BAP1 inactivated melanocytic tumors

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https://wikikids.nl/Luchtballon

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Short history of BAP1

- Discovered in 1998: breast cancer cells -> BAP1 identified as a tumor suppressor in cooperation with BRCA-1: therefore initially named BRCA1 (BReast CAncer) -associated protein 1 later shortened to BAP1

Jensen et al: "BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression". Oncogene. 1998;16(9).

- However the exact role of this gene became more evident in the next decade by studying familial cancers

The Cappadocia story: role of BAP1 in mesothelioma discovered (2001)

- **In Cappadocia** (central Turkey) a mesothelioma epidemic was observed in the early 2000s. Among people living in 3 small villages, 50% of all deaths were caused by this malignant tumor. This malignancy was transmitted in an AD fashion.
- **Culprit: BAP1**

Roushdy-Hammady et al. Lancet. 2001; 357:444–5

https://www.wanderlustchloe.com/istanbul-to-cappadocia

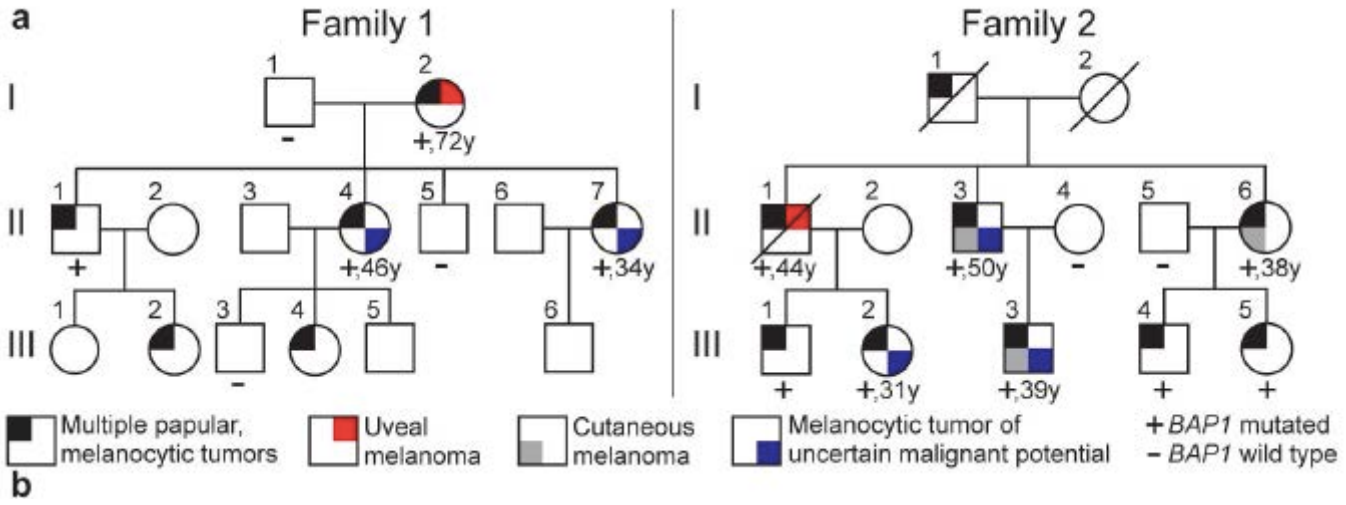
The American story: role of BAP1 in mesothelioma and uvea melanoma established (2011)

- In the **United States**, two unrelated families, L (from Louisiana) and W (from Wisconsin), were found with high incidence of mesothelioma, and each had only minimal exposure to asbestosis. Two members in the L family also developed uvea melanoma.
- Chance for simultaneous occurrence of these rare malignancies in more than one individual in the same family was estimated at 36 per trillion (10^{12}) population.
- **Culprit:** alteration in chromosome region 3p21 in both mesothelioma and UM cases. Sequencing this region of chromosome 3 led to the identification of germline BAP1 as the mutated gene in the L and W families

Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43(10):1022e1025.

The Graz story: role of BAP1 in development of cutaneous melanocytic tumors discovered (2011)

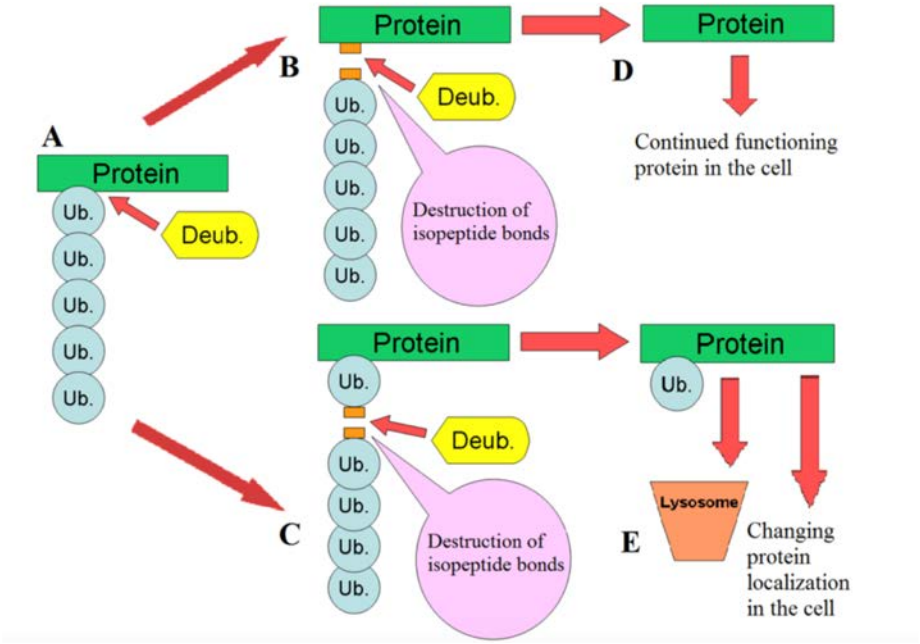
- Wiesner et al described 2 families with 40 melanocytic lesions: 4 MELTUMPs, 2 uvea melanomas, 3 cutaneous melanomas, 15 with several multiple papular melanocytic tumors
- **Culprit: inactivating germline mutations of BAP1**



Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011;43(10):1018e1021

BAP1 gene and function

- Located at 3p21: spans 9.0 kb - composed of 17 exons
- The *BAP1* protein functions as a de-ubiquitinase
- By removing ubiquitin from proteins BAP1 leads to retained protein function and influences localization of proteins in cells



BAP1 protein interacts with multiple partners and therefore has multiple functions. Acts as tumor suppressor, exact mechanism not clear yet

