



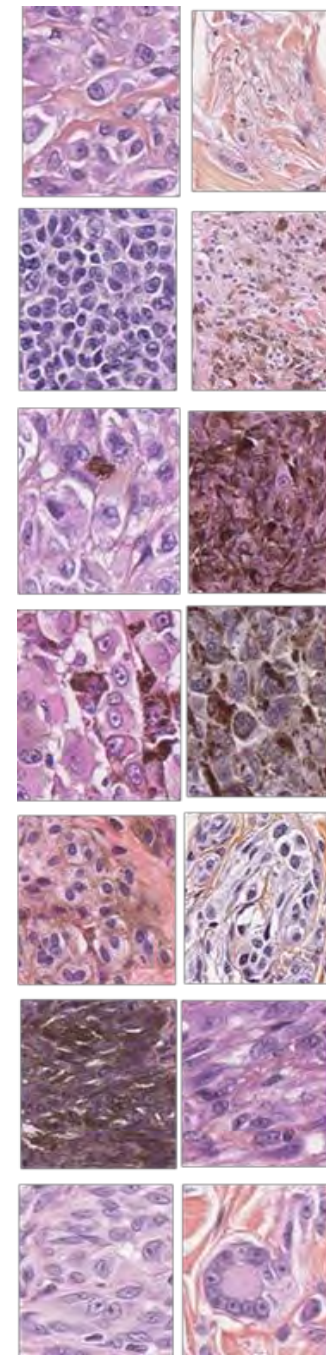
Blue nevus and melanoma ex-blue nevus

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Département de Biopathologie

