SUPPLEMENTARY INFORMATION

Germline mutations in *BAP1* predispose to melanocytic tumors

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Legends of Supplementary Figure 1-4. Clinical pictures.

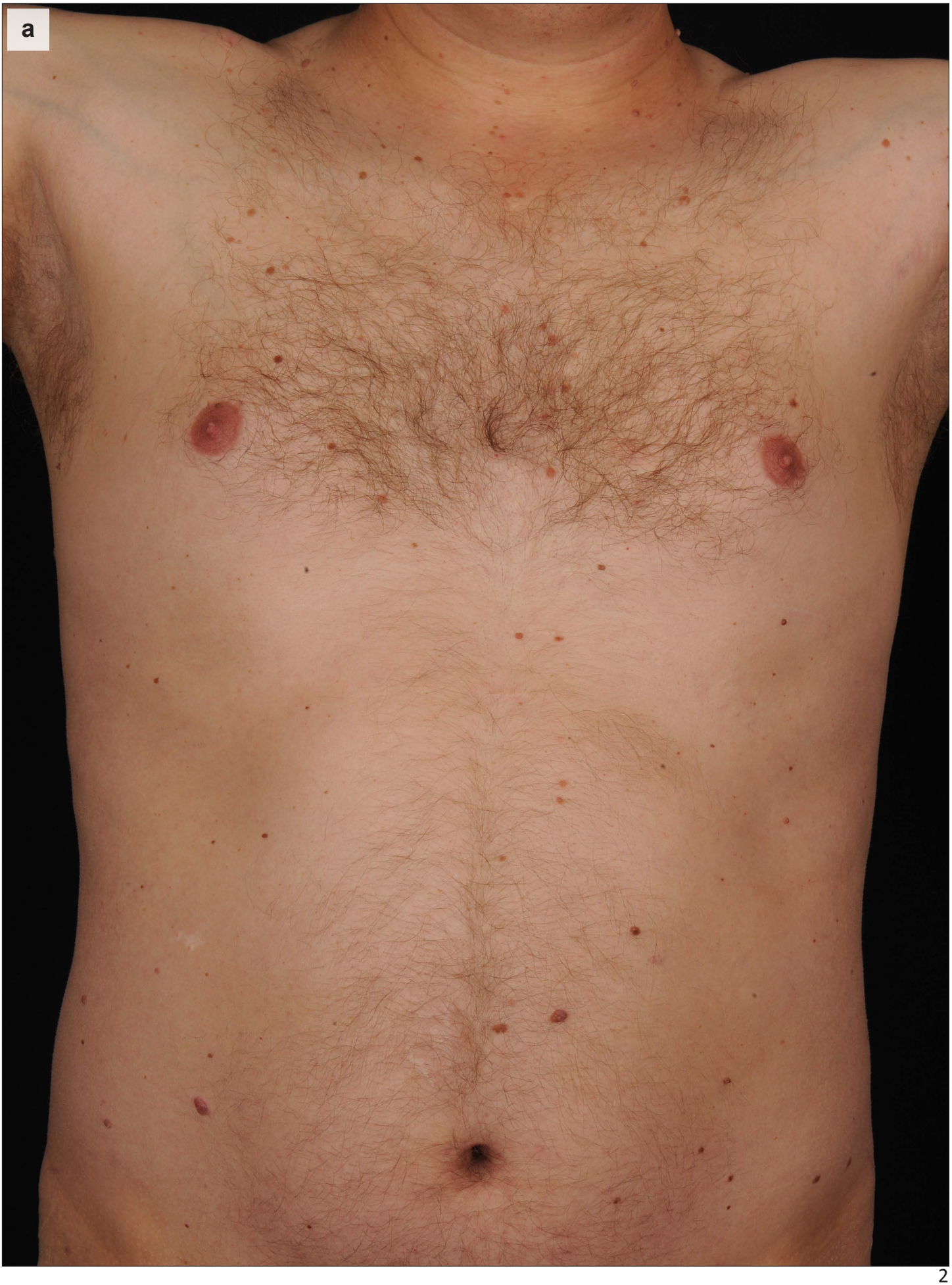
Supplementary Figure 1. Clinical images of subject III-3, family 2, showing numerous papular melanocytic nevi.
(**a-e**) The trunk and (**f-i**) the upper arms show numerous brown pigmented, mostly flat nevi, but in addition also the characteristic, non-pigmented exophytic melanocytic tumors. (**j-l**) Details of non-pigmented, pedunculated skin lesions on the right upper arm. Additional skin-colored, papular to pedunculated melanocytic tumors are found behind the (**m, n**) ear, (**o**) on the neck, (**p**) and on the scalp. A melanoma was excised from the scalp previously.

Supplementary Figure 2. Clinical images of subject II-6, family 2, showing only few papular melanocytic nevi.
(**a**) In contrast to subject III-3, family 2, the back of patient II-6 shows fewer brown, macular nevi and skin-colored papules. (**b-e**) The characteristic exophytic lesions are present on the arms. (**f-i**) Details of the characteristic melanocytic tumors on the right upper arm. This patient had a melanoma that metastasized.

Supplementary Figure 3. Clinical images from various members of family 2 illustrating the similar clinical appearance of the melanocytic tumors.
(**a**) Typical papular, dome-shaped, melanocytic tumors are found on the cheek of subject III-1 and (**b**) on the right upper arm of subject II-3. (**c**) Characteristic slightly pigmented, papular melanocytic tumor on the neck of subject III-4 and, in addition, numerous flat, brown nevi. Some of these flat, brown nevi were excised for diagnostic purposes, but did not show loss of *BAP1* as shown in **Supplementary Figure 13**. (**d**) The left supraclavicular region of subject III-2 displays the characteristic skin-colored, sharply demarcated nevi.

Supplementary Figure 4. Clinical images of subject II-4, family 1.
(**a, b**) The back of the trunk shows inconspicuous, small, skin-colored, sharply demarcated, dome-shaped melanocytic tumors. (**c**) Two typical lesions are shown on the right ear.

Supplementary Figure 1



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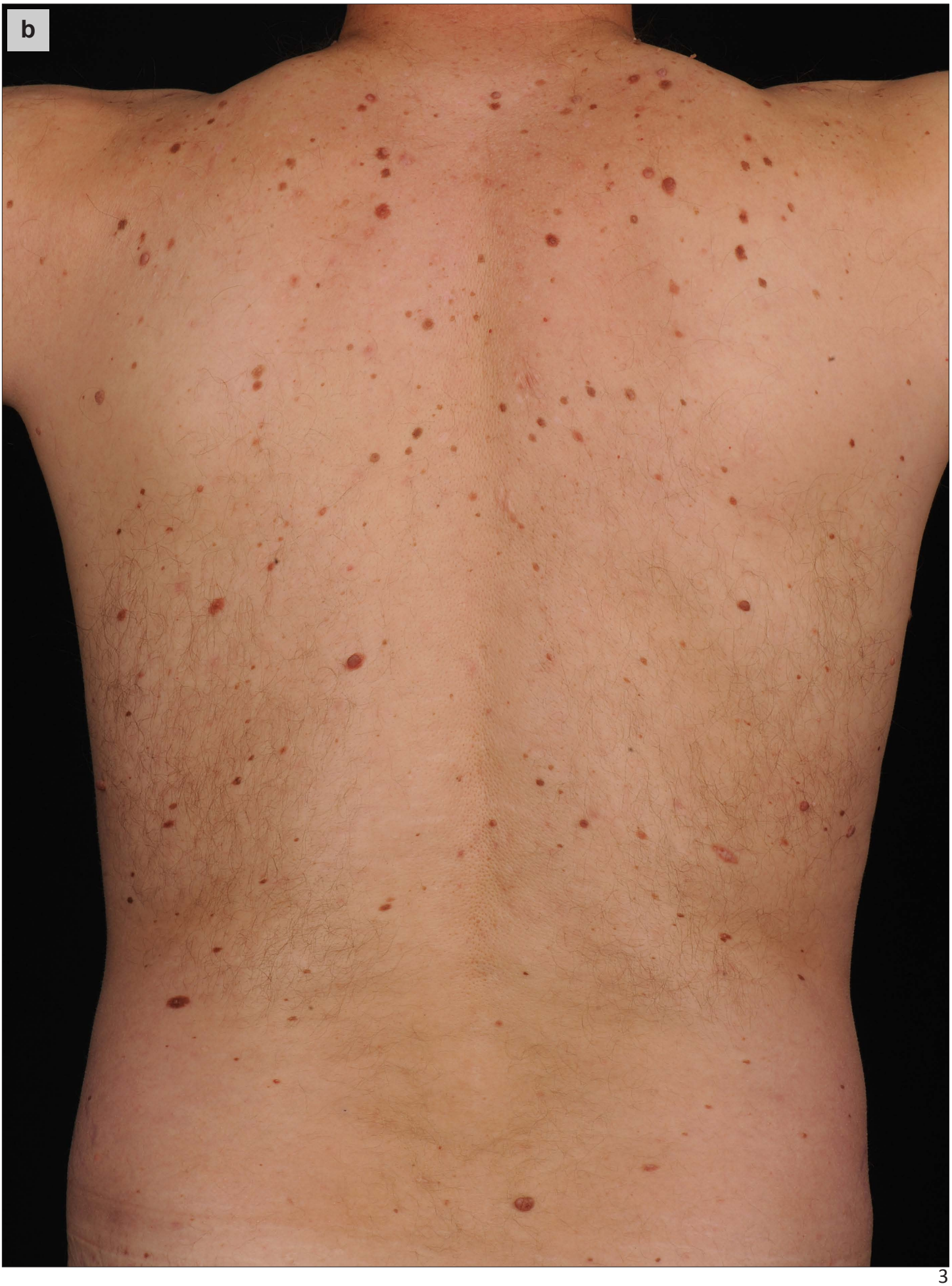

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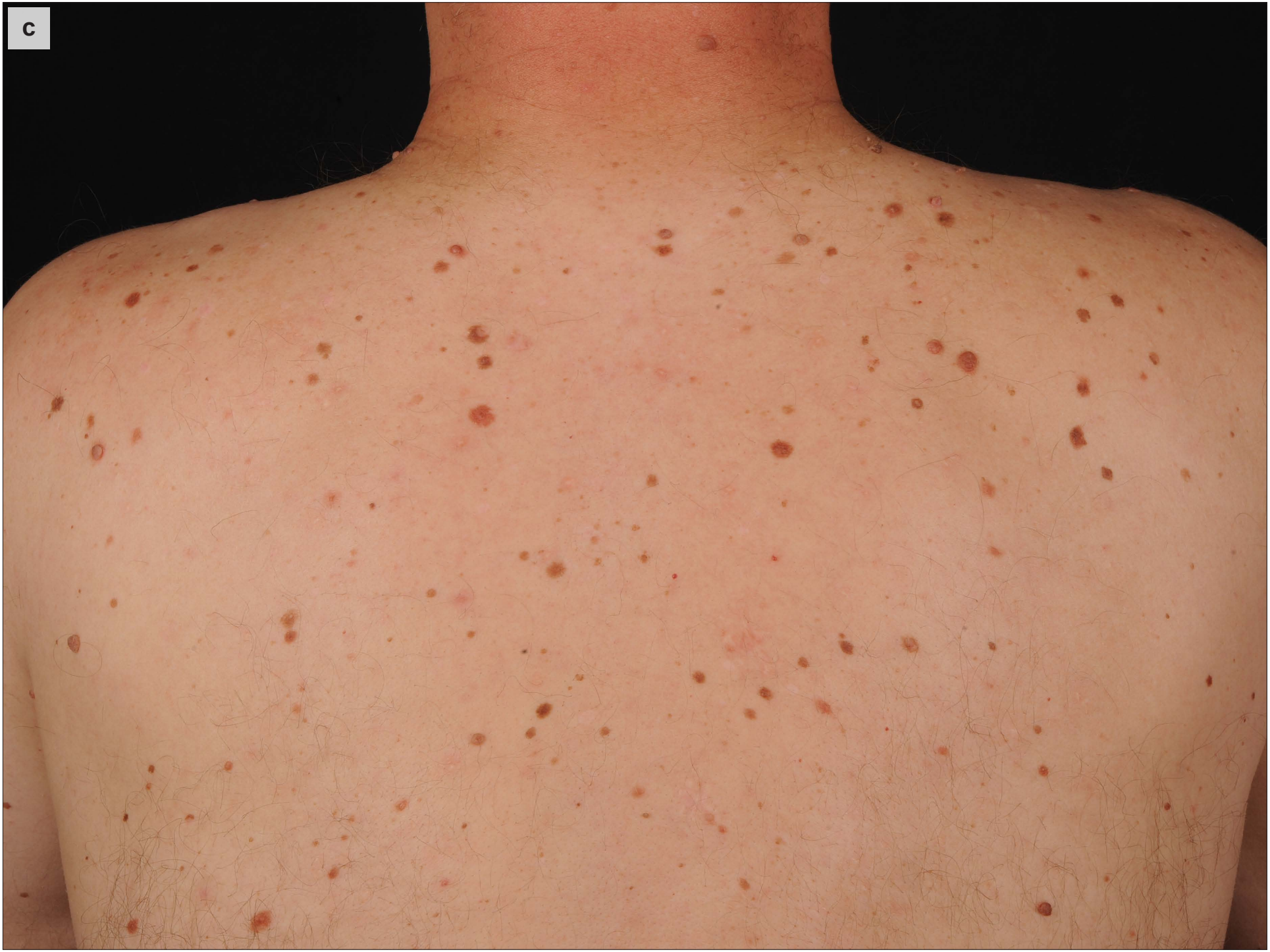

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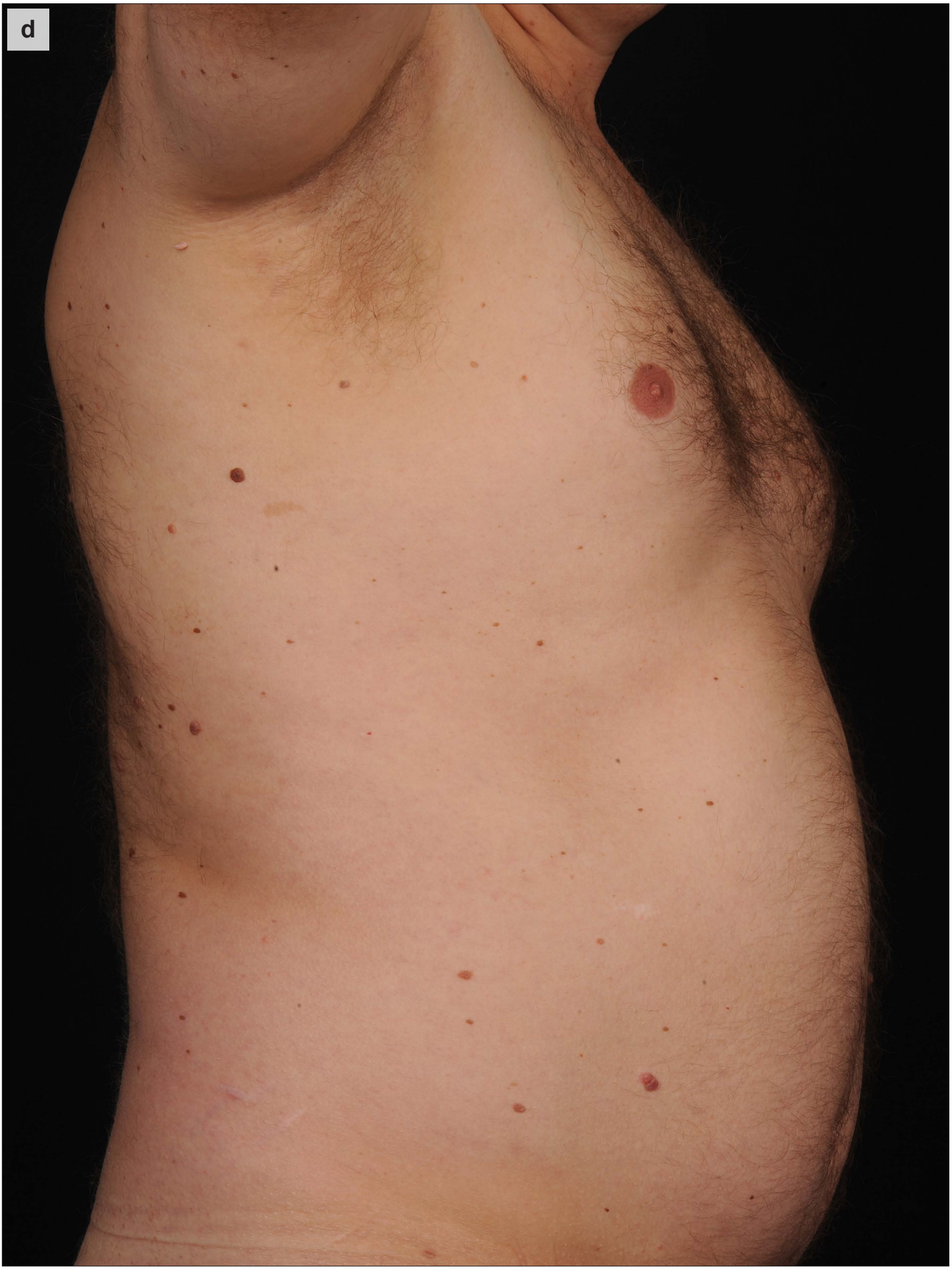