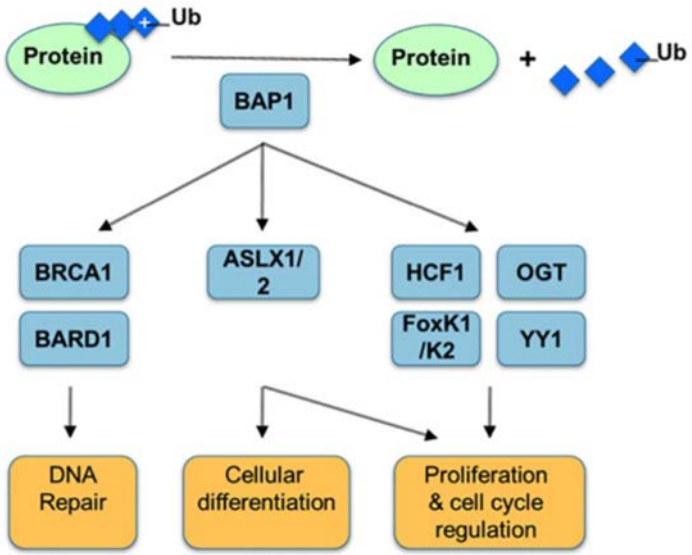


Figure 2 BRCA1-associated protein 1 is a deubiquitinating enzyme. It interacts with multiple protein partners and functions as a tumour suppressor. HCF1, host cell factor 1; OGT, O-linked N-acetylglucosamine transferase; YY1, Ying Yang 1.

Wang A, *et al. J Clin Pathol* 2016;**69**:750–753. doi:10.1136/jclinpath-2016-203866

BAP1 loss can be somatic or germline

- Germline: BAP1 cancer or BAP1-predisposition syndrome
- Somatic: in different tumors BAP1 loss has different implications (related to its complex function)

Somatic BAP1 loss in different malignant tumors

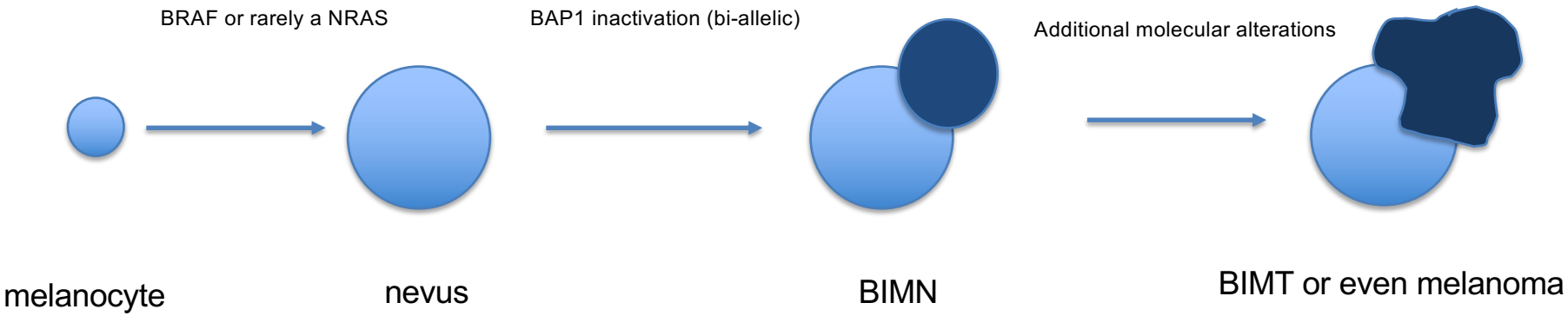
Tumor type	Clinicopathological features	outcome	Frequency BAP1 loss	
Uvea melanoma	Class 2 tumors (stem-like phenotype)	worse	85% of metastatic uvea melanoma	
Malignant mesothelioma	Females, younger age, epithelioid cell type	better	30-60% sporadic cases	
Renal cell carcinoma	Association higher grade, rhabdoid/sarcomatoid transformation	worse	6-17% sporadic clear cell RCC	BAP1 loss: RCC more sensitive to radiation and PARPi
Cutaneous melanoma	More frequent in desmoplastic melanoma	worse	2.5-22% melanomas, 9% metastatic melanomas	

Most relevant for a dermatopathologist: BAP1 inactivated (melanocytic) nevus or tumor (BIMN/T or BIN/T)

New entity in the new WHO Skin tumors (4th Ed 2018), within the group of combined nevi

Relevance: can be an *early marker* for the BAP1 cancer syndrome

Development of BAP1 inactivated melanocytic tumors



Clinical spectrum of BAP1 inactivated melanocytic tumors

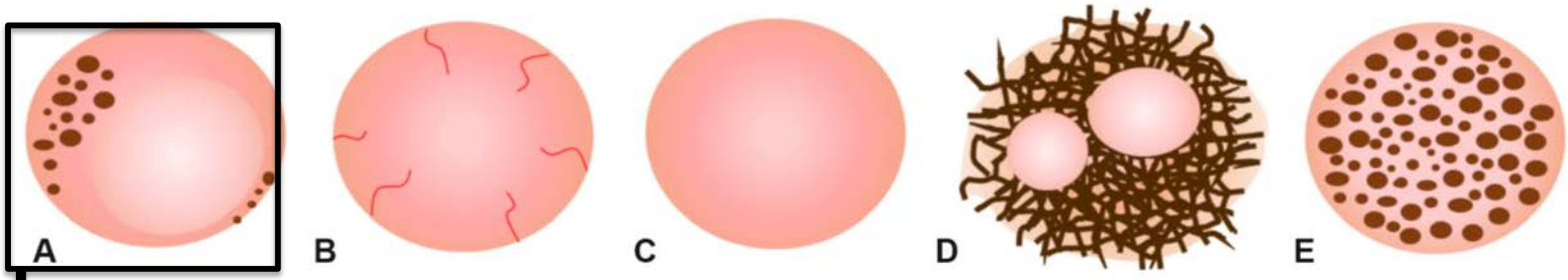
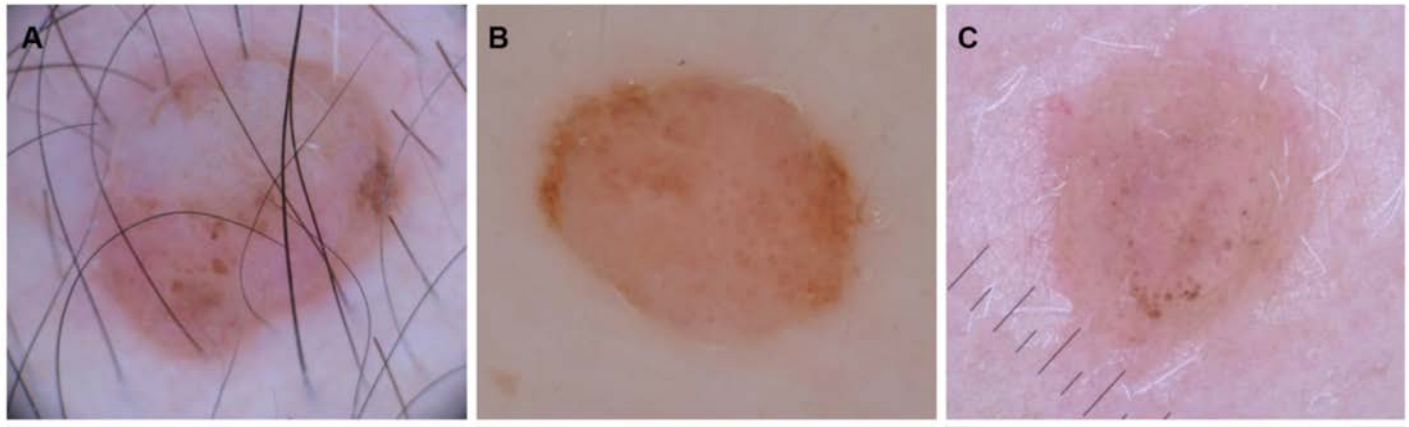


Fig 1. Schematics showing the 5 patterns identified in our cohort of BRCA1-associated protein 1—inactivated melanocytic tumors. **A**, Structureless pink/tan with atypical eccentric clods. **B**, Structureless pink with radial vessels. **C**, Structureless pink/tan. **D**, Network with raised structureless areas. **E**, Globular.

