

Supplementary Table 1

BRAF ^{V600E} ; DCC ^{mut}	Cellularity of the tumor (comparison with control case)	Coating epidermis (comparison with control case)
Tumor-1	+	thickened
Tumor-2	=	moderately thickened
Tumor-3	+	thickened
Tumor-4	=	=
Tumor-5	+	thickened

Supplementary Table 1: Tumor cellularity and epidermis thickening in BRAF^{V600E};DCC^{mut} mice tumors.

Table demonstrating tumor cellularity and epidermis thickening in BRAF^{V600E};DCC^{mut} mice tumors compared to the BRAF^{V600E} control mice tumors.

Supplementary Table 2

BRAF ^{V600E} ; DCC ^{mut}	Comment
Tumor-1	Expanding the dermis, is an infiltrative, nodular, unencapsulated and highly cellular tumor. The neoplasm is composed of spindled to polyhedral cells arranged in short streams and bundles. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and one to several large nucleoli. Anisocytosis and anisokaryosis are present. Mitotic rate can reach up to 4 mitoses high power field (HPF). Scattered melanophages are visible within the neoplasm.
Tumor-2	Expanding the dermis, and elevating the ulcerated epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or loosely arranged within a mucinous matrix, depending on the sections. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild (up to 3 nuclei per cell). Mitotic rate is 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue. The ulcerated epidermis is replaced by fibrinoleucocytic exudate.
Tumor-3	Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and densely cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 2 mitoses per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue. Focally, the epidermis is ulcerated and replaced by fibrinoleucocytic exudate.
Tumor-4	Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells mainly loosely arranged within a mucinous matrix. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongate with stippled chromatin and mostly one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate does not exceed 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.
Tumor-5	Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, and rarely, are loosely arranged a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue. Focally, the epidermis is ulcerated and replaced by fibrinoleucocytic exudate.

Supplementary Table 2: Detailed pathology report for each BRAF^{V600E}; DCC^{mut} tumors.

Tumors from BRAF^{V600E};DCC^{mut} mice were analyzed by a onco-pathologist and a detailed pathology report was generated for each tumor.

Supplementary Table 3

	Benign melanocytic lesions N=36	Malignant melanoma N=205	Total N=241	Test
Tumor score				Fisher Exact P= <0.001
0-25%	2 (5.6%)	2 (1.0%)	4 (1.7%)	
25-50%	13 (36.1%)	9 (4.4%)	22 (9.1%)	
50-75%	15 (41.7%)	62 (30.2%)	77 (32.0%)	
75-100%	6 (16.7%)	132 (64.4%)	138 (57.3%)	
Tumor intensity				Fisher Exact P= <0.001
Weak	16 (44.4%)	36 (17.6%)	52 (21.6%)	
Moderate	16 (44.4%)	78 (38.0%)	94 (39.0%)	
Strong	4 (11.1%)	91 (44.4%)	95 (39.4%)	

Supplementary Table 3: Scores and tumor intensity of netrin-1 in benign melanocytic lesions vs malignant melanoma.

The table describes the scores and tumor intensity of netrin-1 in benign melanocytic lesions vs malignant melanoma. The analysis shows a correlation between the levels of netrin-1 (intensity or score) and the level of malignancy of the nevi.

Supplementary Table 4

	Benign melanocytic lesions N=36	Melanoma without metastasis N=80	Melanoma with metastasis N=125	Total N=241	Test
Tumor score					Fisher Exact P= <0.001
0-25%	2 (5.6%)	1 (1.3%)	1 (0.8%)	4 (1.7%)	
25-50%	13 (36.1%)	9 (11.3%)	0 (0.0%)	22 (9.1%)	
50-75%	15 (41.7%)	51 (63.8%)	11 (8.8%)	77 (32.0%)	
75-100%	6 (16.7%)	19 (23.8%)	113 (90.4%)	138 (57.3%)	
Tumor intensity					Fisher Exact P= <0.001
Weak	16 (44.4%)	35 (43.8%)	1 (0.8%)	52 (21.6%)	
Moderate	16 (44.4%)	35 (43.8%)	43 (34.4%)	94 (39.0%)	
Strong	4 (11.1%)	10 (12.5%)	81 (64.8%)	95 (39.4%)	