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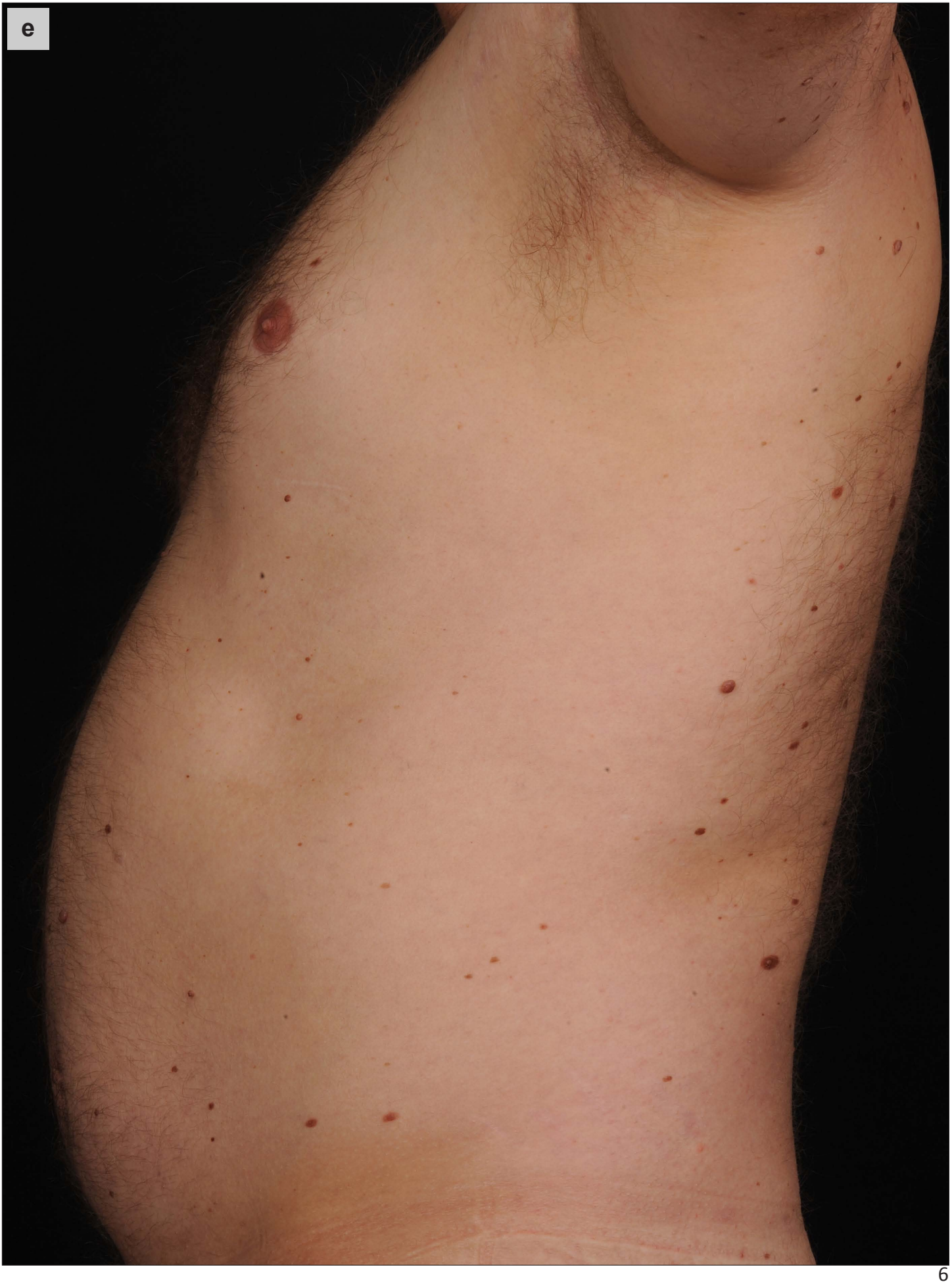

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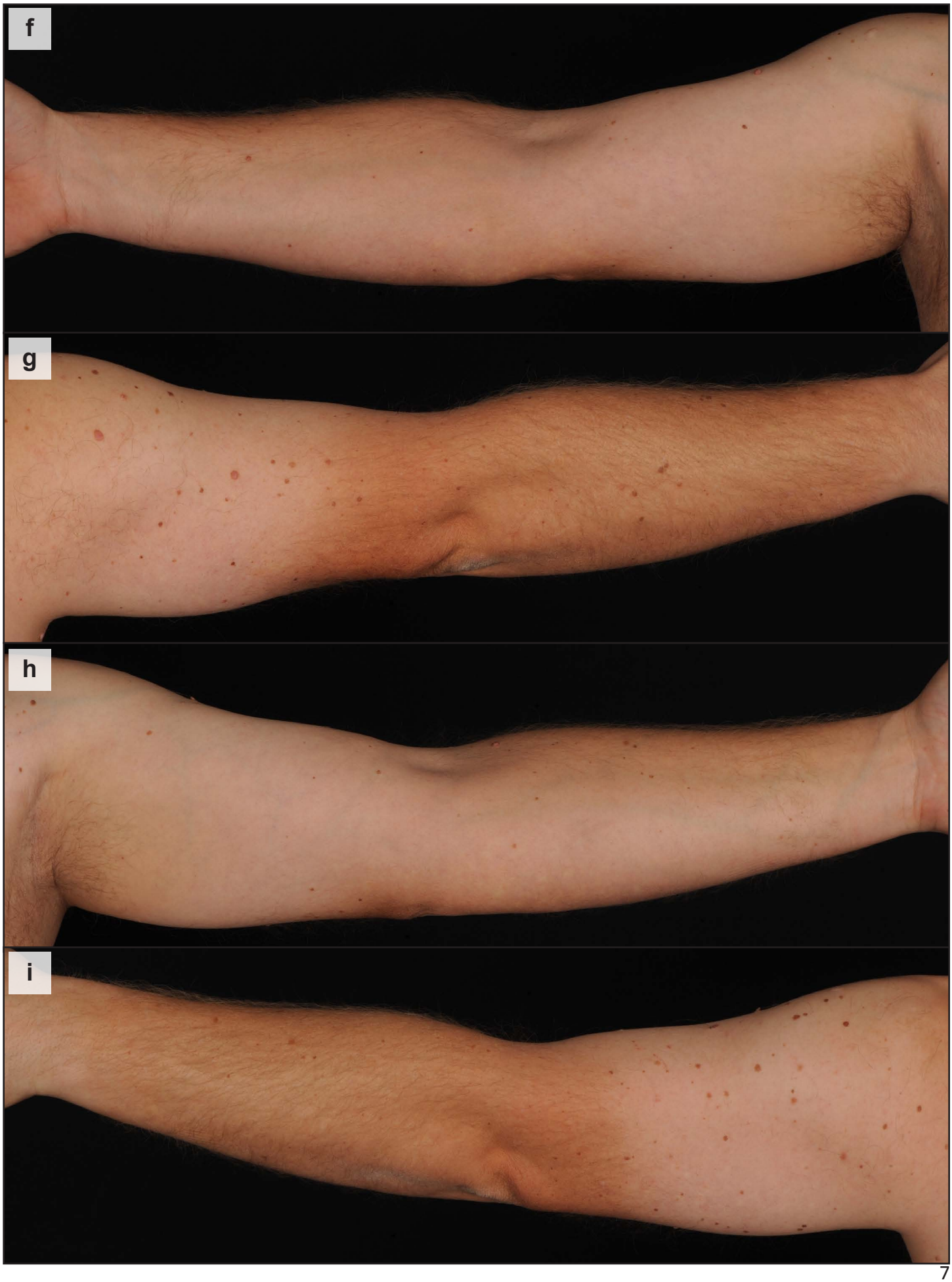

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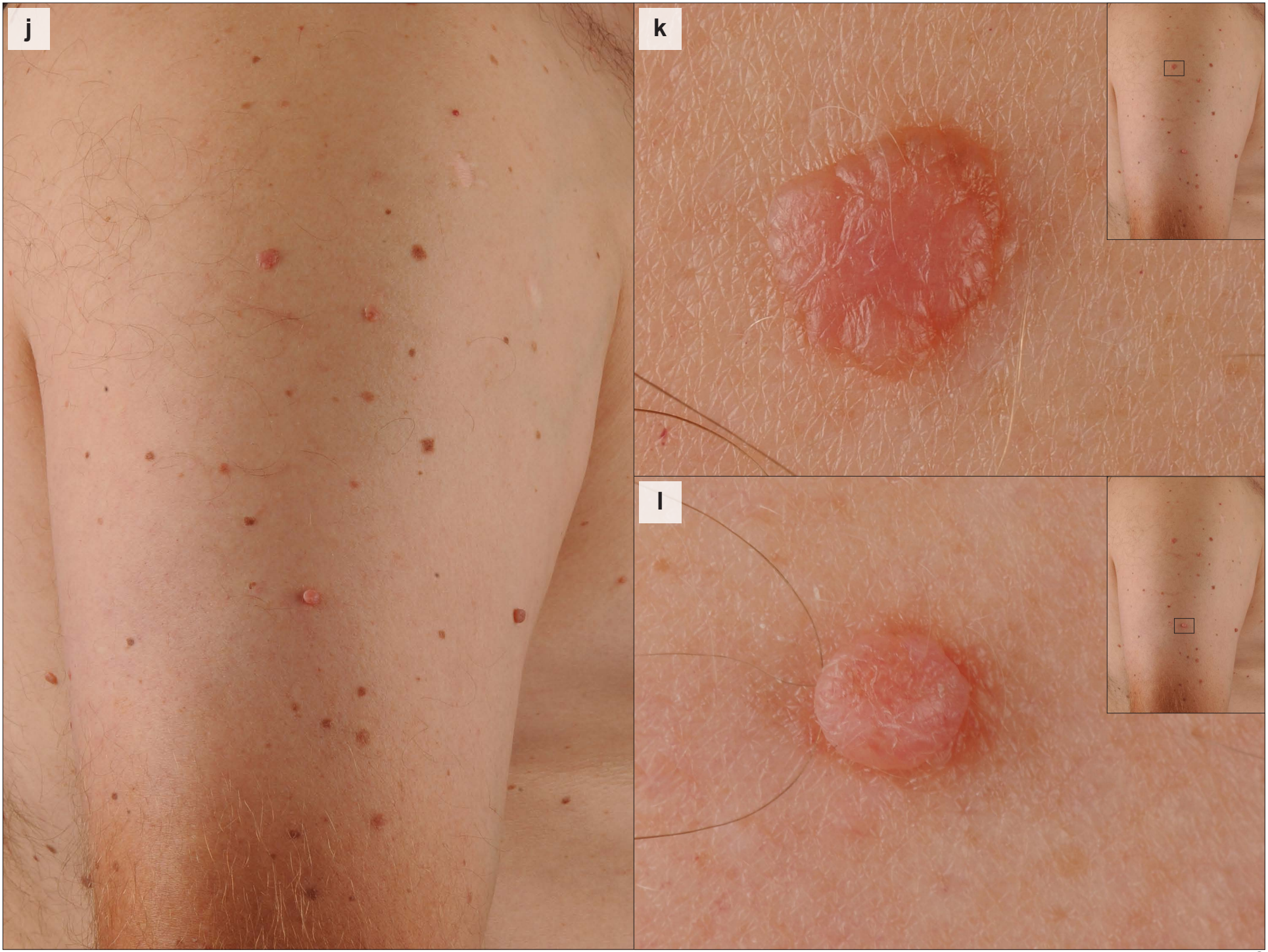

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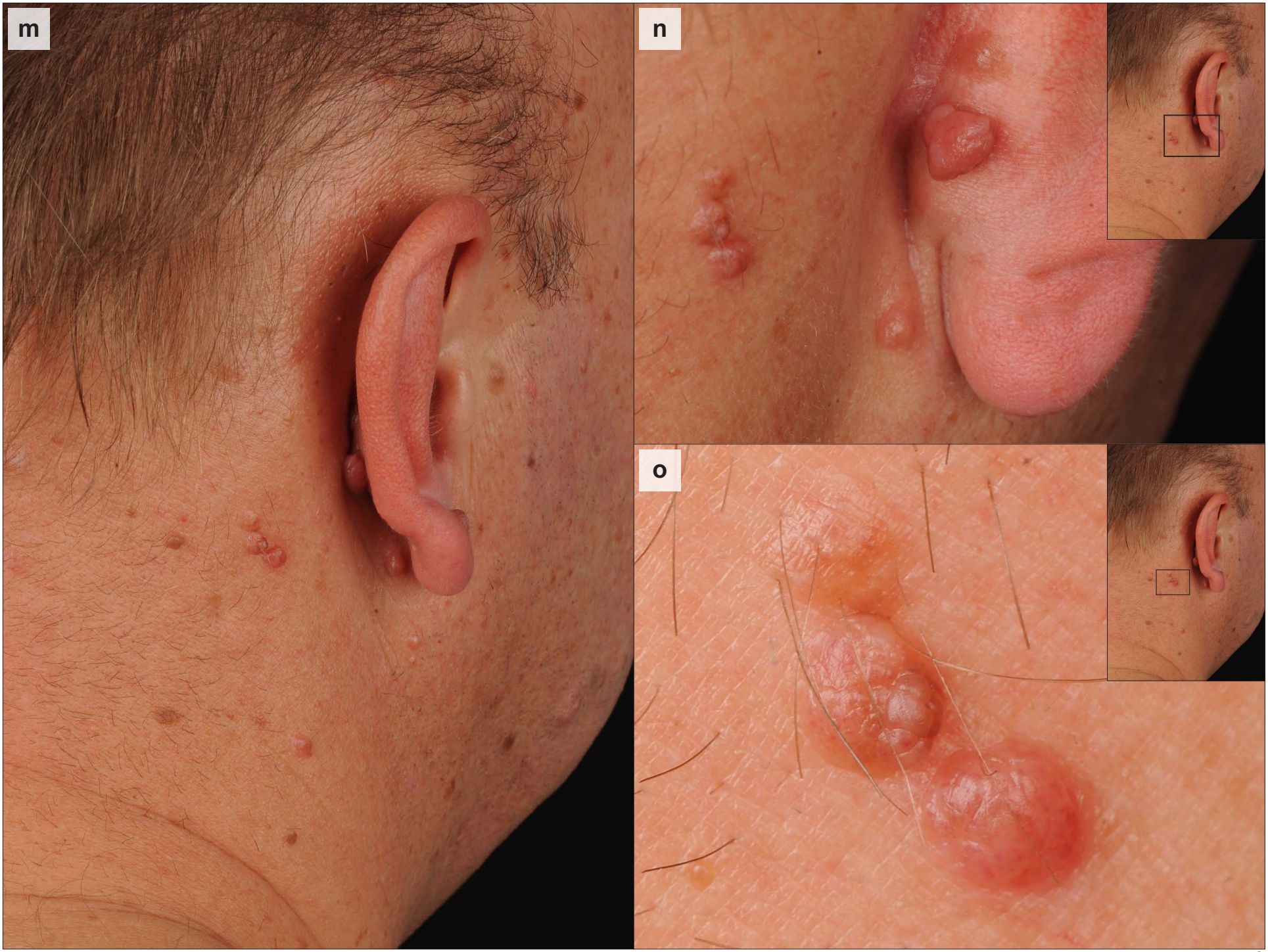