Pattern A significantly more frequent in cases harboring a BAP1 germline mutation (46.15% vs 6.25%)



Clinical and dermoscopic features of cutaneous BAP1-inactivated melanocytic tumors: Results of a multicenter case-control study by the International Dermoscopy Society . Yelamos et al. J Am Acad Dermatol :80; 6 ; 2019

Clinical presentation of *BAP1* inactivated melanocytic tumors in a patient with a BAP1 germline mutation

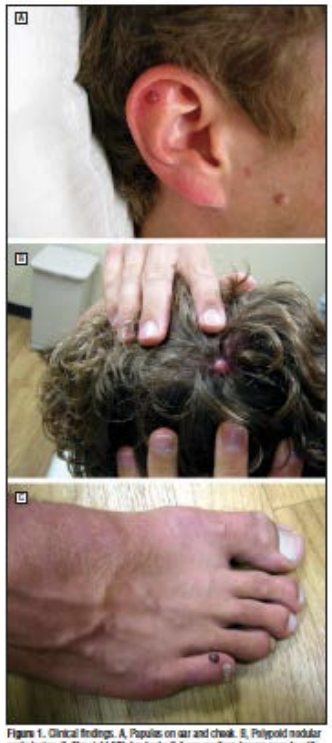


Figure 1. Clinical findings. A, Papules on ear and cheek. B, Polypoid nodular scalp lesion. C, The right fifth toe had a 0.4-cm medium-brown macule with a central dome-shaped papule.

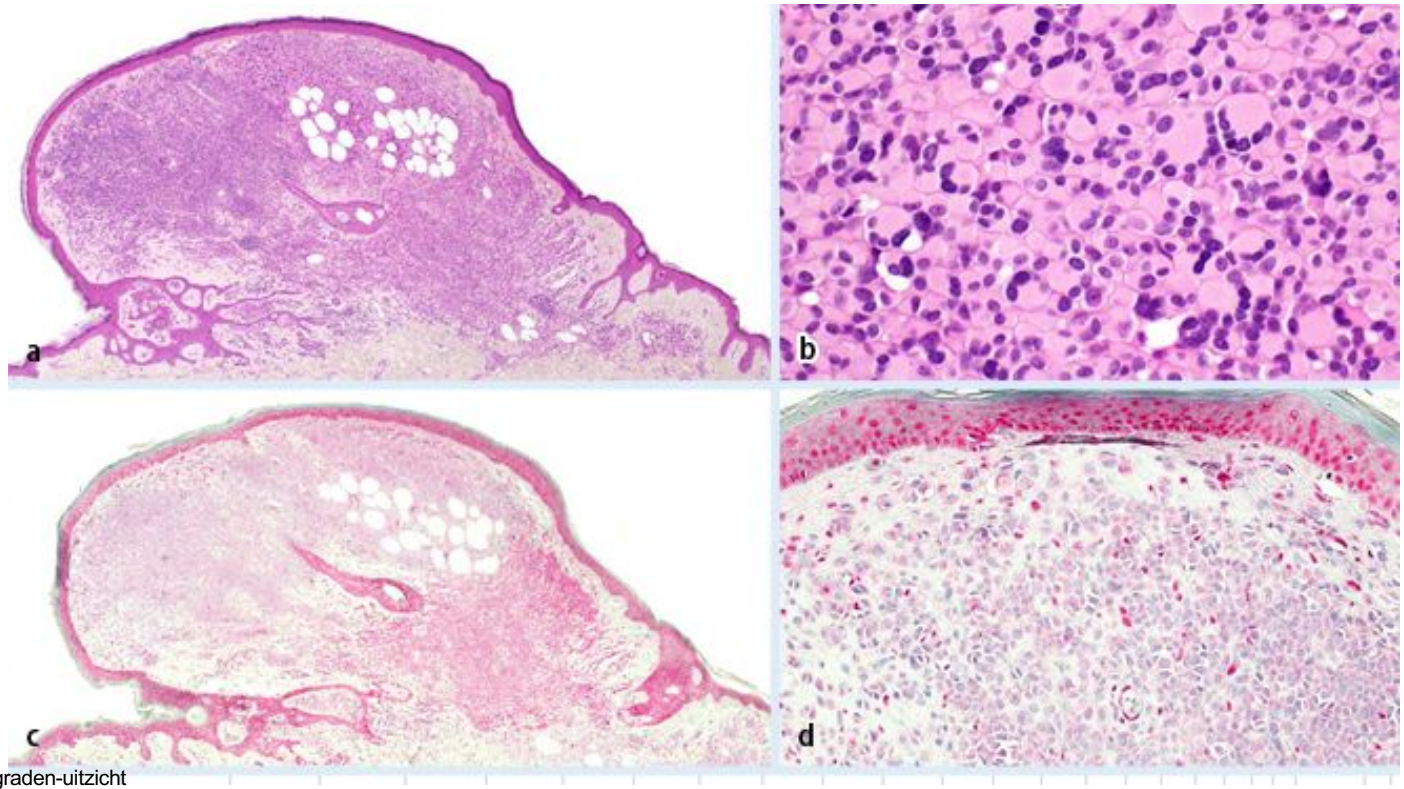
Typically

- Young patient, most often <30 yrs
- Multiple lesions

Busam et al. Multiple epithelioid Spitz nevi or tumors with loss of BAP1 expression: a clue to a hereditary tumor syndrome. JAMA Dermatol 2013Mar;149(3):335-9. doi: 10.1001/jamadermatol.2013.1529.