Centre de Lutte contre le cancer Léon Bérard

Lyon



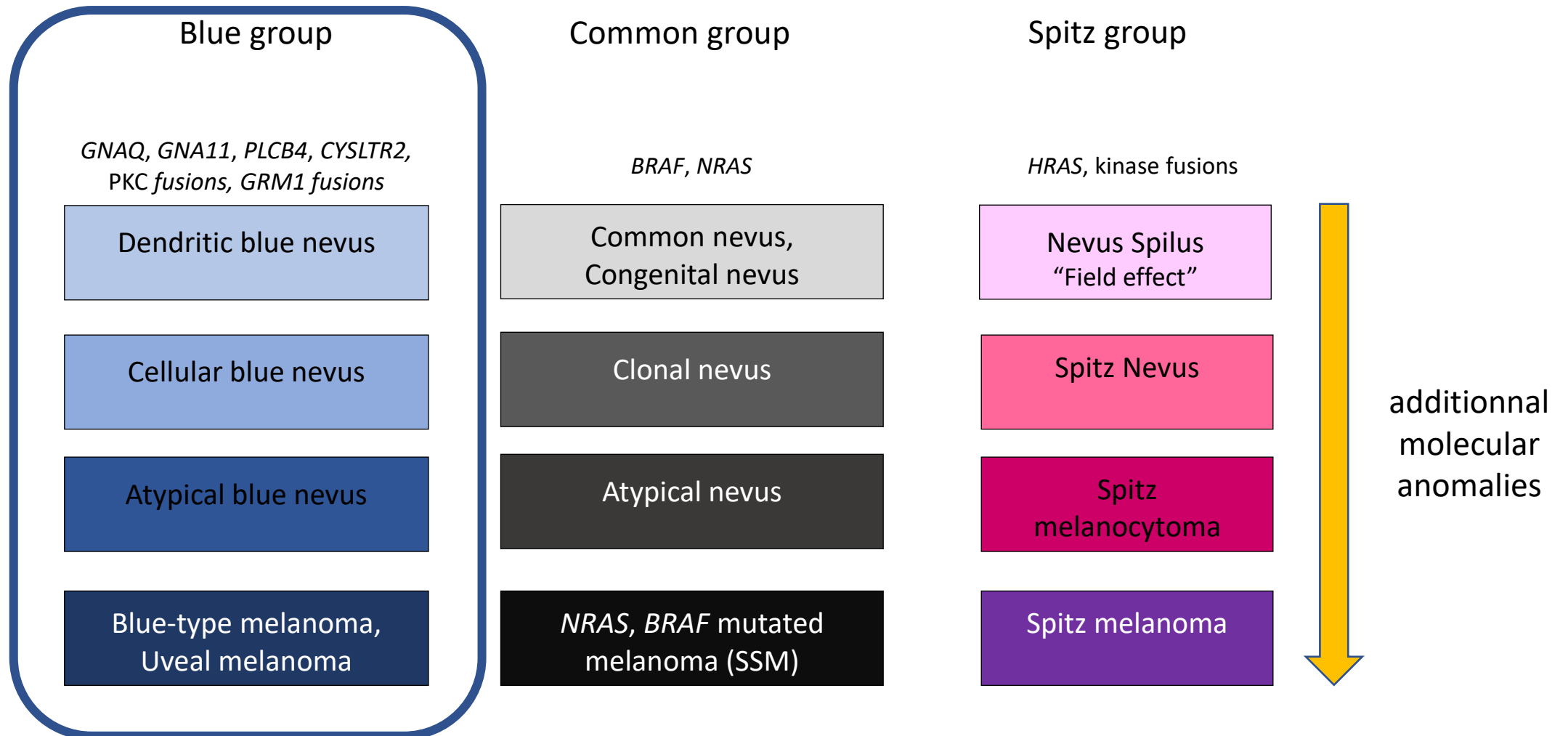
Financial disclosures: none

Teaching points

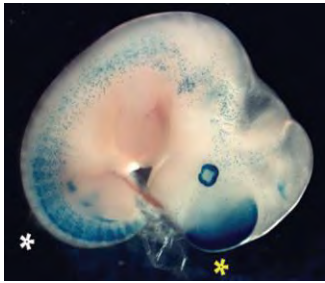
- Multiple examples of the great variations in the clinical and morphological presentations of “classical” blue tumors
- Progression model toward malignancy
- Morphological features of rare/new drivers (*CYSLTR2*, *PKC* and *GRM1*)
- Blue PEM: *PRKAR1A*-inactivation in blue nevi

Integrative classification of melanocytic tumors

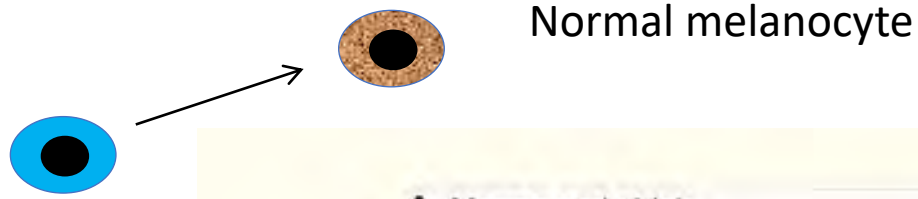
Nevus to melanoma groups



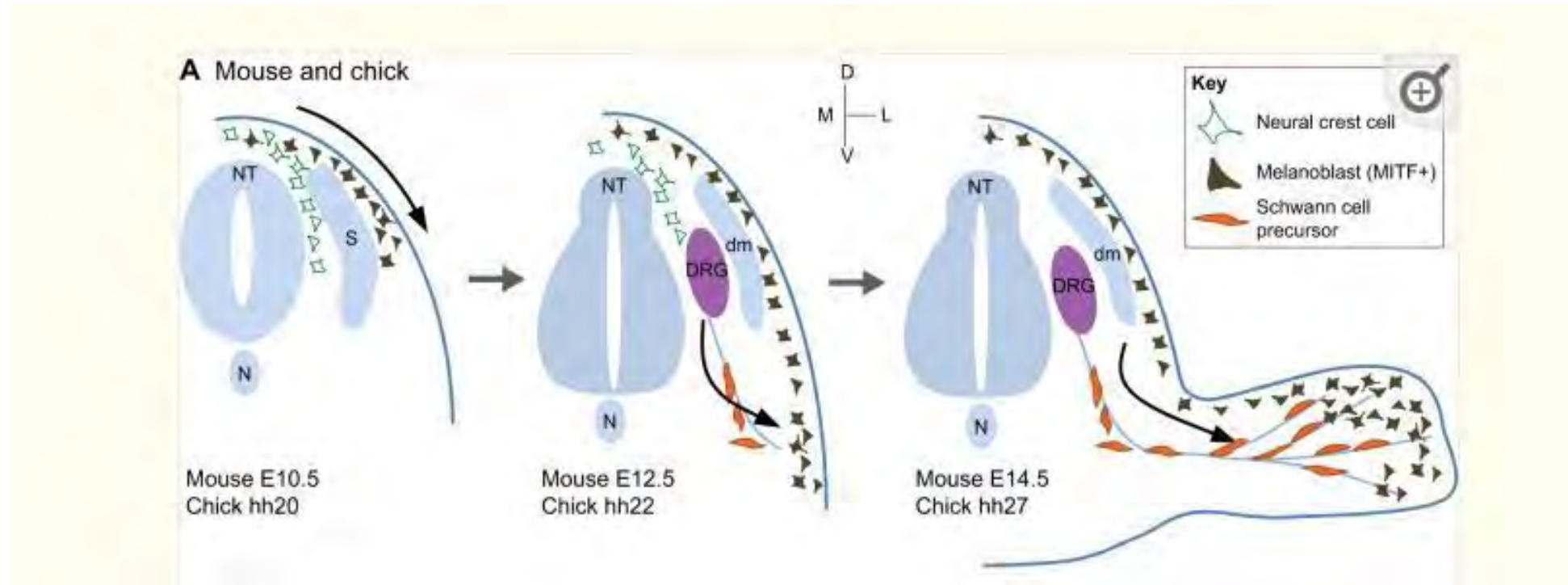
Dorsal-lateral migration of melanoblasts followed by ventral migration