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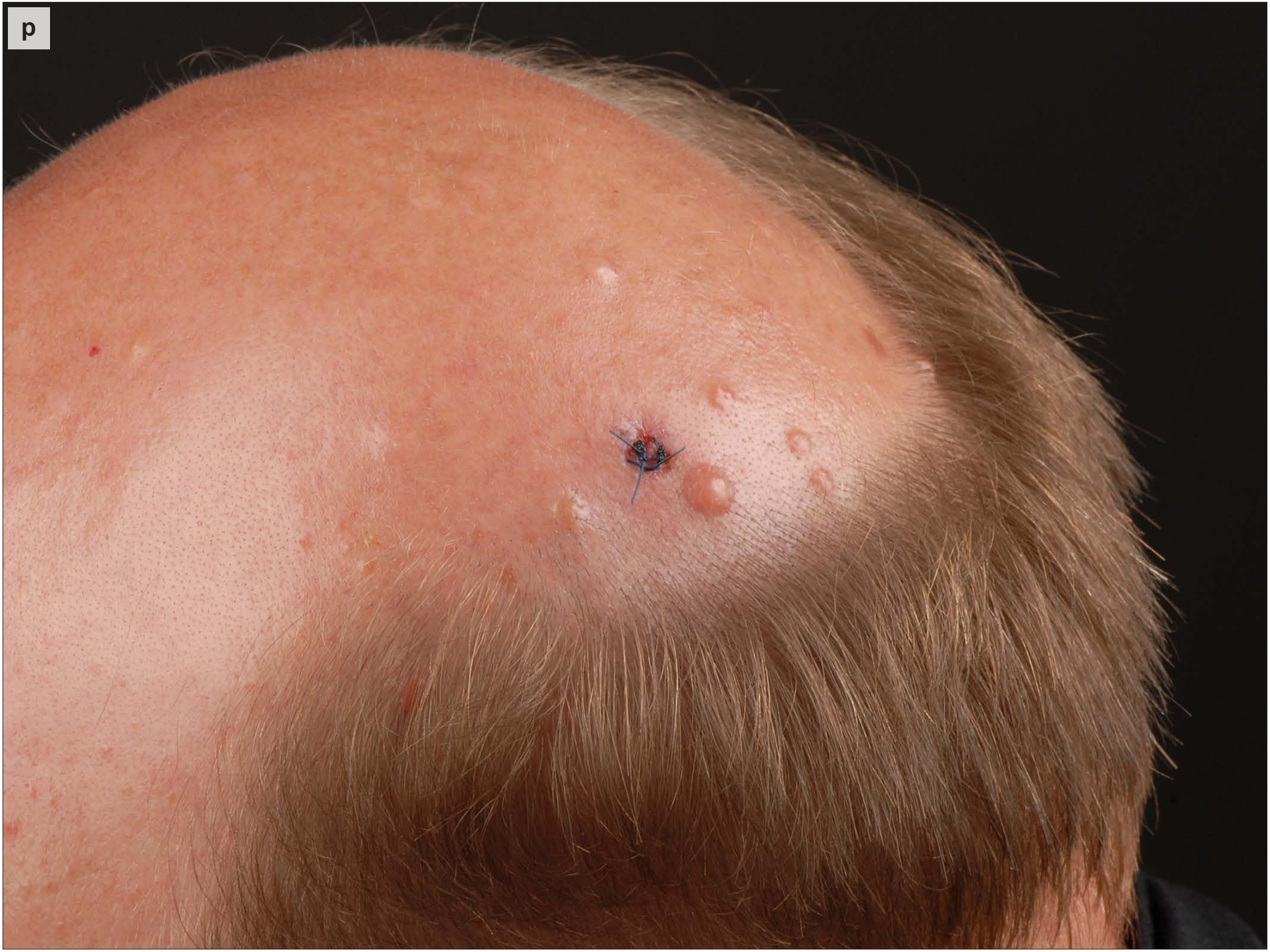

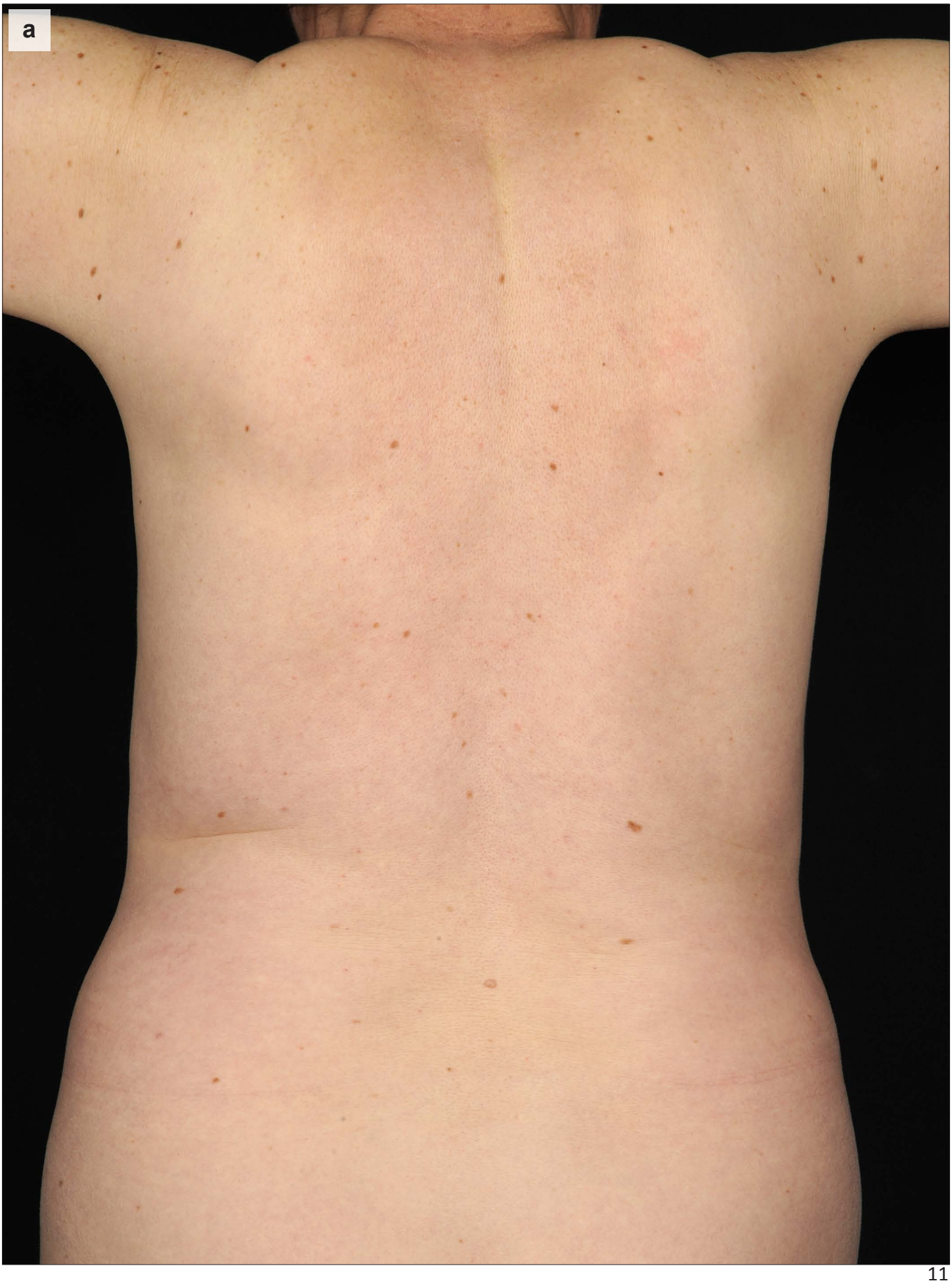
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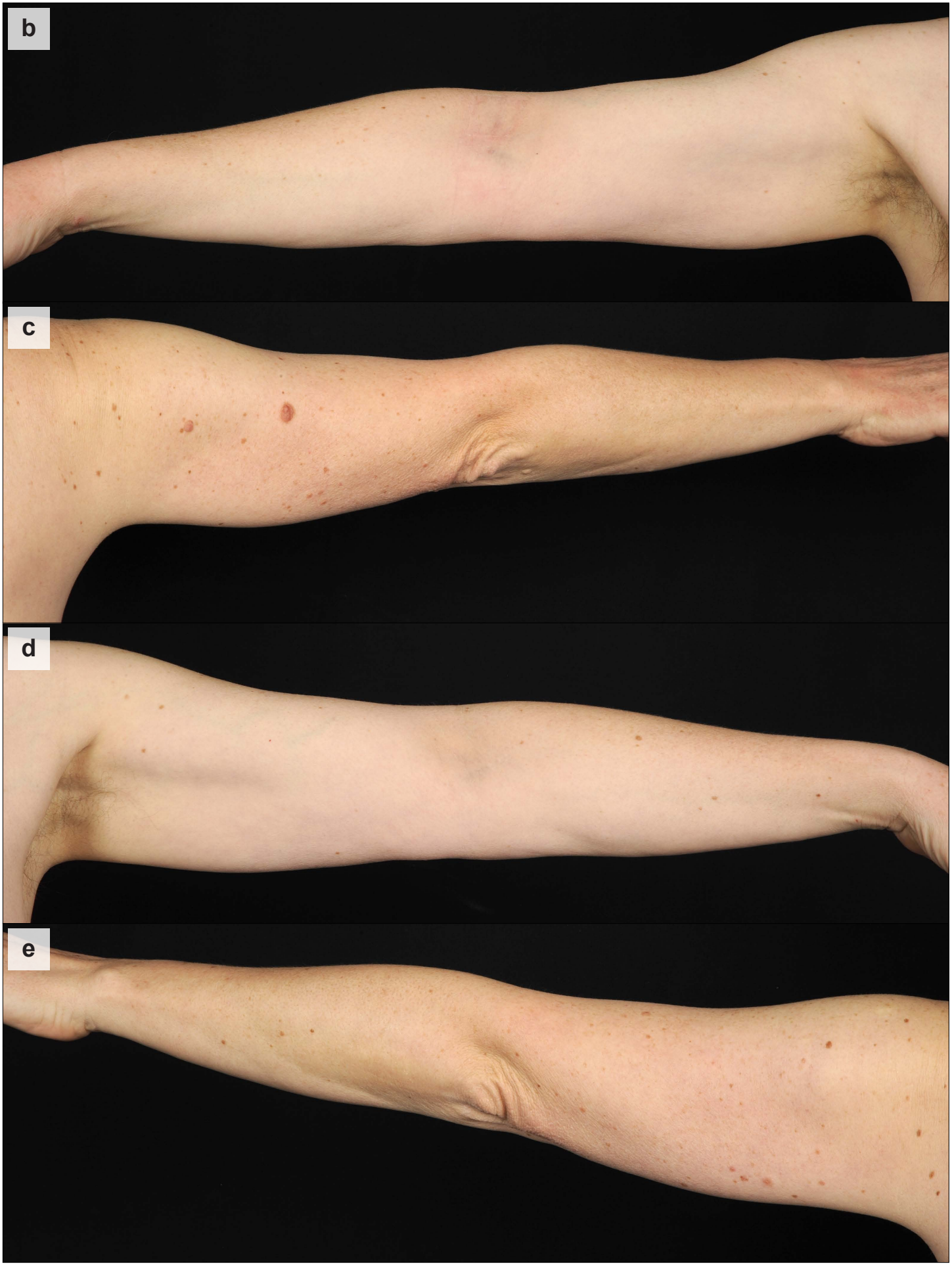

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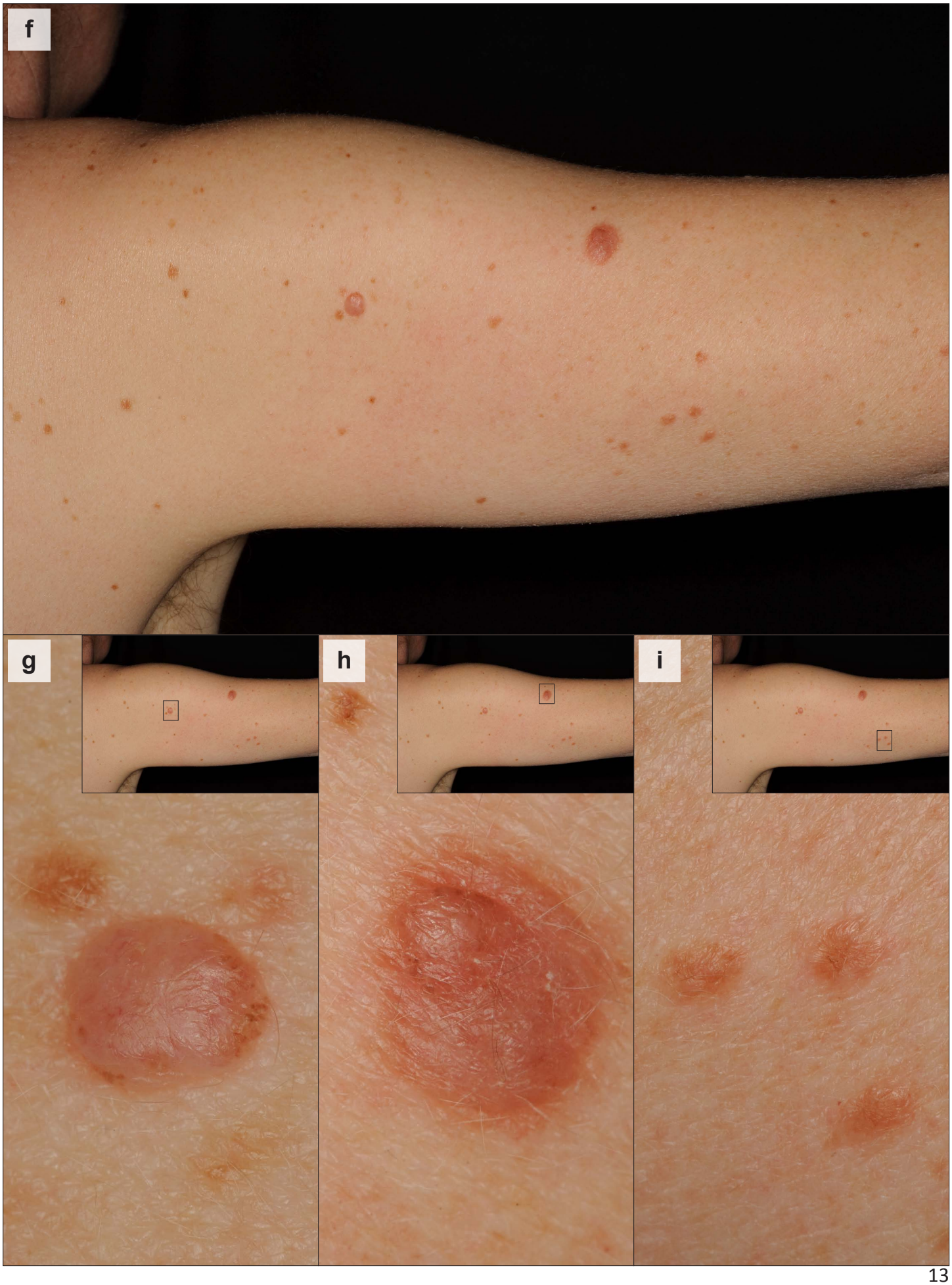