Histology of a typical BIMN/T

-Polypoid contour
-Epithelioid/ “spitzoid cells” or sometimes more rhabdoid cells
-common nevus can be present
-often TILs



https://www.omropfryslan.nl/nieuws/652609-video-een-luchtballon-met-360-graden-uitzicht

T. Wiesner, H. Kutzner. Pathologe 2015 · 36:37–45. DOI 10.1007/s00292-014-1984-1

Typical BAP1 inactivated melanocytic lesion

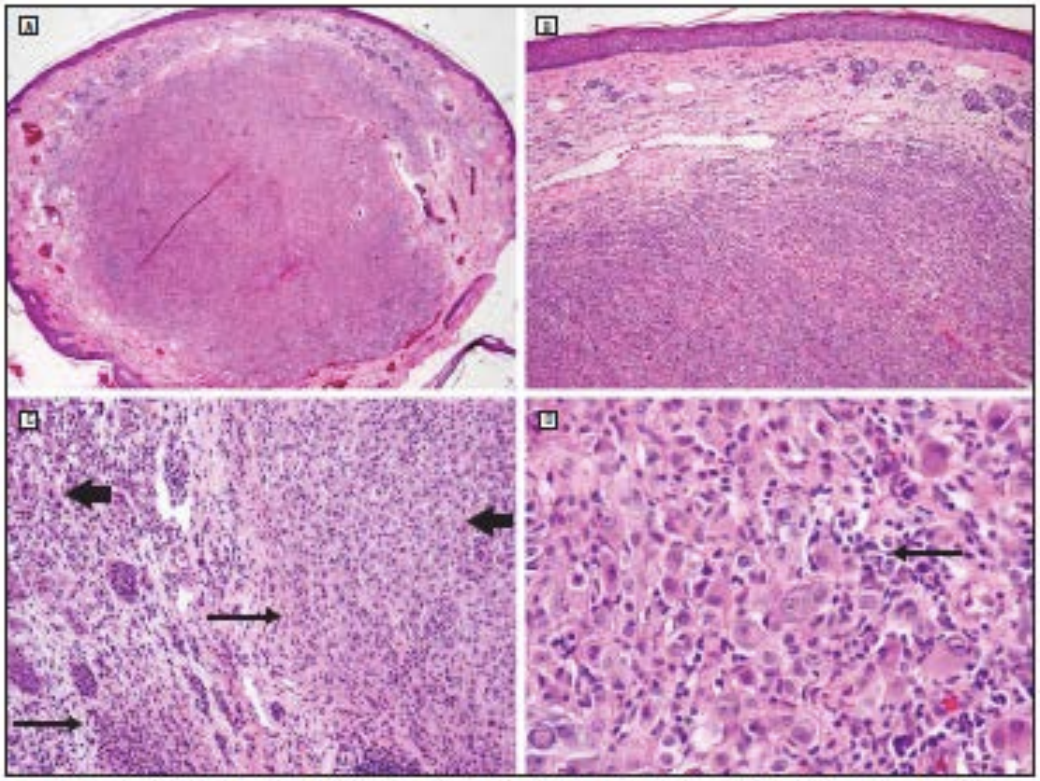
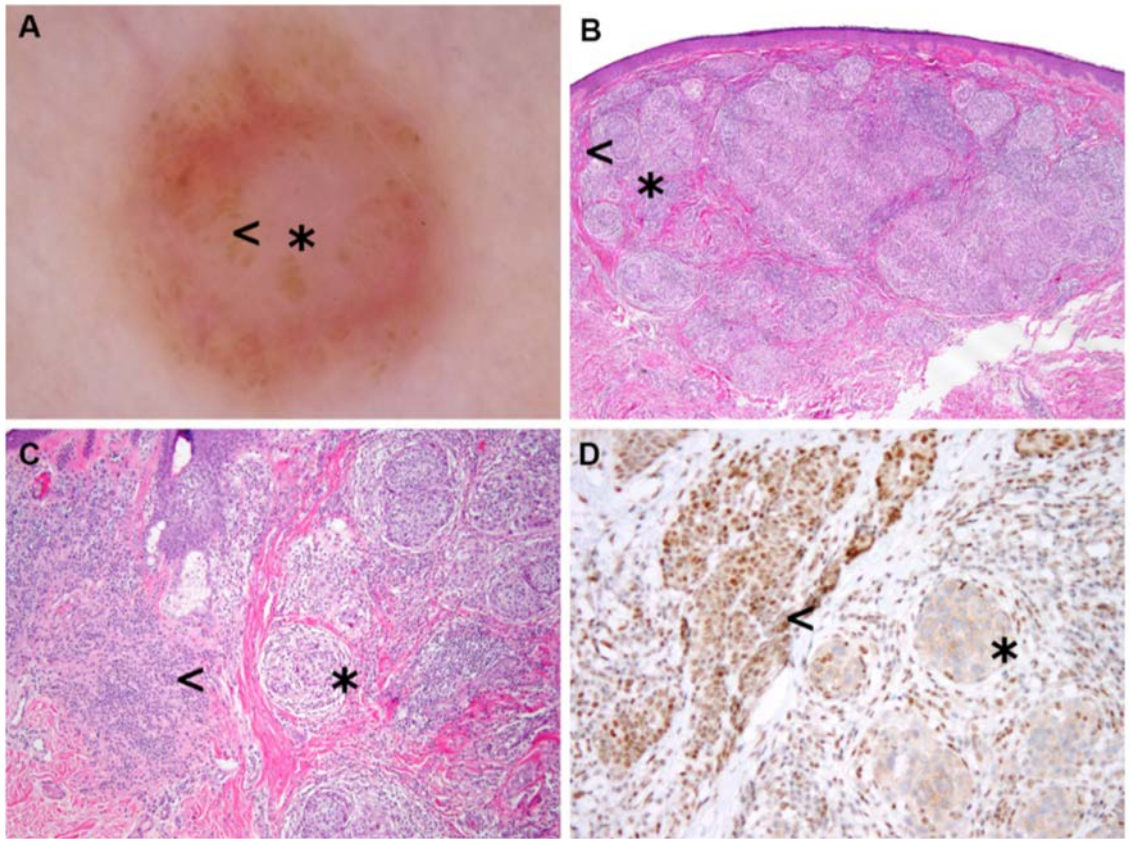


Figure 2. Histopathologic findings. A, Excision of the polypoid nodule shown in Figure 1B. B, A central nodular aggregate of large epithelioid melanocytes is surrounded by aggregates of small melanocytes. The papillary dermal stroma is edematous and contains ectatic vessels and small lymphocytes. C, Large epithelioid melanocytes (thick arrows) are admixed with small epithelioid melanocytes (thin arrows). D, The large epithelioid melanocytes have round to oval nuclei with open vesicular chromatin and distinct nucleoli. They have abundant eosinophilic cytoplasm. Small lymphocytes (thin arrow) are dispersed throughout the entire lesion.

Busam et al. Multiple epithelioid Spitz nevi or tumors with loss of BAP1 expression: a clue to a hereditary tumor syndrome. JAMA Dermatol 2013Mar;149(3):335-9. doi: 10.1001/jamadermatol.2013.1529.

Correlation between dermatoscopy and histology in BAP1 inactivated melanocytic tumor



Clinical and dermoscopic features of cutaneous BAP1-inactivated melanocytic tumors: Results of a multicenter case-control study by the International Dermoscopy Society . Yelamos et al. J Am Acad Dermatol :80; 6 ; 2019

The histological spectrum of BAP1 inactivated melanocytic lesions

Class 1 : looks like a common nevus, but with immunohistochemistry there is loss of nuclear BAP1 staining : only occurs in context of BAP1 cancer syndrome. Therefore only diagnosed in retrospect!