Supplementary Table 4: Scores and tumor intensity of netrin-1 in benign melanocytic lesions vs melanoma with or without metastasis at time of study. The table describes the scores and tumor intensity of netrin-1 in benign melanocytic lesions vs melanoma with or without metastasis at time of study. The analyses show a correlation between the levels of netrin-1 (intensity or score) and the level of malignancy of the nevi.

Supplementary Table 5

BRAF ^{V600E} ; tgNETRIN-1	Cellularity of the tumor (comparison with control case)	Coating epidermis (comparison with control case)
Tumor-1	=	thickened
Tumor-2	+	=
Tumor-3	+	thickened
Tumor-4	=	=
Tumor-5	+	thickened
Tumor-6	=	thickened
Tumor-7	=	thickened
Tumor-8	=	thickened
Tumor-9	=	=
Tumor-10	=	=
Tumor-11	+	=
Tumor-12	+	thickened
Tumor-13	+	=
Tumor-14	=	thickened
Tumor-15	+	=
Tumor-16	=	=

Supplementary Table 5: Tumor cellularity and epidermis thickening in BRAF^{V600E};tgNETRIN-1 mice tumors.

Table demonstrating tumor cellularity and epidermis thickening in BRAF^{V600E};tgNETRIN-1 mice tumors compared to the BRAF^{V600E} control mice.

Supplementary Table 6:

BRAF ^{V600E} ; tgNETRIN-1	Comment
Tumor-1	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of loosely arranged cells within a mucinous matrix. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is low (no more than 1 mitosis) per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>Focally, the epidermis is ulcerated and replaced by fibrinoleucocytic exudate.</p>
Tumor-2	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and densely cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>Adjacent to the melanoma is a focal nevus in upper dermis</p>
Tumor-3	<p>Expanding the dermis, and elevating the ulcerated epidermis is an infiltrative, nodular, unencapsulated and densely cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or loosely arranged within a mucinous matrix, depending on the sections. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate doesn't exceed 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>The ulcerated epidermis is replaced by fibrinoleucocytic exudate.</p>
Tumor-4	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. Skeletal muscle fibers are multifocally infiltrated. The neoplasm is composed of spindled cells arranged in short streams and bundles, and are rarely loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>
Tumor-5	<p>Expanding the dermis, is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled to polyhedral cells arranged in short streams and bundles, and are rarely loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and one to several large nucleoli. Anisocytosis and anisokaryosis are present. Mitotic rate can reach up to 7 or 8 mitoses HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>The epidermis is absent on sections</p>

Tumor-6	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>Focally, the epidermis is ulcerated and replaced by fibrinoleucocytic exudate.</p>
Tumor-7	<p>Expanding the dermis, and elevating the ulcerated epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>The ulcerated epidermis is replaced by a thin fibrinoleucocytic exudate.</p>
Tumor-8	<p>Expanding the dermis, and elevating the ulcerated epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 to 2 mitoses per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>The ulcerated epidermis is replaced by a thin fibrinoleucocytic exudate.</p>
Tumor-9	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and mostly one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>
Tumor-10	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and densely cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>Adjacent to the melanoma is a focal nevus in upper dermis</p>
Tumor-11	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, small nodular, unencapsulated and poorly cellular tumor. Skeletal muscle fibers are multifocally infiltrated. The neoplasm is composed of spindled cells arranged in short streams and bundles, and rarely, are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongate with stippled chromatin and mostly one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>