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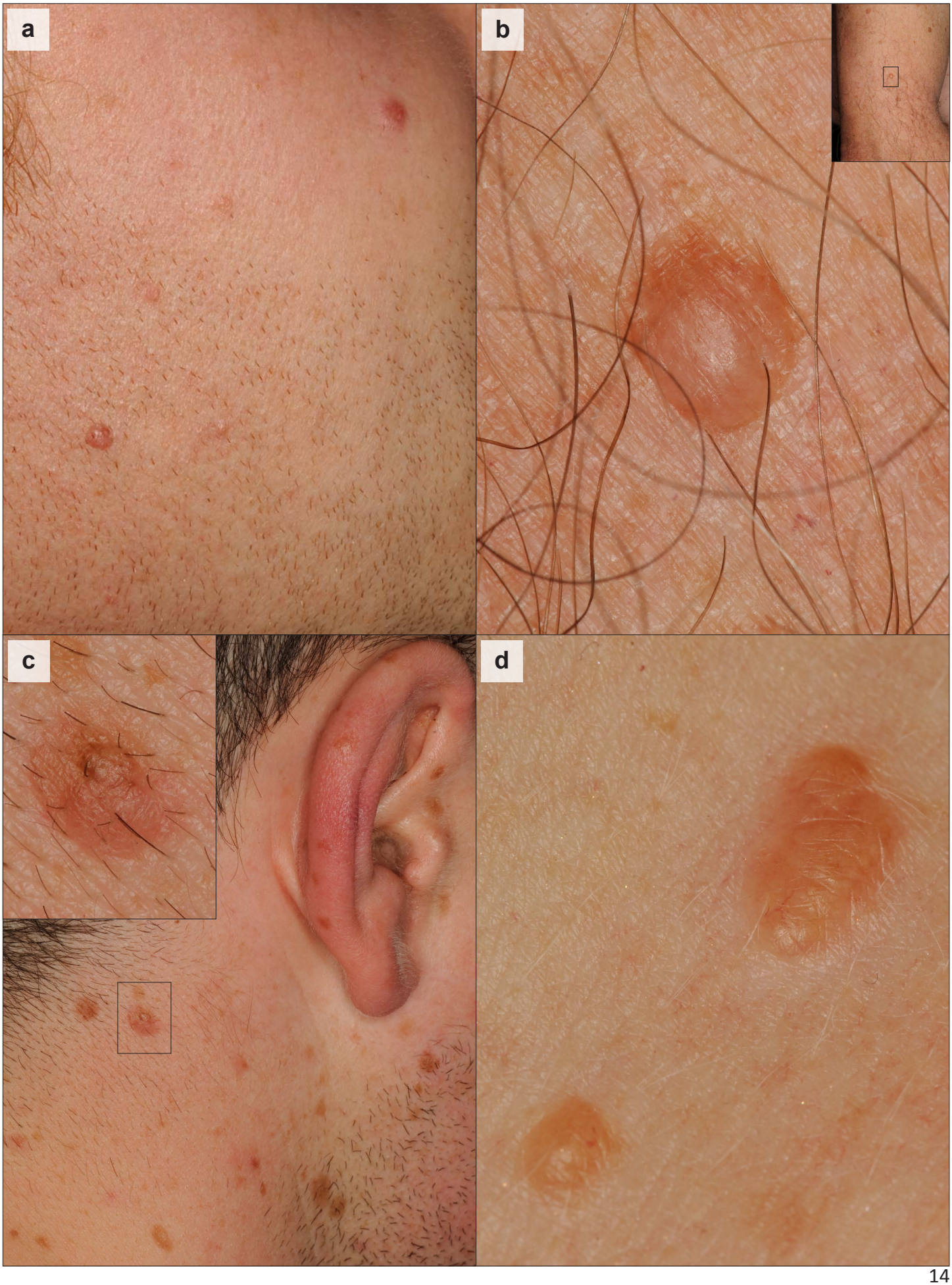

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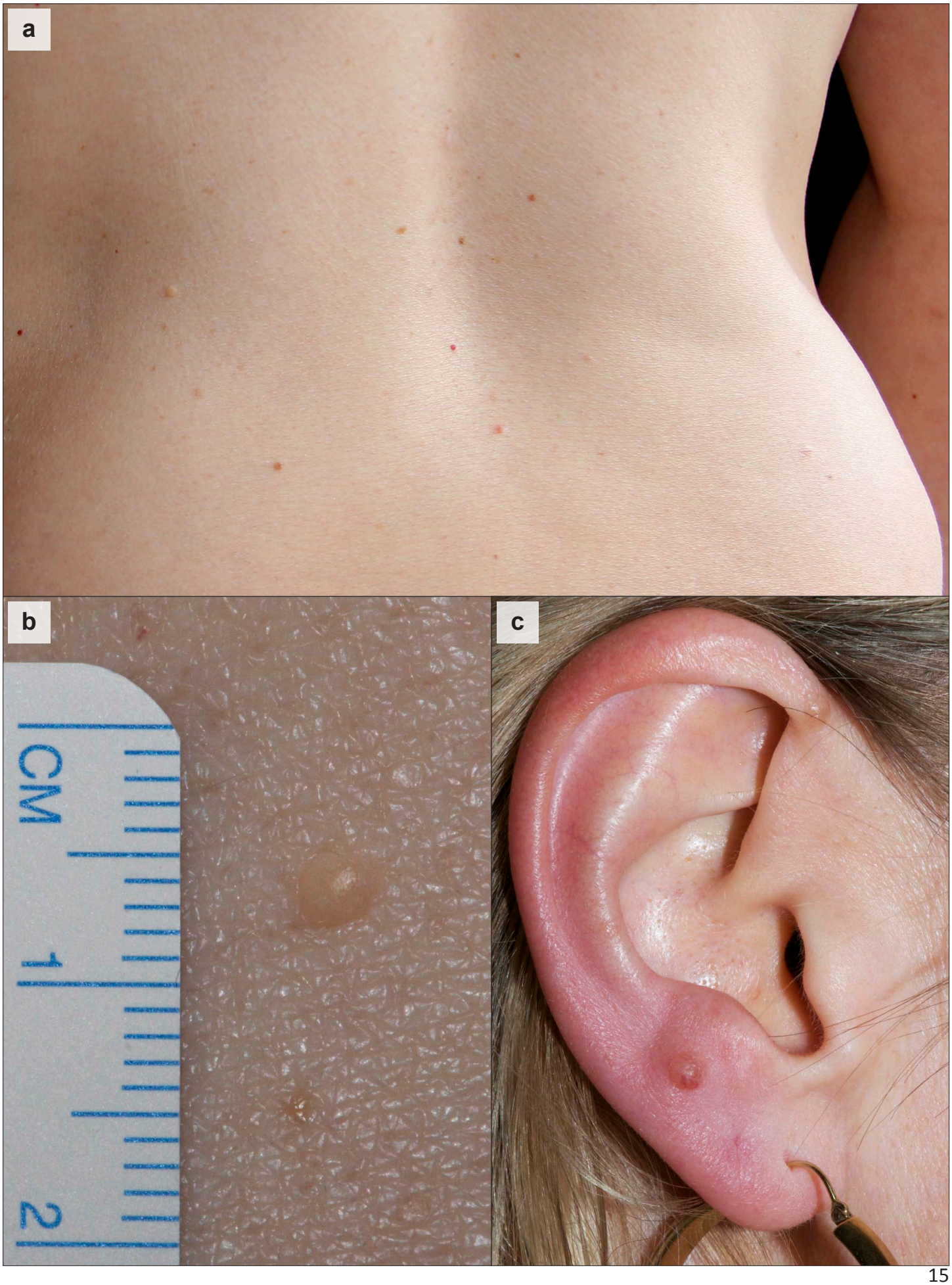

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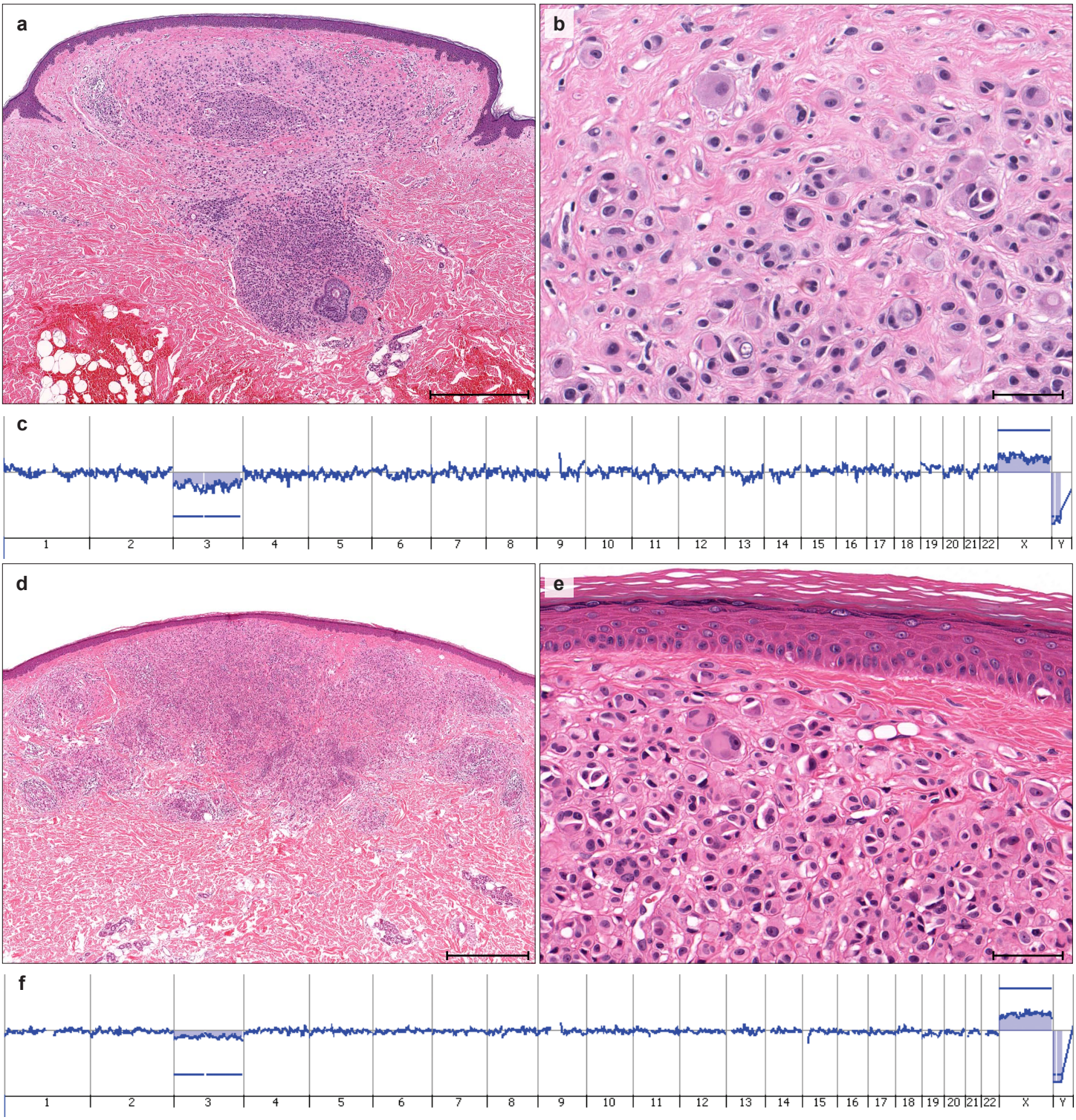
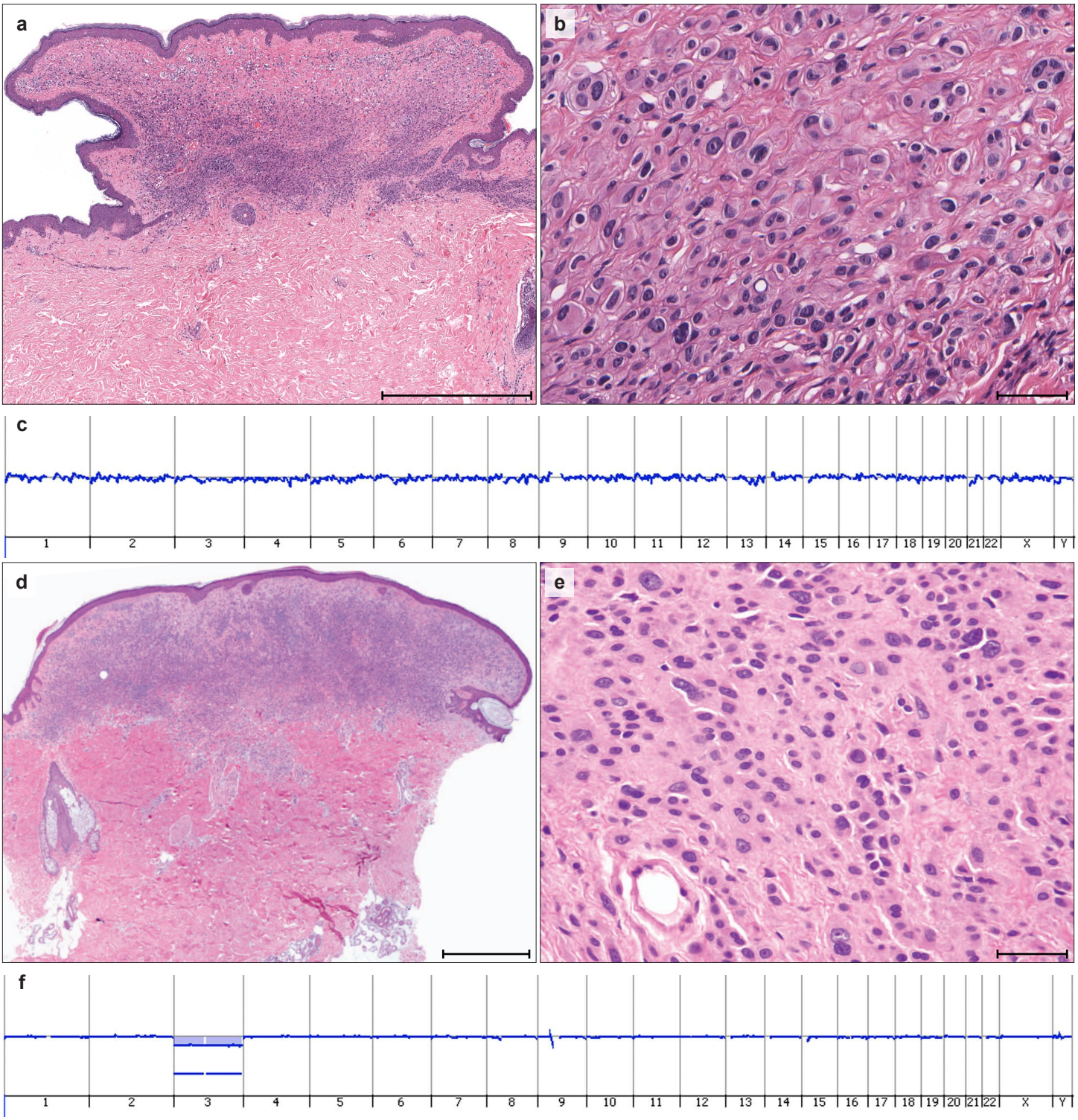


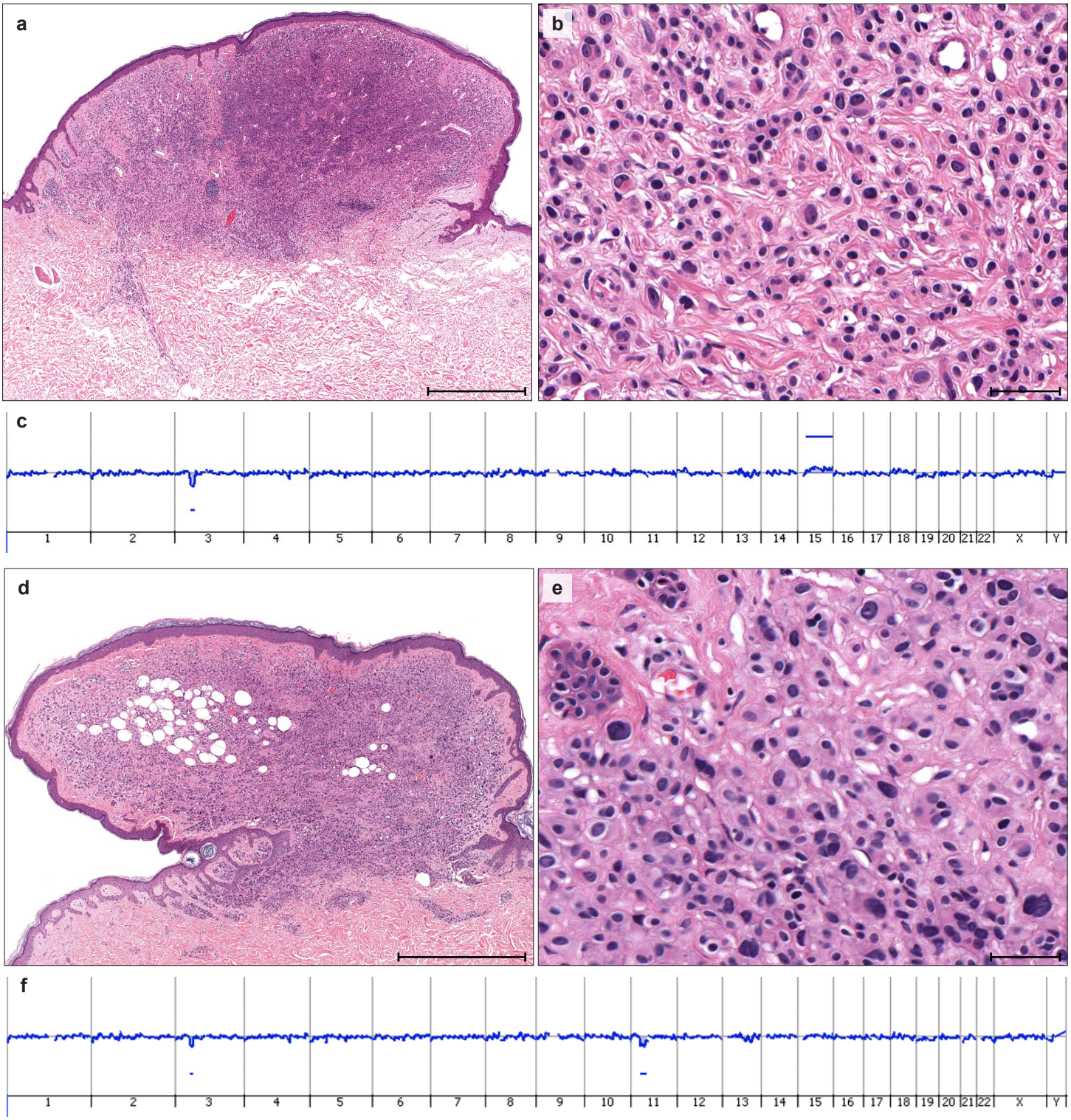
Supplementary Figure 5. Histopathology of melanocytic tumors with loss of chromosome 3.
(**a-c**) Tumor #19, patient II-4 (Supplementary Table 2). (**a**) Intradermal melanocytic tumor. Scale bar, 1 mm. (**b**) The cytological features of some of the cells were reminiscent of Spitz nevi, however, other characteristic features such as junctional nests of melanocytes with clefts and epidermal hyperplasia were consistently absent. Scale bar, 50 µm. (**c**) The aCGH profile shows a loss of the whole chromosome 3.
(**d-f**) Tumor #26, patient III-7 (Supplementary Table 2). (**d**) The dermal melanocytic tumor (scale bar, 1 mm) was composed of (**e**) epithelioid cells with pleomorphic nuclei (scale bar, 50 µm) and (**f**) showed loss of chromosome 3 in aCGH.