Class 2: BAP1 inactivated clone in a nevus or BAP1 inactivated nevus. Mitotic rate and MIB low (melanocytoma).
Advice: complete excision, margin 2mm. Genetic counseling.

Class 3: BAP1 inactivated tumor (BIMT/BIT): more sheet-like growth and mitoses, some genetic alteration in CGH (MELTUMP)
Advice: Consultation referral center. CGH/SNP array. Complete excision 5-10 mm. Oncogenetic counseling.

Class 4: BAP1 inactivated melanoma: CGH several aberrations and mib>20%.
Advice: treat according to melanoma guideline. Oncogenetic counseling.

Chance to develop a BAP1 inactivated melanoma

WHO 2018

- Risk low
- Criteria for BIMT/melanoma?
- Melanoma: >1 mitosis/1mm^2 or > 3 in the whole lesion, ulceration, necrosis, destructive growth, in situ component, strong and variable atypia

Immunohistochemistry in BAP1 inactivated tumors

Melan A is often weak. P16 often heterogeneous
BAP1 is lost in the nuclei of the epithelioid cells.

BAP1 immunostaining

- Immunohistochemistry provides a rapid way to screen for bi-allelic BAP1 loss, which correlates with loss of nuclear staining
- BAP1 immunostaining is cost- effective, and has positive and negative predictive values of 100% and 98.6%, respectively.
- a small number of missense mutations that inactivate the protein without epitope alteration may not be detected.
- Santa Cruz, clone C4
- Dilution: 1/200 (sometimes 1:400 is also reported)
- Ventana Benchmark Ultra

Genetic spectrum of BAP1 inactivated melanocytic tumors

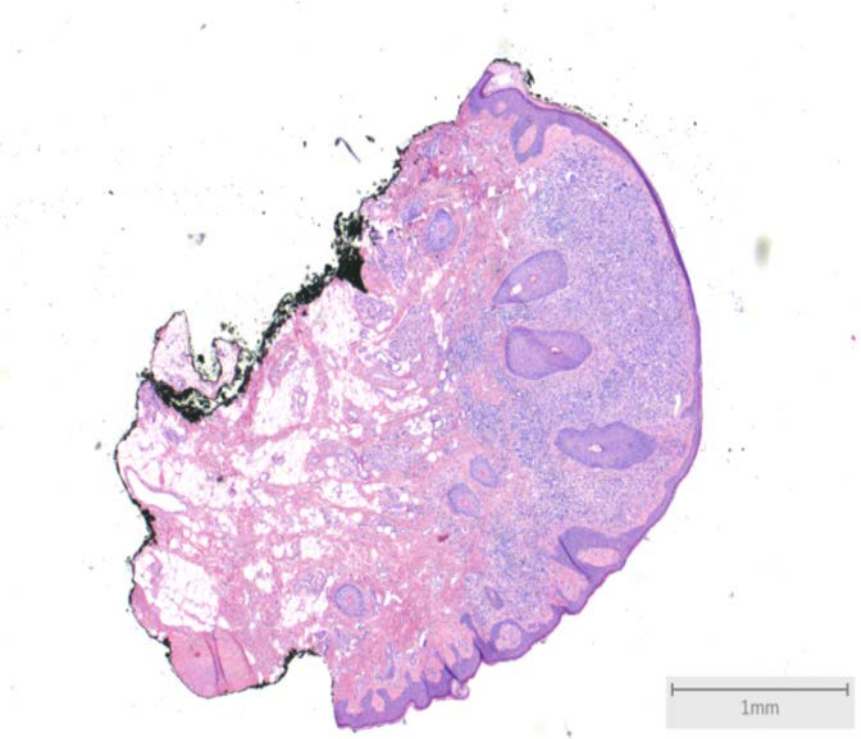
Most cases : combination *BAP1* and $BRAF^{V600E}$ mutation

HRAS tested by *Wiesner et al* in 2012 in sporadic MBAIT cases (n=9): not found

Yeh et al, Am J Surg Pathol 2014: *BRAF* and *NRAS* tested: most cases a BRAF mutation. In **1/17 cases a *NRAS* Q61R** mutation (*BAP1* germline mutation not tested).

Yeh et al, Am J Surg Pathol 2014 Aug;38(8):1088-95 . Ambiguous melanocytic tumors with loss of 3p21.

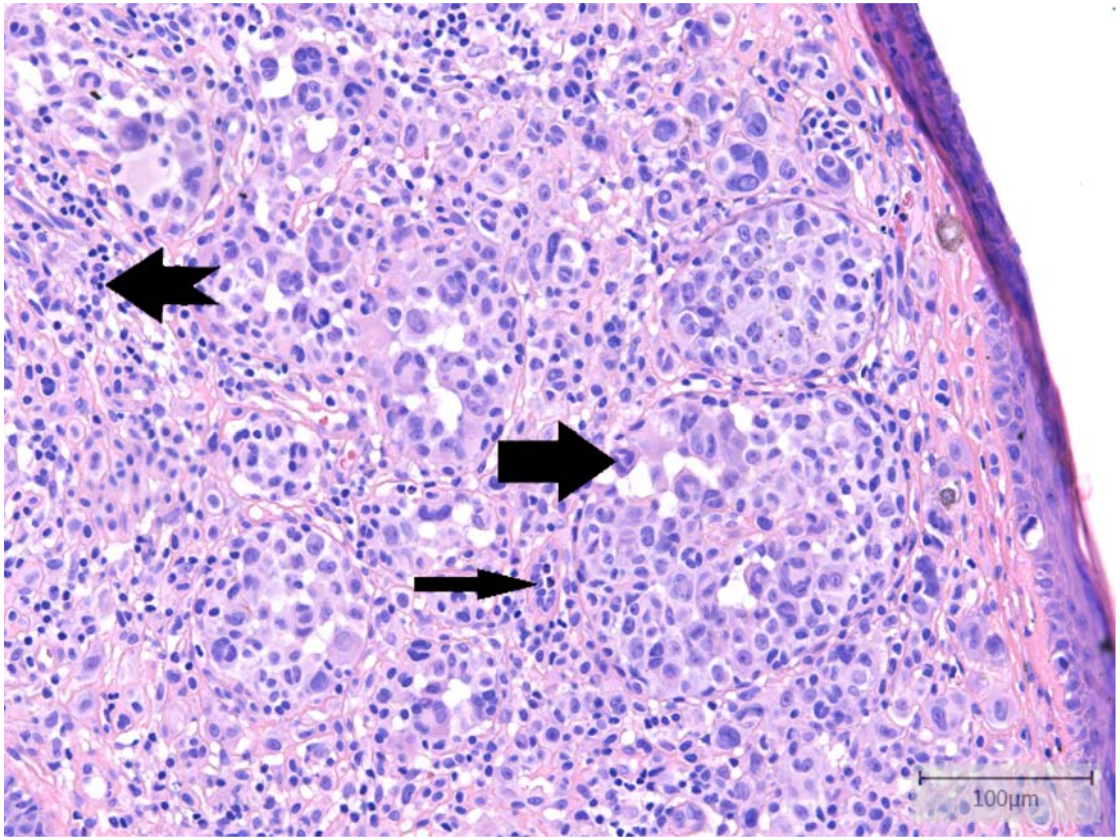
BIMN with *NRAS* mutation



Male 36 yrs
Lesion of the ear
(Coutesy Dr.I. van Lijnschoten,
PAMM Eindhoven)

Blokx et al. Virchows Arch 2015 Jan; 466(1): 117-21
NRAS-mutated melanocytic BAP1-associated intradermal tumor (MBAIT): a case report.