Tumor-12	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, nodular, unencapsulated and densely cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles or rarely, are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 mitosis per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>Adjacent to the melanoma is a focal nevus in upper dermis</p>
Tumor-13	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, small nodular, unencapsulated and moderately cellular tumor. Skeletal muscle fibers are multifocally infiltrated. The neoplasm is composed of spindled cells arranged in short streams and bundles, and are rarely loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is inferior to 1 mitosis per HPF (mean). Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>
Tumor-14	<p>Expanding the dermis, is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled to polyhedral cells arranged in short streams and bundles, and are rarely loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and one to several large nucleoli. Anisocytosis and anisokaryosis are present. Mitotic rate can reach up to 4 mitoses per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>
Tumor-15	<p>Expanding the dermis, and elevating the acanthotic epidermis is an infiltrative, small nodular, unencapsulated and moderately cellular tumor. Skeletal muscle fibers are multifocally infiltrated. The neoplasm is composed of spindled cells arranged in short streams and bundles, and rarely, are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongate with stippled chromatin and mostly one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p>
Tumor-16	<p>Expanding the dermis, and elevating the ulcerated epidermis is an infiltrative, nodular, unencapsulated and moderately cellular tumor. The neoplasm is composed of spindled cells arranged in short streams and bundles, or are loosely arranged within a mucinous matrix. The stroma is collagenous, moderately abundant. Neoplastic cells have mostly indistinct cell borders. Cytoplasm is moderately abundant, eosinophilic and contains rare brown pigments granules (melanin). Nucleus is oval to elongated with stippled chromatin and generally one nucleolus, often poorly distinct. Anisocytosis and anisokaryosis are mild. Mitotic rate is 1 to 2 mitoses per HPF. Scattered melanophages are visible within the neoplasm, and are more abundant at the junction with non neoplastic tissue.</p> <p>The ulcerated epidermis is replaced by a thin fibrinoleucocytic exudate.</p>

Supplementary Table 6: Detailed pathology report for each BRAF^{V600E}; tgNETRIN-1 tumors. Tumors from BRAF^{V600E};tgNETRIN-1 mice were analyzed by our anatomopathologist and a detailed pathology report was generated for each tumor.

Table. S7

Melanoma cell lines	BRAF	NRAS	P53	NF1	Source
M4Be	V600E	n/a	WT	n/a	own data
XPC	V600E	Q61H	WT	n/a	own data
Skmel3	V600E	WT	R267W	WT	CCLE
WM793	V600E	WT	WT	WT	CCLE
Skmel5	V600E	WT	WT	WT	CCLE
M2Ge	n/a	n/a	n/a	n/a	n/a
M3Da	V600E	n/a	WT	n/a	own data
WM115	V600E V600V	WT	WT	WT	CCLE
Skmel24	V600E	WT	WT	WT	CCLE
Malm3M	V600E	WT	WT	WT	CCLE
XP44	V600E	Q61H	WT	n/a	own data
RPMI7951	V600E	WT	S166*	WT	CCLE
G361	V600E	WT	WT	WT	CCLE
A375	V600E	WT	WT	K1290K	CCLE
Skmel28	V600E	WT	L145R L145L	WT	CCLE
H1DL2	n/a	n/a	n/a	n/a	n/a
Skmel31	V600E	WT	WT	S2585F	CCLE
WM9	n/a	n/a	n/a	n/a	n/a
WM239A	V600E	n/a	WT	n/a	own data
HMCB	WT	WT	H193R	Q535H	CCLE
H1Parental	n/a	n/a	n/a	n/a	n/a
Mewo	L255L	WT	Q317* E258K	Q1336* R2053R	CCLE
Skmel2	WT	Q61R	G245S	WT	CCLE

Supplementary Table 7: BRAF, NRAS, TP53 and NF1 mutations identified in the 23 analyzed human melanoma cell lines.

Data were generated in this study when specified and collected from publicly available databases (CCLE: Cancer cell line Encyclopedia). n/a: not analyzed. WT: Wide-Type.