Supplementary Figure 6



Supplementary Figure 6. Histopathology of additional representative melanocytic tumors.
(**a-c**) Tumor #8, patient II-1 (Supplementary Table 2). (**a**) The tumor contains areas composed of smaller nevoid melanocytes as seen in common acquired nevi (darker blue regions) and areas with larger epithelioid cells (pale pink regions). Scale bar, 1 mm. (**b**) Higher magnification shows small melanocytes with oval, monomorphic nuclei and larger epithelioid cells with pleomorphic nuclei. Scale bar, 50 µm.(**c**) The corresponding aCGH profile showed no chromosomal aberrations, but the electropherogram displayed complete loss of the wild-type sequence, indicating maternal uniparental disomy (not shown).
(**d-f**) Tumor #1, patient III-3 (Supplementary Table 3). (**d**) The tumor (scale bar, 1 mm) shows a largely symmetrical proliferation (**e**) of epithelioid melanocytes with pleomorphic nuclei (scale bar, 50 µm). There was imperfect maturation, i.e. the melanocytes did not significantly decrease in size with descent into the dermis. (**f**) The aCGH profile showed a loss of chromosome 3, but no other aberrations.

Supplementary Figure 7

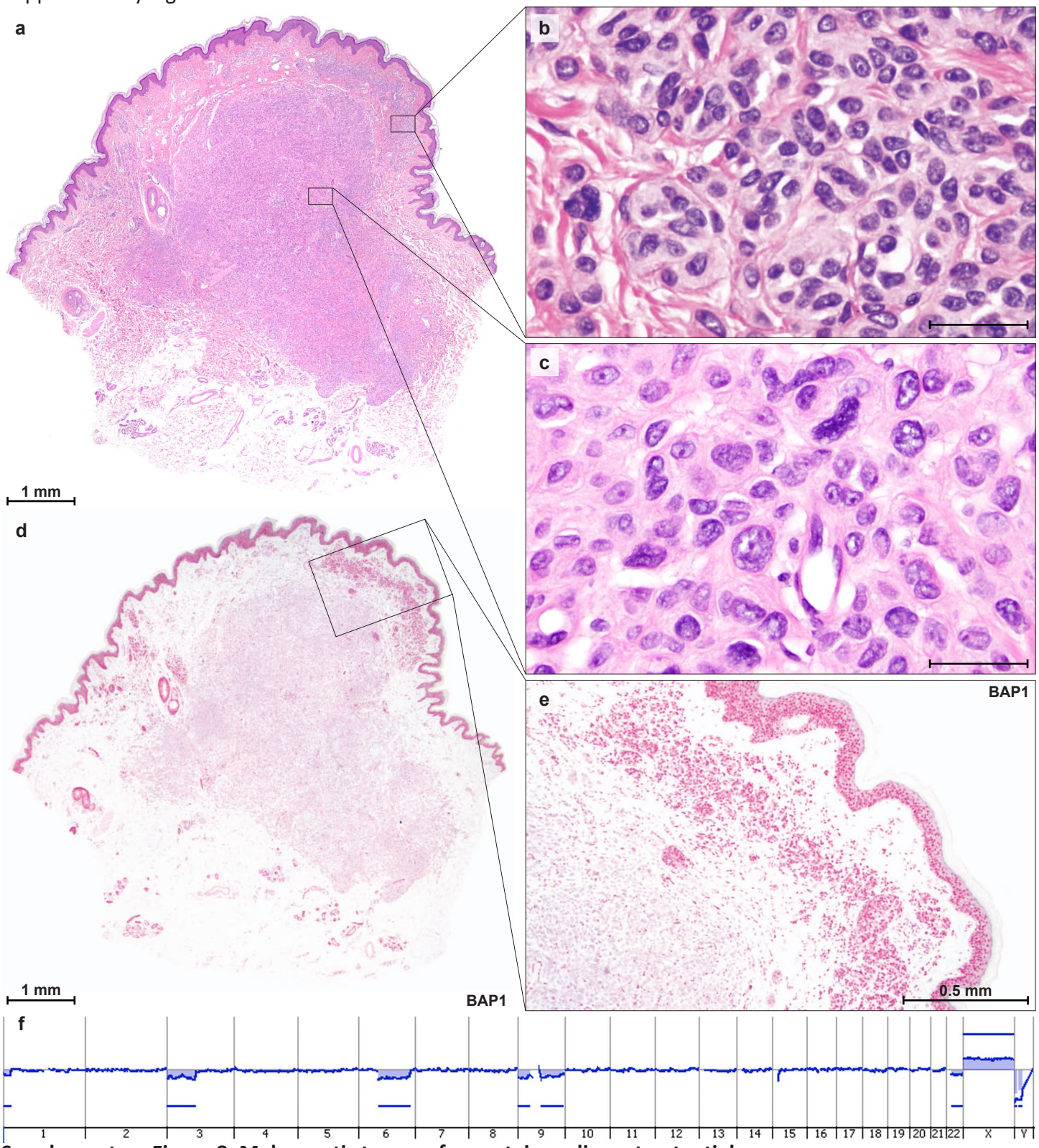


Supplementary Figure 7. Histopathology of melanocytic tumors that show loss of 3p21 and additional chromosomal aberrations.

(**a-c**) Tumor #1, patient II-1 (Supplementary Table 2). (**a**) The dome shaped tumor (scale bar, 1 mm) showed (**b**) small melanocytes with oval, monomorphic nuclei and larger epithelioid cells with pleomorphic nuclei. Scale bar, 50 µm. Mitotic figures were scarce. (**c**) The aCGH profile showed, in addition to the loss of 3p21, a gain of chromosome 15.

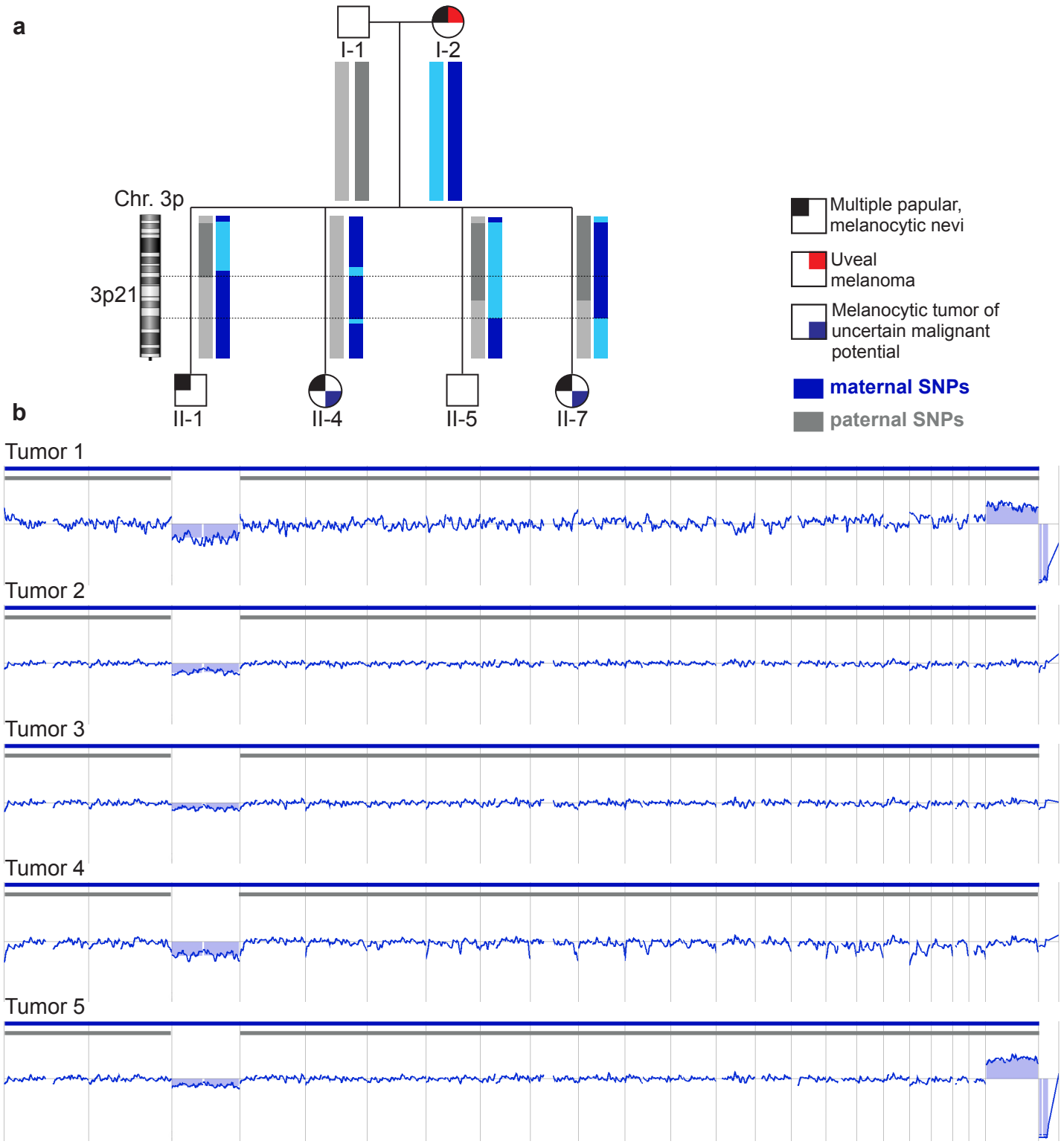
(**d-f**) Tumor #2, patient II-1 (Supplementary Table 2). (**d**) The polypoid intradermal tumor (scale bar, 1 mm) with admixed adipocytes showed (**e**) pleomorphic epithelioid melanocytes. Scale bar, 50 µm. (**f**) The aCGH profile showed two losses: one in chromosome 3p21 and one in chromosome 11.

Supplementary Figure 8



Supplementary Figure 8. Melanocytic tumor of uncertain malignant potential.
(**a-f**) Tumor #8, patient III-2 (Supplementary Table 3). (**a**) Nodular, asymmetric, predominantly dermal proliferation of (**b**) small melanocytes in the superficial dermis and (**c**) large epithelioid melanocytes in the deeper dermis. Scale bar, 50 µm) The atypical epithelioid melanocytic cells show considerable nuclear pleomorphism, moderate to large amounts of cytoplasm, and focally prominent nucleoli. One mitotic figure was found. (**d, e**) Immunohistochemistry of *BAP1* shows no expression in the larger epithelioid cells, but strong nuclear expression in the small melanocytes situated in the superficial dermis. (**f**) aCGH showed typical chromosomal aberrations seen in melanoma, including losses of chromosomes 1, 3, 6, 9 and 22. The numerous genomic aberrations support the presumption of uncertain malignant potential.

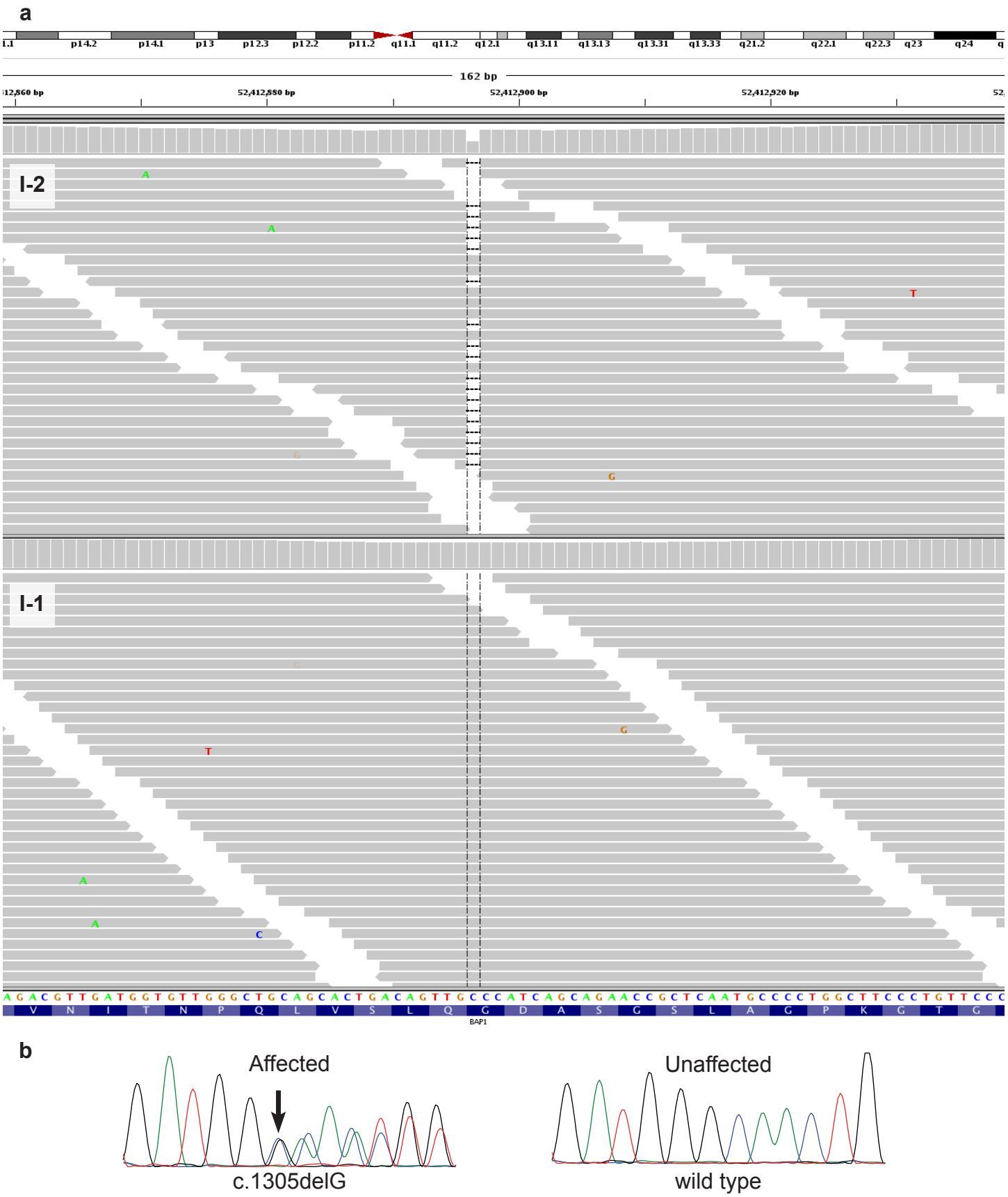
Supplementary Figure 9



Supplementary Figure 9. Reconstruction of the haplotypes of 6 members of family 1 and loss of the paternal chromosome 3 in the melanocytic tumors.