NRAS mutated BIMN: *BAP1* germline mutation excluded



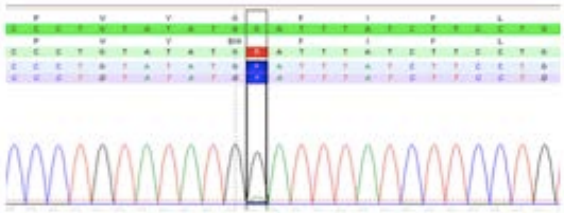


Figure 3A: BAP1 mutations in exon 4. BAP1: c.134G>A, p.G45E

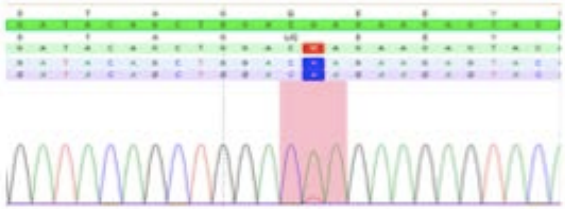


Figure 3B: NRAS mutation in exon 3. NRAS: c.182A>T, p.Q61L

How to report a BAP1 inactivated melanocytic lesion

The diagnosis fits with a BAP1 inactivated melanocytic lesion (nevus/tumor/melanoma).

These lesions may be found as a sporadic finding or with increased incidence in patients with germline mutations in the BAP1 gene.

If there is a personal or family history of uveal melanoma, mesothelioma, renal cell carcinoma, cutaneous melanoma or other similar BAP1-associated cutaneous neoplasms, a clinical work-up for the familial BAP1-associated cancer syndrome should be considered.

Treatment advice / follow-up BAP1 inactivated melanocytic lesion

-complete excision, margin dependent on dx of either nevus (2mm), tumor (5mm), or melanoma (according to guideline for melanoma)

-dermatological screening

-patient and family history

-in case of a germline mutation: screening for malignancies

Pitfalls/ caveats BAP-1 like lesions

- Not every melanocytic tumor with epithelioid cells is BAP1 inactivated
- Not every BAP1 inactivated melanocytic lesion has the classical appearance
- BAP1 immunostaining: not constant in performance
- BAP1-like lesions occur in other syndromes
- Risk of overdiagnosis of melanoma: several consultation cases per year in which a BAP1 inactivated lesion was not in the differential

BAP-1 like lesions in other cancer syndromes /germline mutations

Atypical cutaneous melanocytic tumours arising in two patients with Li–Fraumeni syndrome

Julien Jacquemus[1], Emilie Perron[1,2,3], Daniel Pissaloux[1], Laurent Alberti[1], Arnaud de la Fouchardière[1,

Pathology 2017

Jacquemus et al: Pathology 2017

Girl 5 yr old known with Li-Fraumeni syndrome.
History of an adrenocortical carcinoma,
AML and this skin tumor.
BAP1 not lost, p53 positive.
BRAF mutation.

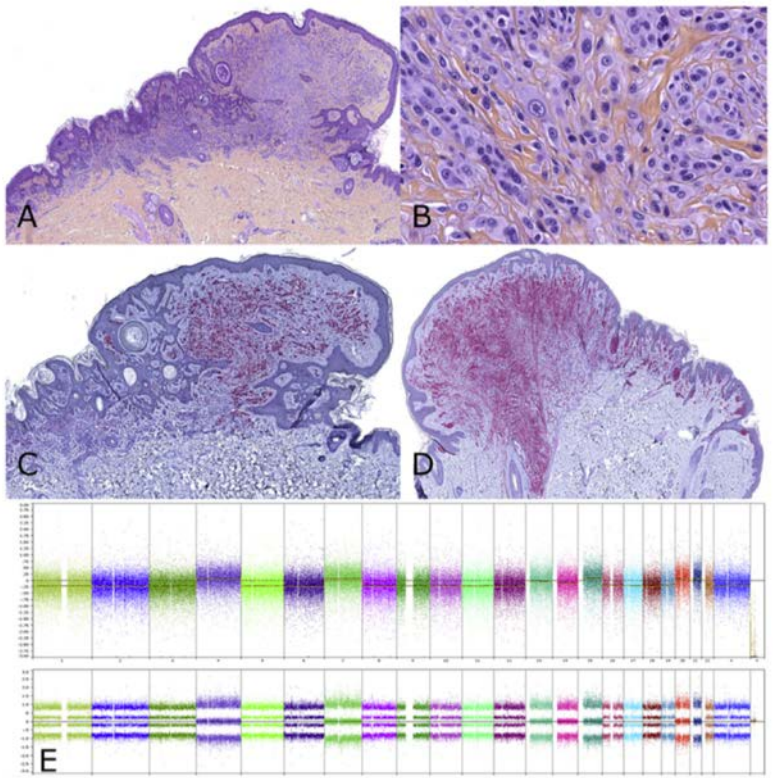


Fig. 1 Case 1. (A) Biphenotypic architecture with a dense dermal nodule arising within a small congenital-like naevus. (B) Large atypical epithelioid melanocytes with a mitotic figure. (C). Strong labelling of the nodule with anti-p53 antibody contrasting with the weak staining of the conventional naevus viewed on the left side. (D) Anti-BRAF VE1 Ab diffuse staining in all melanocytes. (E) Comparative genomic hybridisation (CGH): near-haploid karyotype.

Array comparative genomic hybridisation (CGH) performed on the nodule showed a near-haploid profile with monosomy of all chromosomes, excluding pairs 4, 7, 15, 20 and 21 (Fig. 1E). TP53 DNA sequencing found a p.R273H mutation (nucleotide substitution c.818G>A) in exon 8 matching the known germline mutation.

