53* mutations	51 (100)	27 (100)	9 (100)	87 (100)
TP53 mutations with a UVR signature	34 (66.6667)	13 (48.1482)	5 (55.5556)	52 (59.7701)