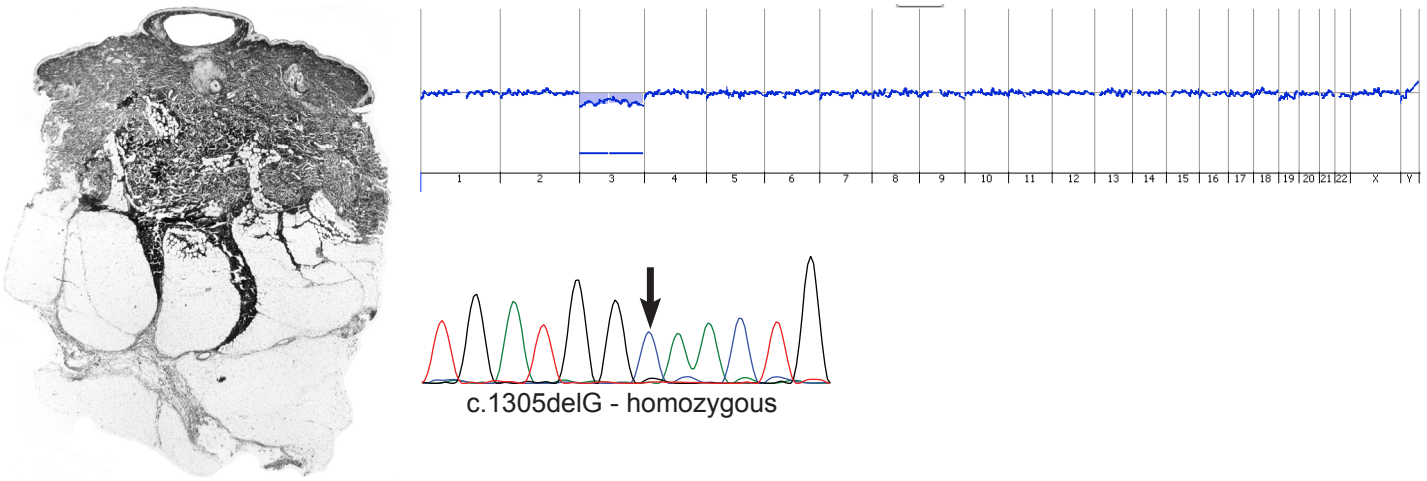
(**a**) Pedigree of family 1. The haplotypes of the father (I-1) are shown in gray and those of the mother (I-2) in blue. The corresponding haplotypes of their children were reconstructed with the Affymetrix GeneChip Mapping 500K array NspI chip. Note that all three affected children (II-1, II-4, and II-7) have the same maternal allele for the candidate region (dark blue) whereas the non-affected son (II-5) inherited the other maternal allele (light blue). We were not able to narrow down the candidate region with the genotyping data, because the conjointly inherited 3p21 region overlapped the minimal deleted region in aCGH on both sides by few Mb. (**b**) SNP-arrays of tumors with chromosome 3 loss illustrated that the paternal copy carrying wild-type allele of *BAP1*, but not the maternal allele harboring the mutated allele was lost.

Supplementary Figure 10

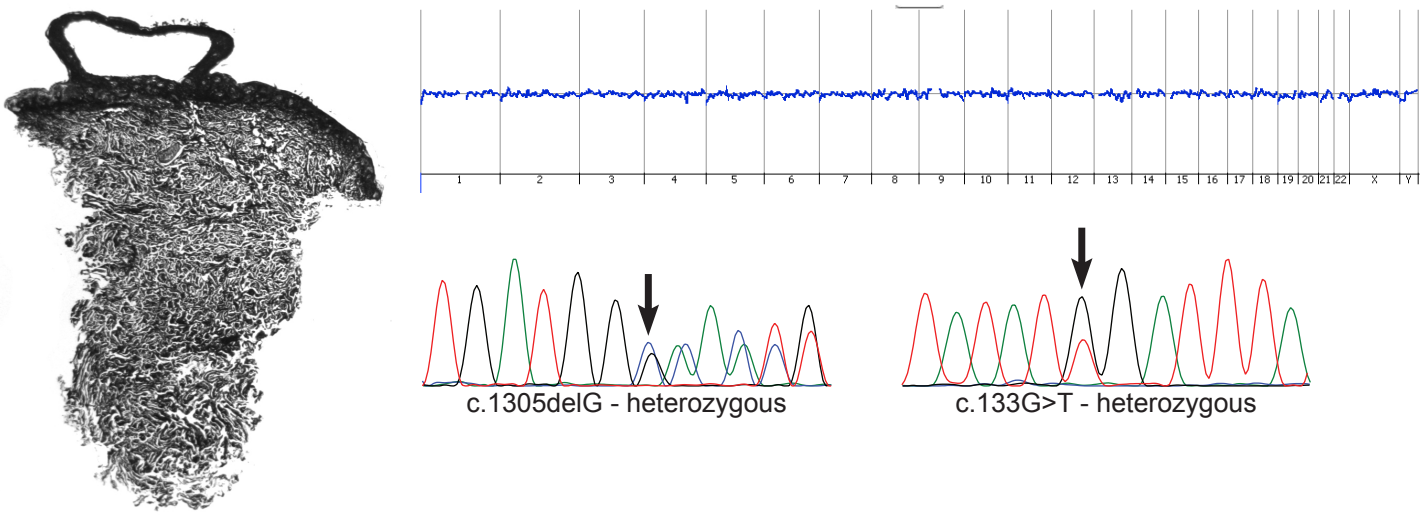


Supplementary Figure 10. *BAP1* germline mutation in family 1.
(**a**) Illustration of the *BAP1* mutation in the Integrative Genomics Viewer (http://www.broadinstitute.org/igv). Patient I-2 has a 1 base pair deletion in exon 13 of *BAP1*, which is evident in the sequence reads (gray arrows). The unaffected subject I-1 does not show this deletion. (**b**) Representative electropherograms from affected and unaffected individuals of family 1.

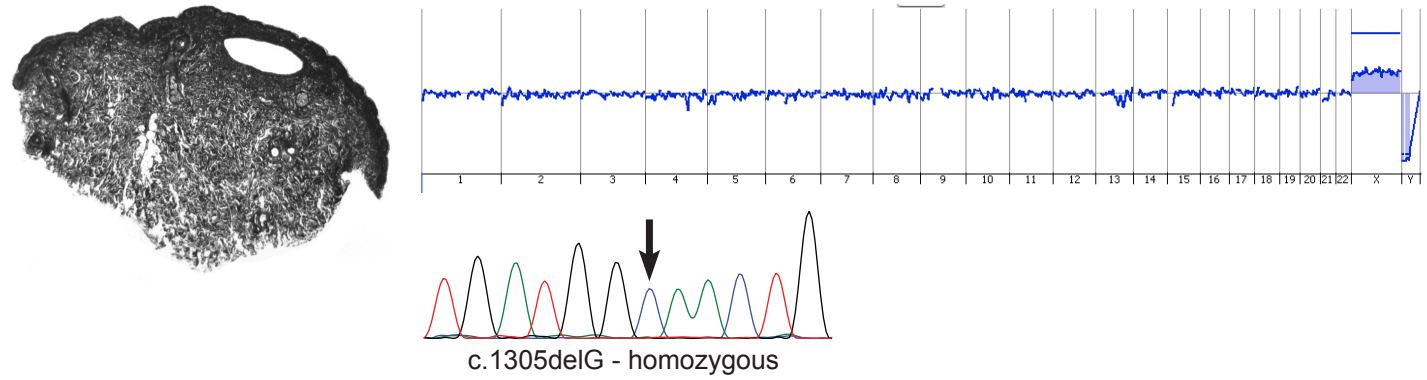
a Loss of chromosome 3



b Compound heterozygosity



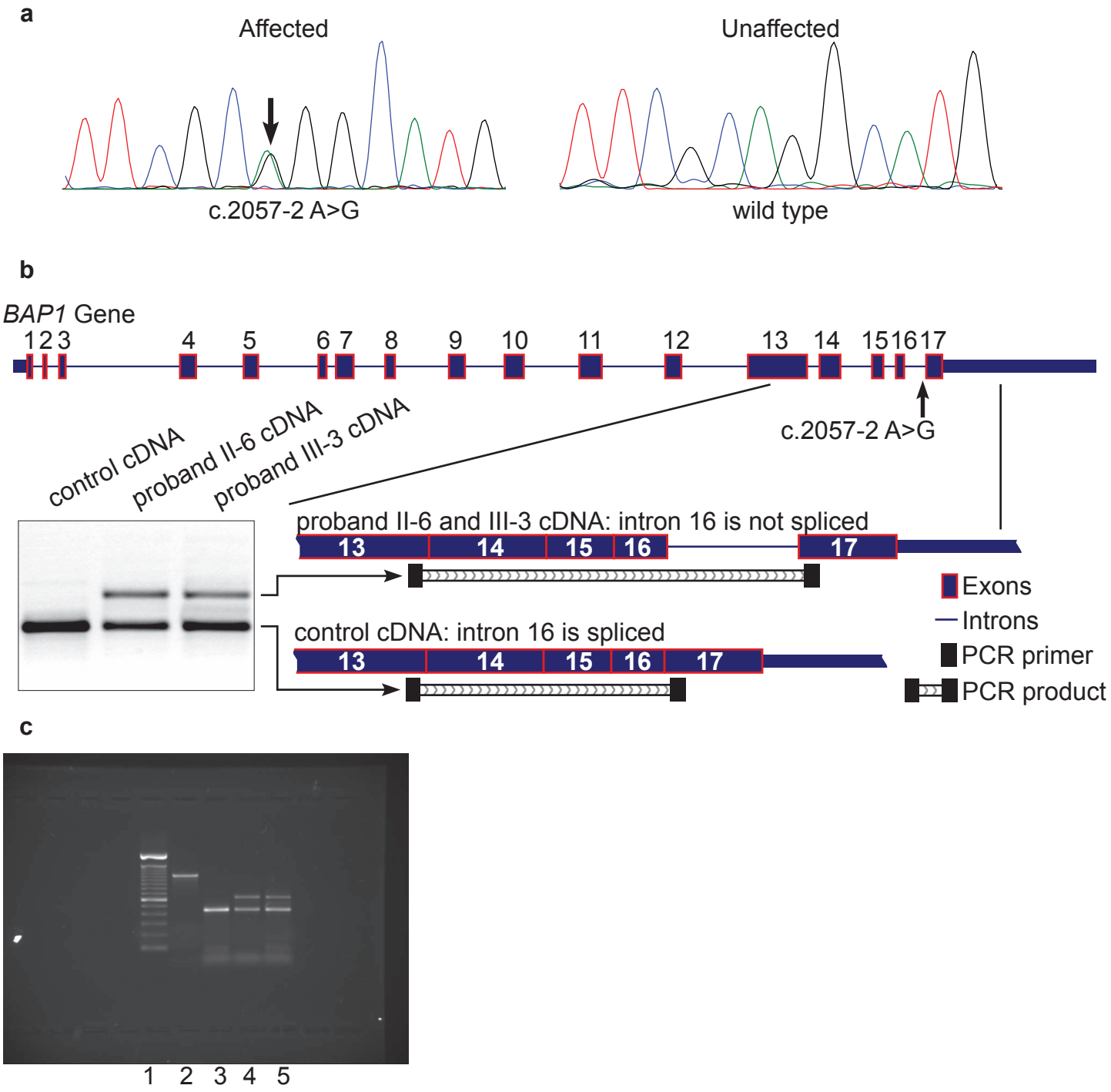
c Maternal uniparental disomy



Supplementary Figure 11. Inactivation of the second *BAP1* allele in three melanocytic tumors by various mechanisms.

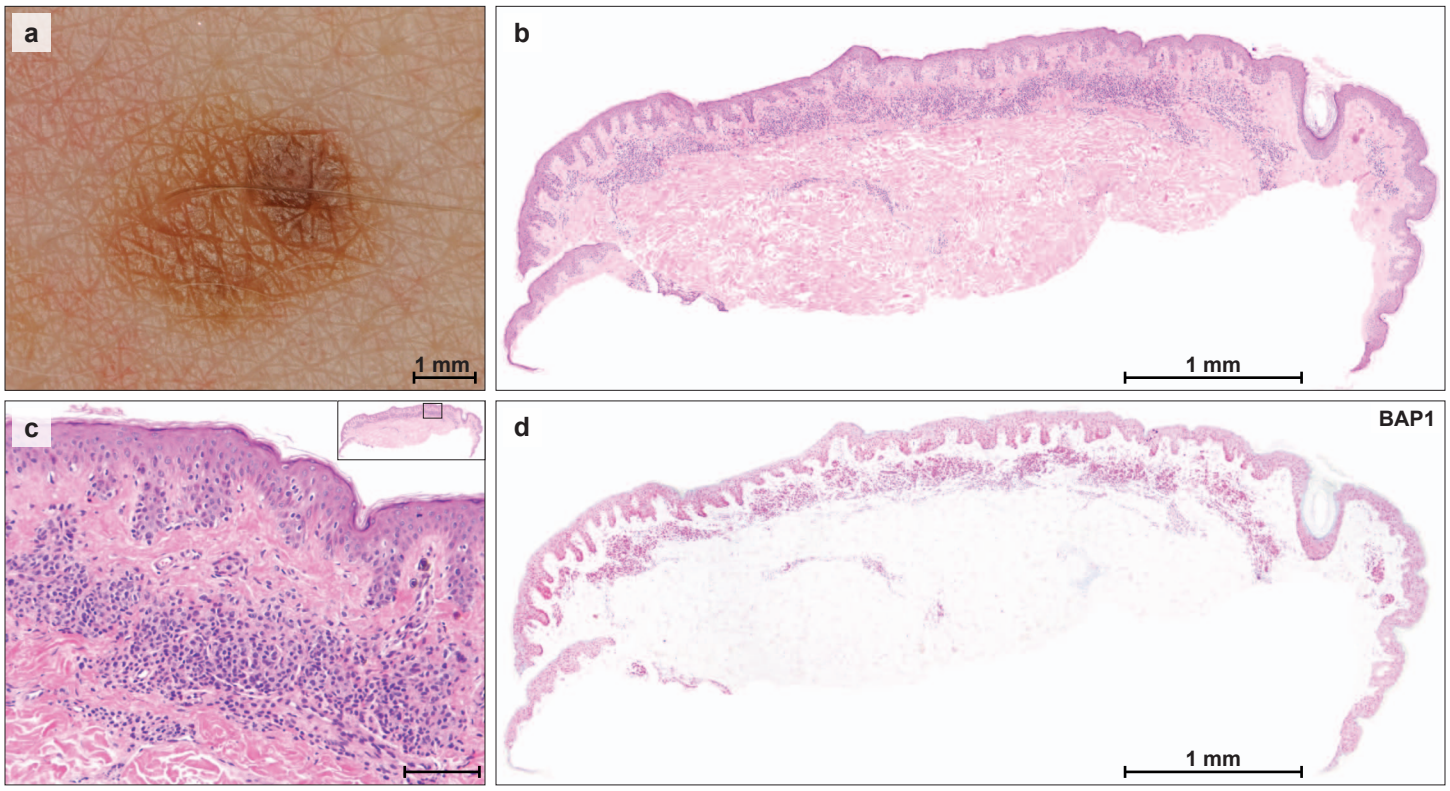
Left panel: Laser-capture microdissection images of histologic sections; right upper panel: aCGH profile; right lower panel: sequencing electropherograms of *BAP1*. (**a**) aCGH shows a loss of chromosome 3 and the sequencing electropherogram indicates a complete loss of the wild type sequence. (**b**) aCGH reveals no copy number changes, but in addition to the germline mutation, a second mutation (c.133G>T, p.Gly45*) was found. (**c**) Although aCGH shows no loss of 3p21, the electropherogram indicates a complete loss of the wild type sequence indicative of maternal uniparental disomy.