BAP1 cancer /predisposition syndrome (BAP1-TPDS)

- Caused by BAP1 germline mutation: no hot spot mutations
- The spectrum of associated tumors is still expanding
- The molecular mechanisms and cellular pathway responsible for leading to specific tumor types, and the difference in disease outcome remain unclear.
- BAP1 inactivated melanocytic tumors are often develop at a young age (0-20yrs) and can enable early detection of the syndrome before malignancies develop

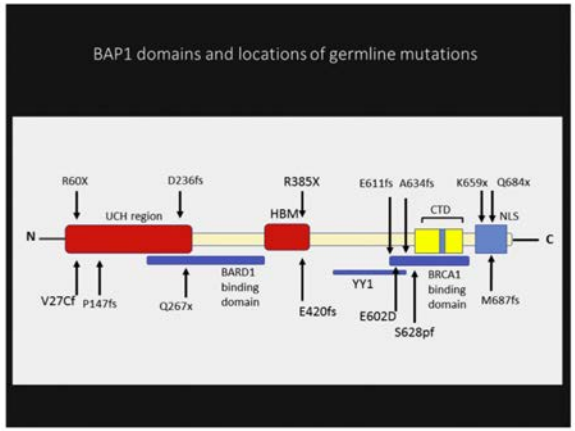


Fig. 1. Schematic structure of BRCA1-associated protein-1 (BAP1) domains and locations of reported germline mutations. Consists of: ubiquitin carboxyl hydrolase (UCH) domain; HBM, host cell factor 1 (HCF1) binding domain; nuclear localization signals (NLS); C-terminal domain (CTD), additional sex combs like (ASXL1/2) binding domain; BRCA1-associated RING domain protein 1 (BARD1) binding region; Breast Cancer type 1 (BRCA1) binding region and Ying Yang 1 (YY1) binding region.

Source: B. Masoomian et al. / Journal of Current Ophthalmology 30 (2018) 102e109
Overview of BAP1 cancer predisposition syndrome and the relationship to uveal melanoma

Spectrum of tumors in patients with a confirmed BAP1 germline mutation

Table II. Spectrum and frequency of familial cancers in patients with confirmed germline mutations in BAP1 (patients 1-8) and patients who were suspected of having germline mutations as a result of multiple BIMT diagnoses but were lost to clinical follow-up (patients 9-11)

Patient No.	Confirmed germline mutation?	Mutation	Uveal melanoma	Meso-thelioma	Other lung cancer	Renal cell carcinoma	Cutaneous melanoma	NMSC	Multiple BIMTs	Glio-blastoma	Thyroid cancer	Colon cancer	Prostate cancer	Breast cancer	Liver cancer	Leukemia	B-cell lymphoma	Pancreatic cancer
Patient 1	Yes	p.Q253			X		X							X				
Patient 2	Yes	g.1777C>T					X	X			X				X		X	X
Patient 3	Yes	g.1777C>T					X	X			X				X		X	X
Patient 4	Yes	c.1717delC, p.L573fs*3							X									
Patient 5	Yes	chr3, g.52435660 delC		X			X											
Patient 6	Yes	c.1321C>T		X		X	X		X									
Patient 7	Yes	p.A258Yfs*2	X				X	X	X	X	X	X	X	X				
Patient 8	Yes	c.592G>T, p.Glu198X			X		X	X	X									
Patient 9	No, but suspected	Unknown						X	X						X	X		
Patient 10	No, but suspected	Unknown							X									
Patient 11	No, but suspected	Unknown							X									

BAP1, BRCA1-associated protein 1; *BIMT*, BAP1-inactivated melanocytic tumor; *NMSC*, nonmelanoma skin cancer.

Histomorphologic spectrum of germline-related and sporadic BAP1-inactivated melanocytic tumors.
Garfield et al, JAAD, 2018 Sep;79(3):525-534. doi: 10.1016/j.jaad.2018.05.005

Frequency of malignancies in BAP1-TPDS

Table 1
BAP1 tumor predisposition syndrome (BAP1-TPDS). Frequency of related malignancies.

Common BAP1-TPDS tumors	Study #1 Rai et al[24]	Study #2 Carbone et al[27]
Uveal melanoma (UM)	54/174 (31%)	6/72 (8.5%)
Mesothelioma	39/174 (22%)	12/72 (17%)
Cutaneous melanoma (CM)	23/174 (13%)	2/72 (3%)
Renal cell carcinoma (RCC)	18/174 (10%)	2/72 (3%)
Atypical Spitz tumor (MBAIT)	32/174 (18%)	Unknown
Other tumors[a]		
Breast cancer	9/95 (9.5%)	3/37 (8.2%)
Basal cell carcinoma	11/174 (6.3%)	3/72 (4.2%)
Lung cancer	6/174 (3.5%)	2/72 (3%)
Ovarian carcinoma	3/95 (3%)	0/37 (0%)
Prostate cancer	2/67 (3%)	2/35 (6%)
Sarcoma	4/174 (2.3%)	2/72 (3%)
Cholangiocarcinoma	4/174 (2.3%)	0/72 (0%)
Meningioma	3/174 (2%)	0/72 (0%)
Neuroendocrine cancer	2/174 (1.2%)	0/72 (0%)
Colorectal cancer	2/174 (1.2%)	2/72 (3%)
Patients with ≥1 BAP1-TPDS common tumors[b]	134/174 (77%)	22/72 (31%)
Patients with ≥2 BAP1-TPDS common tumors[b]	16/174 (9%)	3/72 (4.2%)

BAP1-TPDS: BAP1 tumor predisposition syndrome.
MBAIT: Melanocytic BAP1-mutated Atypical Intradermal Tumor Information gathered from reference Rai et al.[24] and Carbone et al.[27]
[a] There are limited data supporting their inclusion in BAP1-TPDS.
[b] Except Atypical Spitz tumor (MBAIT).

Source: B. Masoomian et al. / Journal of Current Ophthalmology 30 (2018) 102e109
Overview of BAP1 cancer predisposition syndrome and the relationship to uveal melanoma

BAP1 gene mutation penetrance and prevalence

- Inheritance: autosomal dominant
- penetrance of BAP1 mutation is fairly high, and more than 80% of gene carriers are ultimately affected by at least one type of cancer : tumor types can vary among members of the same family

Chance of having a BAP1 germline mutation in case of a diagnosis of BAP1-inactivated melanocytic tumor

- 10-20%
- Higher risk in case of a junctional component in histology, multiple melanocytic lesions clinically, and positive family or personal history of tumors associated with BAP1 TPDS

Histomorphologic spectrum of germline-related and sporadic BAP1-inactivated melanocytic tumors. *Garfield et al,* JAAD, 2018 Sep;79(3):525-534. doi: 10.1016/j.jaad.2018.05.005

Occurrence of BAP1 germline mutations in cutaneous melanocytic tumors with loss of BAP1-expression: A pilot study. *Cabaret et al,* Genes Chromosomes Cancer 2017 Sep;56(9):691-694. doi: 10.1002/gcc.22473

Screening recommendation in case of confirmed BAP1 predisposition syndrome

Annual eye examination > 12 yrs

Annual dermatological screening > 20 yrs; monthly self-examination skin

Annual ultrasound kidneys >30 yrs

Annual examination lungs >30yrs

Genetic counseling of 1st and 2nd degree relatives to exclude carriership

Note: age of start of the screening is debated: dependent on first tumor manifestation in a family member: start 5 yrs before in other family members

Reference: Ipenburg et al. MBAITs and the BAP1 tumor predisposition syndrome. Nederlands Tijdschrift voor Dermatologie en Venereologie 26(11):655-658 · December 2016

Relevance of BAP1 in other melanocytic tumors than BAP1 inactivated melanocytic tumors

- In uvea melanoma: BAP1 loss/monosomy 3 associated with poor prognosis
- In blue nevus like melanoma: often loss of BAP1

Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevi

Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp

Sebastian Costa, MD, Michelle Byrne, MBBS,† Daniel Pissaloux, PhD,* Veronique Haddad, PharmD,* Sandrine Paindavoine, Msc,* Luc Thomas, MD, PhD,‡ Francois Aubin, MD, PhD,§ Thierry Lesimple, MD,‖ Florent Grange, MD, PhD,¶ Bertille Bonniaud, MD,# Laurent Mortier, MD, PhD,** Christine Mateus, MD,†† Brigitte Dreno, MD,‡‡ Brigitte Balme, MD,§§ Beatrice Vergier, MD, PhD,‖‖ and Arnaud de la Fouchardiere, MD, PhD**

(Am J Surg Pathol 2016;40:368–377)

Melanomas associated with blue nevus or mimicking cellular blue nevus

Costa et al, Am J Surg Pathol 2016;40:368–377

11 cases of melanoma (with a blue nv or mimicking cellular blue nv)

- Scalp (91% scalp, 1 shoulder)
- Adults, 21-82 yrs
- 8/11 cases *GNA11*, 1 case *GNAQ*
- 7/11 cases loss of nuclear BAP1 staining
- Several gains and losses CGH (overlap uvea melanoma: gain 8q, 6p, deletion 3p and 1p (BAP1 – cases resemble class 2 uvea melanoma)
- 4/11 regional or distant metastasis

24 cases cellular blue nevus

- 13/24 sacral, 6 cases dorsum hand/feet, 4 scalp
- 6-86 yrs
- All *GNAQ* mutation
- No loss of nuclear BAP1 staining
- 3 cases CGH: flat and 1 case single 4q segmental loss
- No recurrences

Case from the paper.
Male 21, scalp.
BAP1 loss.
Patient developed liver metastasis and died of disease

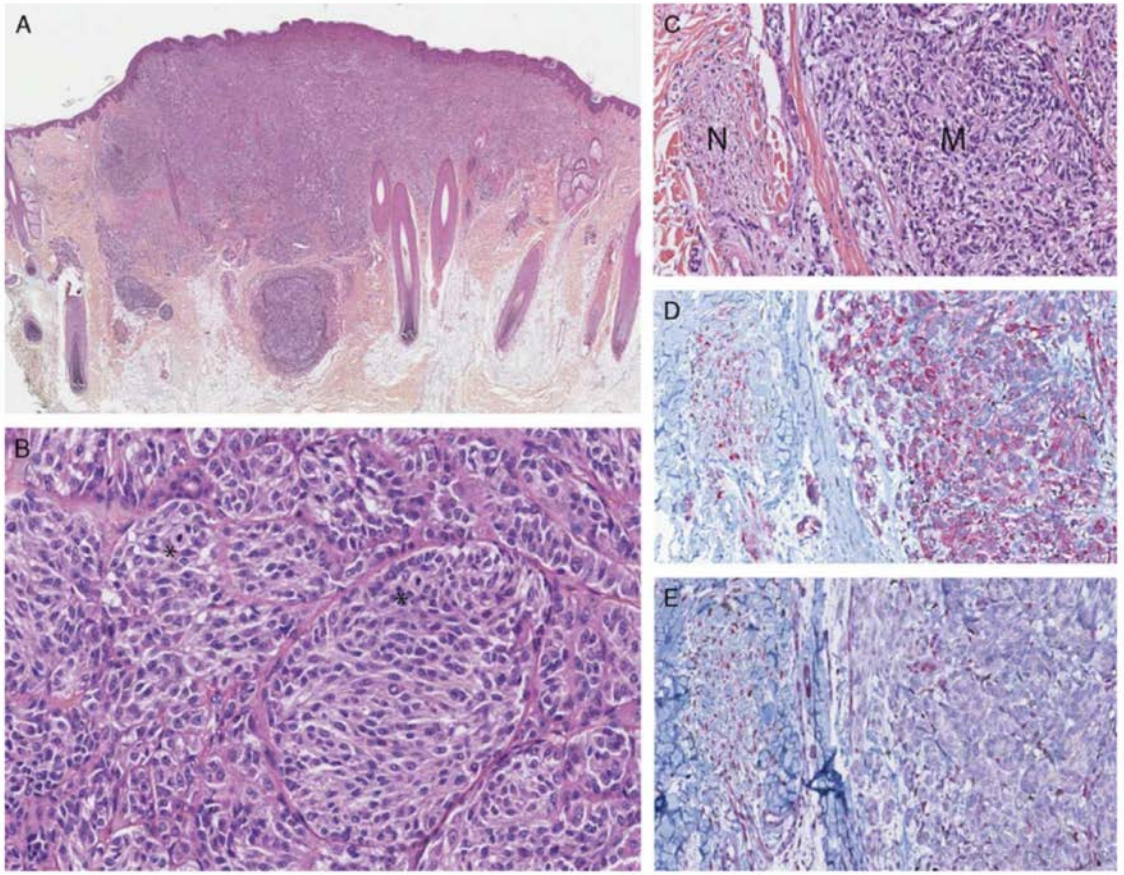


FIGURE 2. MABN with loss of BAP1 (case 1). A, Dense, nodular dermal infiltration. B, Packed nest of atypical melanocytes, mitotic figures (*). C, Patches of common BN (N) adjacent to melanoma nests (M). D, Same area as C; positive HMB45 staining in nevi and melanoma cells. E, Same area as C; nuclear expression of BAP1 is positive in BN, negative in melanoma nests (BAP1 IHC).

Costa et al (Am J Surg Pathol 2016;40:368–377)

Spectrum of BAP1 lesions from daily and consultation practice: for privacy reasons not made public

https://www.puzzels123.com/nl/luchtballonnen-1500-stukjes-puzzel-17977-educa.html

Take home messages

- Always think of BAP1 in case of epithelioid / spitzoid morphology and “air balloon configuration”. Pathologists are very important in early recognition of BAP1 predisposition syndrome
- In case of a BAP1 inactivated lesion, mention in your report on the possibility of BAP1 predisposition syndrome and give advise on dermatological screening and genetic counseling (not all clinicians are familiar with consequences of dx)
- BAP1 immunostaining can be challenging and some cases can be missed with only IH!
- Morphological spectrum of BAP1 tumors is highly variable: common nevus component and TILs not always present, number of epithelioid cells can be low and can only focally be present
- Do not over-diagnose melanoma in BAP1 lesions
- Think of BAP1 like lesions associated with other germline mutations