Supplementary Figure 12



Supplementary Figure 12. *BAP1* germline mutation in family 2.
(**a**) Representative electropherograms from affected and unaffected individuals of family 2. (**b**) Consequences of *BAP1* mutations on mRNA splicing. Control RNA and RNA from 2 individuals from family 2 (II-6, III-3) was reverse transcribed into cDNA, amplified with PCR primers annealing on exon 13 and 17 (Supplementary Table 9), and separated on a 1% agarose gel. While the PCR product of control cDNA contains only the exons (introns are spliced out) and has the correct predicted size of 355 bp, the PCR products of the two affected patients have two sizes: one is the correctly spliced form (355bp) and the other – as a consequence of the splice site mutation – is an abnormal PCR product of 535 bp (355 + 180 bp of intron 16). (**c**) Non-cropped, original gel picture of Supplementary Figure 12b. Lane 1: 100bp ladder; Lane 2: PCR product of DNA, which includes all exons and intron between exon 13 and 17 showing an expected size of 1106bp. Lane 3: PCR product of control cDNA with an expected size of 355bp. Lane 4, 5: cDNA from subject II-6 and III-3 showing two PCR products with the expected size of 355bp (normal) and 535 bp (splice site mutation).

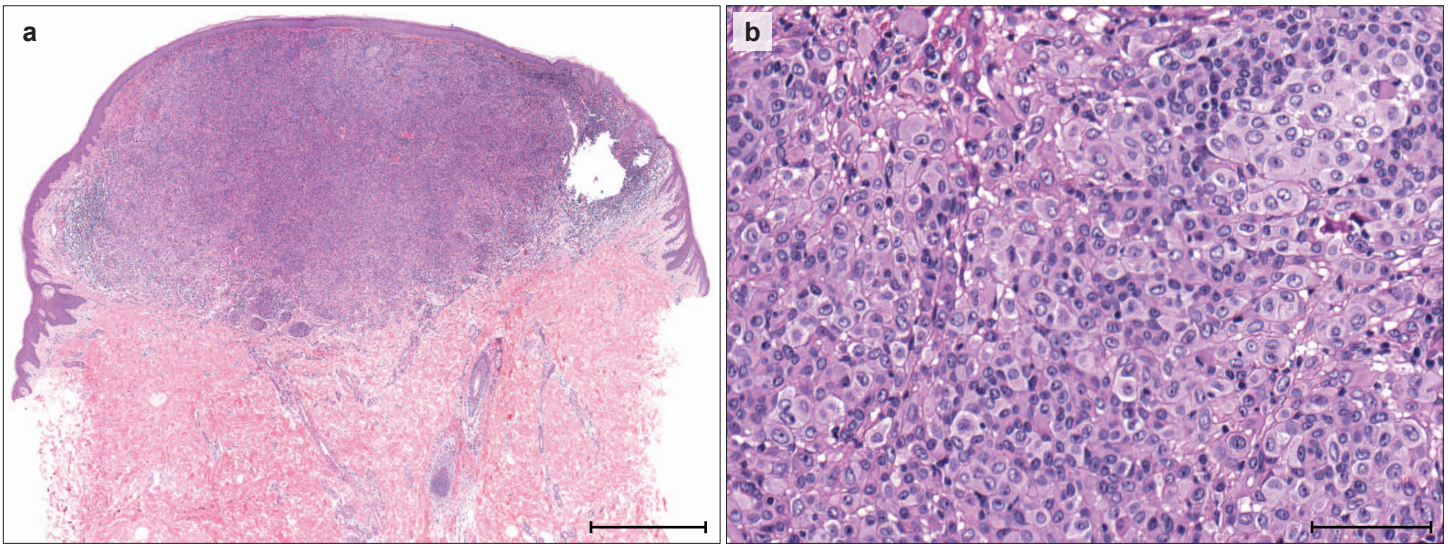
Supplementary Figure 13



Supplementary Figure 13. Flat, brown nevi composed of small uniform melanocytes do not show alterations of *BAP1*.

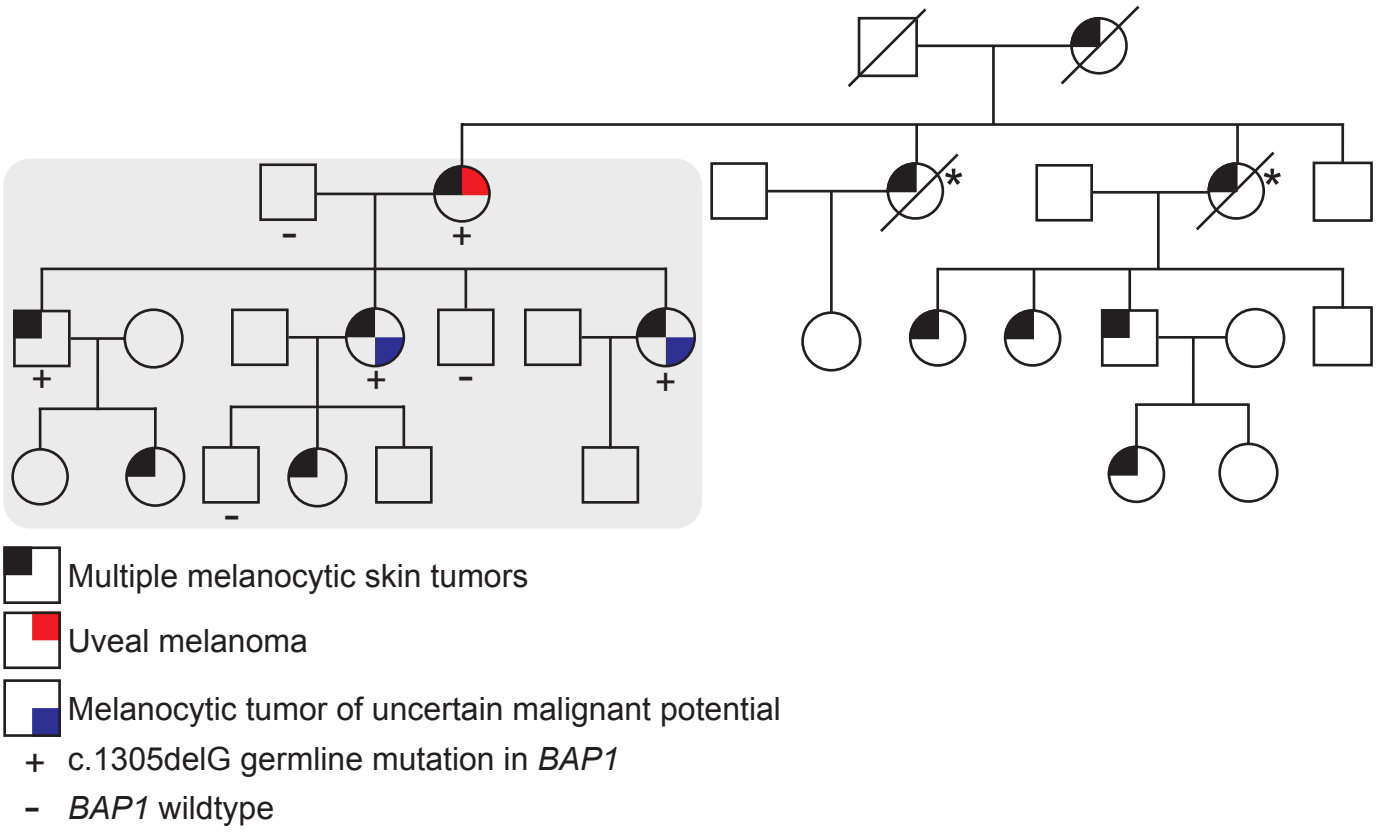
(**a**) A small and flat, brown pigmented nevus of patient III-4, family 2. (**b**) Low magnification shows a band-like proliferation of melanocytes. (**c**) Higher magnification shows small uniform melanocytes in the dermis and at the dermo-epidermal junction, but no large epithelioid cells. Scale bar, 100 µm. (**d**) Immunohistochemisty shows strong expression of BAP1 in the melanocytes. These results suggest that the clinical manifestations of *BAP1* mutated melanocytic neoplasms are usually non-pigmented papules, rather than flat, brown macules.

Supplementary Figure 14



Supplementary Figure 14. Sporadic atypical Spitz tumor with a somatic acquired *BAP1* mutation.
(**a**) Low magnification of an atypical Spitz tumor from a 13-year-old boy (case #2, Supplementary Table 6) showing a relatively symmetrical nodular melanocytic proliferation. No junctional component or epidermal hyperplasia is present. Scale bar, 1 mm. (**b**) Higher magnification shows large epithelioid melanocytes exhibiting abundant cytoplasm, varying degrees of nuclear pleomorphism, vesicular chromatin, and prominent nucleoli. The histological presentation is very similar to the melanocytic neoplasm observed in the family. Sequencing of *BAP1* revealed a nonsense mutation at codon 590, and a *BRAF* V600E mutation. BAP1 was not expressed by immunohistochemistry. Scale bar, 100 µm.

Supplementary Figure 15



Supplementary Figure 15. Extended pedigree of family 1.
Subjects in the grey shaded area are shown in Fig. 1a. In addition to the melanocytic tumors, two other subjects (marked by *) in this family had cancer (one cervical carcinoma and one multiple myeloma). Tissue of these tumors was not available for analysis.

Supplementary Tables

Supplementary Table 1: Clinico-pathological details of melanoma and melanocytic tumors of uncertain malignant potential.

Patient	Age at Diagnosis	Sex	Localization	Histopathological diagnosis	Tumor thickness	Histopathologic features
Family 1						
I-2	72	F	Eye	Uveal melanoma	0.2mm	Transretinal biopsy. Epithelioid and spindle cells with irregular, vesicular and hyperchromatic nuclei; some cells with pronounced nuclear atypia, pleomorphism, and large nucleoli.
II-4	46	F	Shoulder right ventral	Melanocytic tumor of uncertain malignant potential	0.8mm	Asymmetrical proliferation of atypical epithelioid melanocytes in the dermis and focally in the epidermis. Some mitoses. No maturation.
II-7	34	F	Shoulder, left dorsal	Melanocytic tumor of uncertain malignant potential	2.9mm	Relatively symmetrical proliferation of atypical epithelioid melanocytic cells with considerable nuclear pleomorphism. Nucleoli are focally prominent. Also nests of smaller melanocytes with oval nuclei and grayish cytoplasm. Patchy lymphocytic infiltrate. No mitotic figures.
Family 2						
II-1	44	M	Eye	Uveal melanoma	1.5mm	Large, pigmented tumor cells with vesicular nuclei and prominent nucleoli. Predominantly epithelioid cells. Tumor infiltration of the sclera.
II-3	50	M	Right back	Melanoma	1.6mm	Melanoma arising in association with a dysplastic nevus. Focally superficial spreading pattern. Areas of lymphocytic infiltration and sclerosis.
II-3	62	M	Upper left arm	Melanocytic tumor of uncertain malignant potential	0.7mm	Shave biopsy. Asymmetrical proliferation of moderately atypical epithelioid and oval melanocytes in nests and in single cell formation at the dermo-epidermal junction and in the dermis. Foci of inflammation and fibrosis.
III-2*	31	F	Lower right arm	Melanocytic tumor of uncertain malignant potential	4.9mm	Nodular, predominantly dermal proliferation with a predominant population of atypical epithelioid melanocytic cells with considerable nuclear pleomorphism and moderate to large amounts of cytoplasm. Nucleoli are focally prominent. A few smaller nevocellular melanocytes, with oval nuclei and scant cytoplasm, situated in the superficial dermis. No mitotic figures.
II-6	38	F	Dorsum of foot	Melanoma	3.9mm	Ulcerated tumor composed of highly atypical melanocytes with highly pleomorphic nuclei. Mitoses.
II-6	52	F	Inguinal	Lymph node metastasis	45mm (size)	Bulky metastasis extensively replacing lymph node, exhibiting central necrosis. Highly pleomorphic epithelioid melanocytes with abundant eosinophilic cytoplasm, prominent nucleoli and frequent mitoses.
III-3	39	M	Left parietal	Melanoma	0.3mm	Biopsy. Atypical melanocytes in single cell formations and in nests with different size and shape.
III-3	40	M	Right parietal	Melanocytic tumor of uncertain malignant potential	n.a.	Atypical melanocytic proliferation in sun-damaged skin.

n.a. not available, *tumor shown in **Supplementary Figure 8**

Supplementary Table 2: *BAP1* status in melanocytic tumors of family 1.

Patient	#	Localization	Histology	*BAP1*		Predicted functional consequences	3p21 loss in aCGH	*BRAF* V600E
				Allele	Status			
II-1	1[1]	upper back	combined	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	2[2]	upper back	combined	A	c.1305del	p.Gln436Asnfs*135		wt
				B	loss		+	
	3	upper back	combined	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	4	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	c.133G>T	p.Gly45*	-	
	5	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	6	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	UPD		-	
	7	upper back	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	8[3]	upper back	combined	A	c.1305del	p.Gln436Asnfs*135		+
				B	UPD		-	
	9	shoulder	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	c.1768C>T	p.Gln590*	-	
	10	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	UPD		-	
	11	neck	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	12	lower back	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	13	knee dorsal	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	14	knee dorsal	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	15	shoulder	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss/UPD		n.a.	
	16	lower back	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	wt		n.a.	
	17	knee ventral	epithelioid	A	c.1305del	p.Gln436Asnfs*135		wt
				B	wt		n.a.	
	18	lower leg	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss/UPD		n.a.	

Supplementary Table 2 (continued).

Patient	#	Localization	Histology	*BAP1*		Predicted functional consequences	3p21 loss in aCGH	*BRAF* V600E
				Allele	Status			
II-4	19[4]	shoulder	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	20	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	wt		-	
	21	lower arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	wt		-	
	22	upper back	epithelioid	A	c.1305del	p.Gln436Asnfs*135		wt
				B	UPD		-	
	23	lower arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss/UPD		n.a.	
	24	lower back	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	wt		n.a.	
	25	ear	combined	A	c.1305del	p.Gln436Asnfs*135		+
				B	c.1145dup	p.Arg383Profs*15	n.a.	
II-7	26[5]	shoulder	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	loss		+	
	27	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	UPD		-	
	28	upper arm	epithelioid	A	c.1305del	p.Gln436Asnfs*135		+
				B	c.901G>A	p.Ala301Thr	-	
	29	upper arm	combined	A	c.1305del	p.Gln436Asnfs*135		+
				B	UPD		-	
I-2	30[6]	eye	uveal melanoma	A	c.1305del	p.Gln436Asnfs*135		wt
				B	loss		+	

wt: wild type; n.a.: not available

epithelioid: melanocytic tumor composed of cells with epithelioid morphology.

combined: melanocytic tumor composed predominately of epithelioid cells and some admixed nevoid cells.

UPD: uniparental disomy of maternal sequences, as assessed by markedly suppressed residual wild type sequences in the electropherograms, but no loss of 3p21 in aCGH.

UPD/loss: analysis of the electropherograms indicated a loss of the wild type allele, but differentiation between UPD and loss of 3p21 was not possible, because aCGH was not performed.

+: loss of the 3p21 region or BRAF V600E mutation, -: no loss of 3p21

[1]tumor is shown in **Supplementary Figure 7a-c**.

[2]tumor is shown in **Supplementary Figure 7d-f**.

[3]tumor is shown in **Supplementary Figure 6a-c**.

[4]tumor is shown in **Supplementary Figure 5a-c**.

[5]tumor is shown in **Supplementary Figure 5d-f**.

[6]harbors a *GNAQ* mutation (c.626A>C, p.Gln209Pro).

Supplementary Table 3: *BAP1* status in melanocytic tumors of family 2.

Patient	#	Localization	Histology	*BAP1*		Predicted functional consequences	3p21 loss in	*BRAF* V600E
				Allele	Status			
III-3	1[1]	neck	combined	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss		+	
	2	occipital	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss/UPD		n.a.	
	3	upper back	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss/UPD		n.a.	
	4	upper back	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss/UPD		n.a.	
	5[2]	upper arm	combined	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss		+	
	6	upper arm	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	UPD		-	
	7	shoulder	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	wt		n.a.	
III-2	8[3]	lower arm	MELTUMP	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss		+	
	9	ear	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	loss/UPD		n.a.	
II-3	10	lower back	epithelioid	A	c.2057-2 A>G	p.Met687Glufs*28		wt
				B	wt		n.a.	
	11	lower leg	combined	A	c.2057-2 A>G	p.Met687Glufs*28		wt
				B	wt		n.a.	
	12	lower back	epithelioid	A	c.2057-2A>G	p.Met687Glufs*28		+
				B	wt		n.a.	
	13	upper arm	MELTUMP	A	c.2057-2A>G	p.Met687Glufs*28		+
				B	loss/UPD		n.a.	
	14	upper back	cutaneous melanoma	A	c.2057-2A>G	p.Met687Glufs*28		wt
				B	loss/UPD		n.a.	
II-6	15	dorsum of the foot	cutaneous melanoma	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	wt		-	
	16	inguinal	lymphnode metastasis	A	c.2057-2 A>G	p.Met687Glufs*28		+
				B	wt		+	
II-1	17[4]	eye	uveal melanoma	A	c.2057-2 A>G	p.Met687Glufs*28		wt
				B	loss		+	

wt: wild type; n.a.: not available; epithelioid: melanocytic tumor composed of epithelioid cells; combined: melanocytic tumor composed predominately of epithelioid cells and some admixed nevoid cells; MELTUMP: melanocytic tumor of uncertain malignant potential; UPD: uniparental disomy of maternal sequences, as assessed by markedly suppressed residual wild type sequences in the electropherograms, but no loss of 3p21 in aCGH; UPD/loss: analysis of the electropherograms indicates a loss of the wild type allele, but differentiation between UPD and loss of 3p21 was not possible, because aCGH was not performed; +: loss of the 3p21 region or BRAF V600E mutation; -: no loss of 3p21; [1]tumor is shown in **Fig. 3a-d**; [2]tumor is shown in **Supplementary Figure 6d-f**; [3]tumor is shown in **Supplementary Figure 8**; [4]harbors a GNAQ mutation (c.625C>A, p.Gln209Lys).

Supplementary Table 4: Somatic mutations of *BAP1* in common acquired melanocytic nevi.

#	Sex	Age	Localization	Diagnosis	*BAP1* Mutation	Predicted functional consequences	*BRAF* V600E
1	M	33	upper back	common nevus, dermal	wt	-	+
2	F	61	cheek	common nevus, dermal	wt	-	+
3	F	32	upper back	common nevus, dermal	wt	-	+
4	F	32	upper back	common nevus, dermal	wt	-	+
5	F	44	neck	common nevus, dermal	wt	-	+
6	F	58	upper back	common nevus, dermal	wt	-	+
7	M	44	chest	common nevus, dermal	wt	-	+
8	F	69	shoulder	common nevus, mainly dermal	wt	-	+
9	F	69	shoulder	common nevus, mainly dermal	wt	-	+
10	F	46	axilla	common nevus, mainly dermal	wt	-	+
11	M	25	back	common nevus, mainly dermal	wt	-	+
12	F	21	flank	common nevus, mainly dermal	wt	-	+
13	F	46	flank	common nevus, mainly dermal	wt	-	+
14	M	43	neck	common nevus, mainly dermal	wt	-	+
15	M	43	neck	common nevus, mainly dermal	wt	-	+
16	F	42	back	common nevus, mainly dermal	wt	-	+
17	F	19	back	common nevus, mainly dermal	wt	-	+
18	F	47	knee	common nevus, mainly dermal	wt	-	+
19	F	47	neck	common nevus, mainly dermal	wt	-	+
20	F	39	shoulder	common nevus, mainly dermal	wt	-	+
21	F	48	back	common nevus, mainly dermal	wt	-	+
22	M	17	chest	common nevus, mainly dermal	wt	-	+
23	F	80	upper arm	common nevus, mainly dermal	wt	-	+
24	M	25	upper back	common nevus, mainly dermal	wt	-	+
25	F	68	neck	common nevus, mainly dermal	wt	-	+
26	F	19	back	common nevus, mainly dermal	wt	-	+
27	M	25	chest	common nevus, mainly dermal	wt	-	+
28	F	34	axilla	common nevus, mainly dermal	wt	-	+
29	F	34	belly	common nevus, mainly dermal	wt	-	+

wt: wild type

Supplementary Table 5: Somatic mutations of *BAP1* in Spitz nevi.

#	Sex	Age	Localization	Diagnosis	*BAP1* Mutation	Predicted functional consequences	*BRAF* V600E
1	M	29	upper arm	Spitz nevus, dermal	wt	-	wt
2	F	6	nose	Spitz nevus, dermal	wt	-	wt
3	M	34	neck	Spitz nevus, dermal	wt	-	wt
4	M	12	cheek	Spitz nevus, dermal	wt	-	wt
5	M	14	ear	Spitz nevus, dermal	wt	-	wt
6	M	18	upper back	Spitz nevus, dermal	wt	-	wt
7	M	22	lower leg	Spitz nevus, dermal	wt	-	wt
8	M	7	neck	Spitz nevus, dermal	wt	-	wt
9	F	22	chin	Spitz nevus, compound	wt	-	wt
10	M	8	hip	Spitz nevus, compound	wt	-	wt
11	M	12	knee	Spitz nevus, compound	wt	-	wt
12	F	27	rima ani	Spitz nevus, compound	wt	-	wt
13	M	12	retroauricular	Spitz nevus, compound	wt	-	wt
14	F	7	cheek	Spitz nevus, compound	wt	-	wt
15	F	33	upper back	Spitz nevus, compound	wt	-	wt
16	F	74	axilla	Spitz nevus, compound	wt	-	wt
17	F	31	ankle	Spitz nevus, compound	wt	-	wt

wt: wild type

Supplementary Table 6: Somatic mutations of *BAP1* in atypical Spitz tumors.

#	Sex	Age	Localization	Diagnosis	*BAP1* Mutation	Predicted functional consequences	*BRAF* V600E
1	F	44	upper back	Spitz tumor, atypical	c.178C>T	p.(Arg60*)	+
2	M	13	upper back	Spitz tumor, atypical	c.1768C>T	p.(Gln590*)	+
3	M	4	thigh	Spitz tumor, atypical	wt	-	wt
4	M	38	upper arm	Spitz tumor, atypical	wt	-	wt
5	F	13	lower leg	Spitz tumor, atypical	wt	-	wt
6	M	49	lower back	Spitz tumor, atypical	wt	-	wt
7	M	2	chin	Spitz tumor, atypical	wt	-	wt
8	M	52	left shoulder	Spitz tumor, atypical	wt	-	wt
9	F	16	back	Spitz tumor, atypical	wt	-	wt
10	F	21	cheek	Spitz tumor, atypical	wt	-	wt
11	M	4	right foot	Spitz tumor, atypical	wt	-	wt
12	F	37	head	Spitz tumor, atypical	wt	-	+
13	F	19	thigh	Spitz tumor, atypical	wt	-	wt
14	F	45	lower back	Spitz tumor, atypical	wt	-	wt
15	F	42	thigh	Spitz tumor, atypical	wt	-	wt
16	F	14	n.a.	Spitz tumor, atypical	wt	-	wt
17	M	26	knee	Spitz tumor, atypical	wt	-	wt
18	F	46	lower leg	Spitz tumor, atypical	wt	-	wt

wt: wild type; n.a.: not available

Supplementary Table 7: Somatic mutations of *BAP1* in sporadic cutaneous melanomas.

#	Sex	Age	Group	Localization	*BAP1* Mutation	Predicted functional consequences
1	M	60	NCSD	arm	c.999_1046del	p.Val335Profs*10
2	F	51	NCSD	upper back	c.278_281del	p.Thr93Metfs*4
3	M	84	NCSD	leg	wt	-
4	M	76	NCSD	chest	wt	-
5	F	60	NCSD	foot	wt	-
6	F	36	NCSD	n.a.	wt	-
7	F	54	NCSD	arm	wt	-
8	M	57	NCSD	back	wt	-
9	n.a.	n.a.	NCSD	n.a.	wt	-
10	M	58	NCSD	chest	wt	-
11	M	63	NCSD	back	wt	-
12	M	27	NCSD	temple	wt	-
13	M	52	NCSD	chest	wt	-
14	M	62	NCSD	back	wt	-
15	F	70	NCSD	arm	wt	-
16	M	77	CSD	scalp	wt	-
17	M	61	CSD	cheek	wt	-
18	F	83	CSD	ear	wt	-
19	F	62	CSD	head	wt	-
20	F	71	CSD	eyelid	wt	-
21	M	61	CSD	scalp	wt	-
22	F	61	CSD	scalp	wt	-
23	M	64	CSD	cheek	wt	-
24	M	42	CSD	temple	wt	-
25	F	n.a.	CSD	neck	wt	-
26	M	73	CSD	neck	wt	-
27	n.a.	n.a.	CSD	neck	wt	-
28	M	67	CSD	ear	wt	-
29	F	55	CSD	cheek	wt	-
30	F	67	CSD	cheek right	wt	-
31	n.a.	71	AM	foot, plantar	c.2090C>G[1]	p.Ser697Cys[1]
32	n.a.	n.a.	AM	foot, plantar	wt	-
33	n.a.	58	AM	foot, plantar	wt	-
34	M	40	AM	foot, plantar	wt	-
35	F	50	AM	foot, plantar	wt	-
36	F	53	AM	hand, palmar	wt	-
37	M	55	AM	foot, plantar	wt	-
38	F	63	AM	foot, plantar	wt	-
39	M	42	AM	foot, plantar	wt	-
40	M	66	AM	foot, plantar	wt	-

Supplementary Table 7 (continued).

#	Sex	Age	Group	Localization	*BAP1* Mutation	Predicted functional consequences
41	M	52	AM	foot, plantar	wt	-
42	n.a.	n.a.	AM	hand, palmar	wt	-
43	F	67	AM	hand, palmar	wt	-
44	n.a.	n.a.	AM	foot, plantar	wt	-
45	n.a.	n.a.	AM	foot, plantar	wt	-
46	M	69	MM	glans penis	wt	-
47	F	51	MM	vagina	wt	-
48	F	66	MM	anus	wt	-
49	M	31	MM	oral	wt	-
50	M	66	MM	anus	wt	-
51	F	70	MM	bladder	wt	-
52	F	70	MM	Anorectal	wt	-
53	F	46	MM	n.a.	wt	-
54	F	62	MM	vulva	wt	-
55	M	72	MM	oral	wt	-
56	F	66	MM	vulva	wt	-
57	F	56	MM	vagina	wt	-
58	n.a.	n.a.	MM	rectal	wt	-
59	F	n.a.	MM	n.a.	wt	-
60	M	58	MM	rectal	wt	-

wt: wild type; n.a.: not available.
NCSD: Melanoma on skin without chronic sun-induced damage
CSD: Melanoma on skin with chronic sun-induced damage
AM: Acral Melanoma
MM: Mucosal Melanoma
[1]Mutation affects the "Interaction with BRCA1" domain and its functional consequence was assessed with computational functional significance predictors: MutationAssessor: medium impact; PolyPhen: possibly damaging; SIFT: not scored. Mutated amino acid is conserved at least back to Zebrafish.

Supplementary Table 8: Somatic mutations of *BAP1* in primary uveal melanomas.

#	Sex	Age	*BAP1* mutations	Predicted functional	Chromosomal changes (aCGH)				GNAQ/GNA11 status
					loss 3	loss 1p	loss 6q	gain 8q	
1	F	69	c.1153C>T	p.Arg385*	+	+	-	+	*GNAQ* Q209P
2	F	n.a.	c.219del	p.Asp73Glufs*5	+	+	-	+	*GNA11* Q209L
3	M	75	c.58G>T	p.Glu20*	+	+	+	-	*GNA11* Q209L
4	M	53	c.643del	p.Glu212Serfs*1	+	-	-	+	*GNAQ* Q209L
5	F	79	c.915dup	p.Glu306*	+	-	-	+	*GNA11* Q209L
6	M	82	c.812_821del	p.Ile271Thrfs*61	+	-	-	+	*GNAQ* Q209P
7	M	64	c.226_239del	p.Ile76Valfs*45	+	+	-	-	*GNA11* Q209L
8	M	48	c.6dup	p.Lys3*	+	-	-	+	*GNA11* Q209L
9	M	73	c.993del	p.Lys331Asnfs*4	+	+	+	+	*GNAQ* Q209P
10	M	49	c.243C>A[1]	p.Phe81Leu[1]	+	-	-	+	*GNAQ* Q209P
11	F	84	c.172_179del c.139A>T[1]	p.Ser58Lysfs*8 p.Ile47Phe[2]	+	-	+	+	*GNAQ* Q209P
12	M	63	c.188C>G[1]	p.Ser63Cys[3]	+	-	+	+	*GNA11* Q209L
13	F	83	wt	wt	+	+	-	-	*GNAQ* Q209P
14	F	88	wt	wt	+	-	-	+	*GNAQ* Q209P
15	F	78	wt	wt	+	-	+	+	*GNA11* Q209L
16	F	86	wt	wt	p. +	+	+	+	wt
17	F	79	c.1379C>G	p.Ser460*	p. +	-	-	+	*GNAQ* Q209P
18	F	n.a.	wt	wt	p. +	-	-	+	*GNA11* Q209L
19	M	77	wt	wt	p. +	-	+	-	*GNAQ* Q209P
20	M	78	wt	wt	p. +	+	+	+	*GNAQ* Q209P
21	M	80	wt	wt	p. +	-	-	-	*GNAQ* Q209P
22	M	43	wt	wt	-	-	-	-	*GNAQ* Q209P
23	M	88	wt	wt	-	-	-	-	*GNA11* Q209L
24	M	81	wt	wt	-	-	-	-	wt
25	M	51	wt	wt	-	-	-	+	*GNA11* Q209L
26	F	55	wt	wt	-	-	-	-	*GNAQ* Q209P
27	F	23	wt	wt	-	-	-	+	*GNAQ* Q209P
28	F	52	wt	wt	-	+	-	-	*GNAQ* Q209P
29	M	82	wt	wt	-	-	-	+	*GNA11* Q209L
30	M	66	wt	wt	-	-	-	-	*GNAQ* Q209R
31	M	66	wt	wt	-	-	-	-	*GNAQ* Q209L
32	M	39	wt	wt	-	+	+	+	*GNAQ* Q209P
33	F	46	c.1002A>G	p.(=)	-	-	-	-	*GNAQ* Q209P

wt: wild type; n.a.: not available; chromosomal changes were detected by aCGH: '+' chromosomal aberration, 'p.+' partial loss of chromosome 3, '-' no chromosomal aberrations; [1,2,3]All three mutations affect the "Peptidase_C12: Ubiquitin carboxyl-terminal hydrolase, family 1" domain; all changed amino acids are conserved at least back to Zebrafish. The functional consequences were assessed with computational functional significance predictors:

Mutation:	MutationAssessor	PolyPhen	SIFT
- [1]p.Phe81Leu:	high impact	probably damaging	damaging
- [2]p.Ile47Phe:	high impact	benign	not scored
- [3]p.Ser63Cys:	medium impact	possibly damaging	tolerated

Supplementary Table 9: Primer for *BAP1* sequencing.

Exon	Forward	Reverse
DNA primer		
Exon1-2	GGAGGGCCTGGACATGG	ATGAGTGAGGGCGCAGG
Exon3	GGGCTGTCCTTCCCTACTG	CCTGTTCTCTGGGACCTTCC
Exon4	ATTGTCTTCTCCCCTTTGGC	AACATGGCAGCATCCCAC
Exon5	GTGAGGGGTGCTGTGTATGG	AGTTGGCTGTGAGCCAGG
Exon6	TTTGCCTTCCACCCATAGTC	ACTCCCACCCCACATCAG
Exon7	GCTGATGTGGGGTGGGAG	GGAGGTAGGCAGAGACACCC
Exon8	ACTCAGGGTTTCCTTCTCGC	TCTGTCCCTCCCAAAGTAGG
Exon9	CTCAACCTGATGGCGGG	AATGCAGGGAGGGTTGG
Exon10	CGGGTCTACCCTTTCTCCTC	AGACATTAGCGGGTGGCTC
Exon11	GGAGGTCCTGCCTGTGTTC	GGAACCACATGGGAAAATTG
Exon12	CCGAGCAGCACTTGTTTG	GATCCGAAGCACCTAGAACC
Exon13_1	GCCCGTTCCCTTGCTTC	GTGAGGGCTGCGAGTGTG
Exon13_2	CCTCTCAATTCCTCTGTCCATC	GCAGGCTGTCATCCTCTCC
Exon13_3	CTATCCGCTCAGCCAACC	TCCCTCCTCCCTCCTGG
Exon14	CCACAAAGTGTCCTGCACTC	AGCTCAGGCCTTACCCTCTG
Exon15	GTGGGGCTTTGTTGCTG	CAGTGGACCTCGGGAGAG
Exon16	AGATTGGCTCCAGTGCTCTC	AGCAGGGCATTCCAGTTAAG
Exon17	ATGAGAGCCTCAGCTCCTGG	CACACGGCAAGAGTGGG
cDNA primer		
Exon 13-17	ATCTGGGTCCTGTCATCAGC	ACGGAGATGTTCTGCTCCAC