Melanoblast
(Neural crest)



Normal melanocyte



[Development](#). 2015 Feb 15; 142(4): 620–632.

doi: [10.1242/dev.106567](https://doi.org/10.1242/dev.106567)

doi:10.1038/nature05660

The melanocyte lineage in development and disease

Richard L. Mort,¹ Ian J. Jackson,^{1,2,*} and E. Elizabeth Patton^{1,3}

Specific hotspot «blue» melanocytic»mutations

Some are also found in pigmented uveal and leptomeningeal lesions/angiomas

CYSLTR2

p.L129Q

GRM1 gene fusion

MYO10::GRM1

GNAQ

exon5 (p.Q209) > exon4 (p.R183)

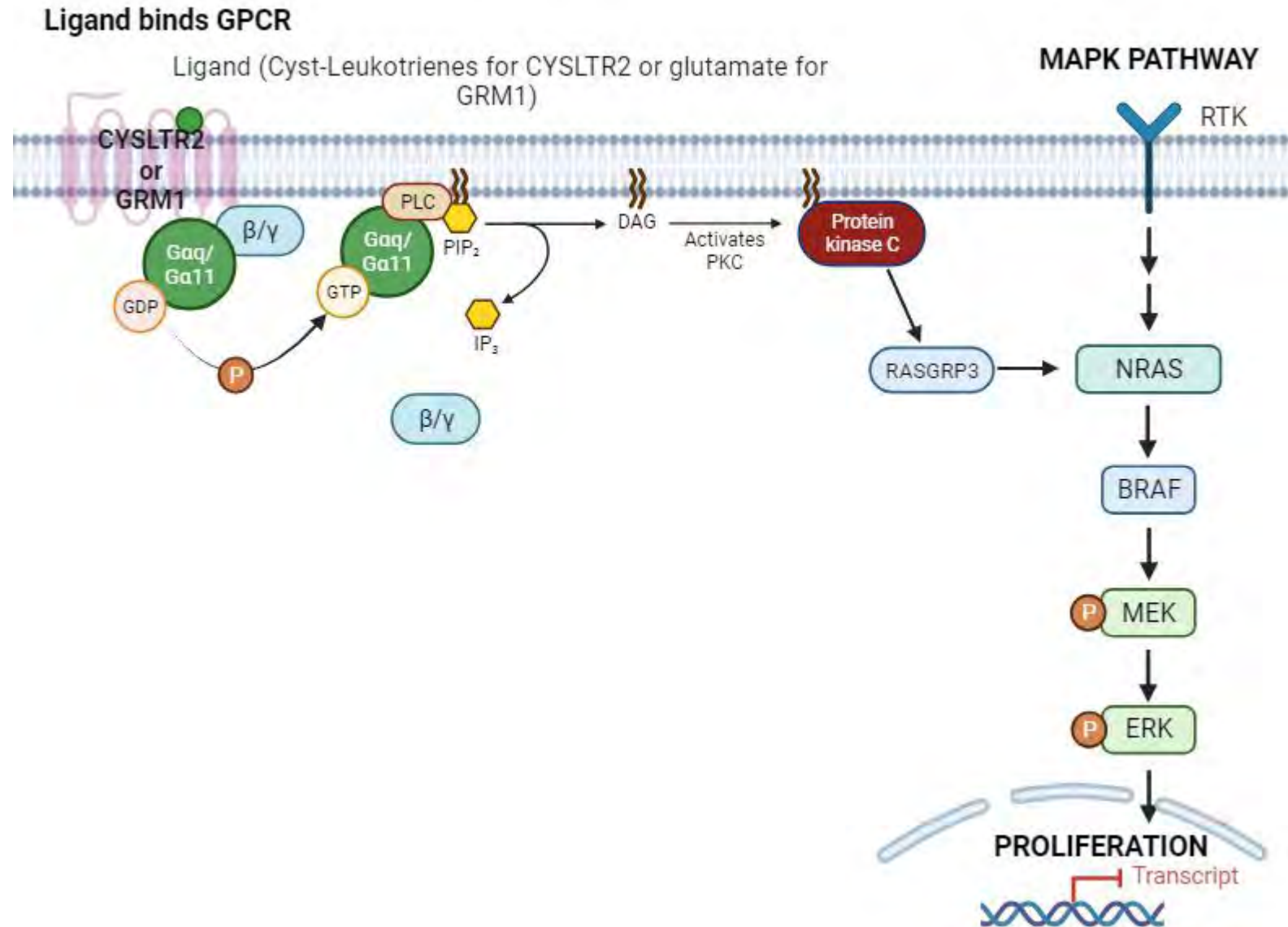
GNA11

exon5 (p.Q209) > exon4 (p.R183)

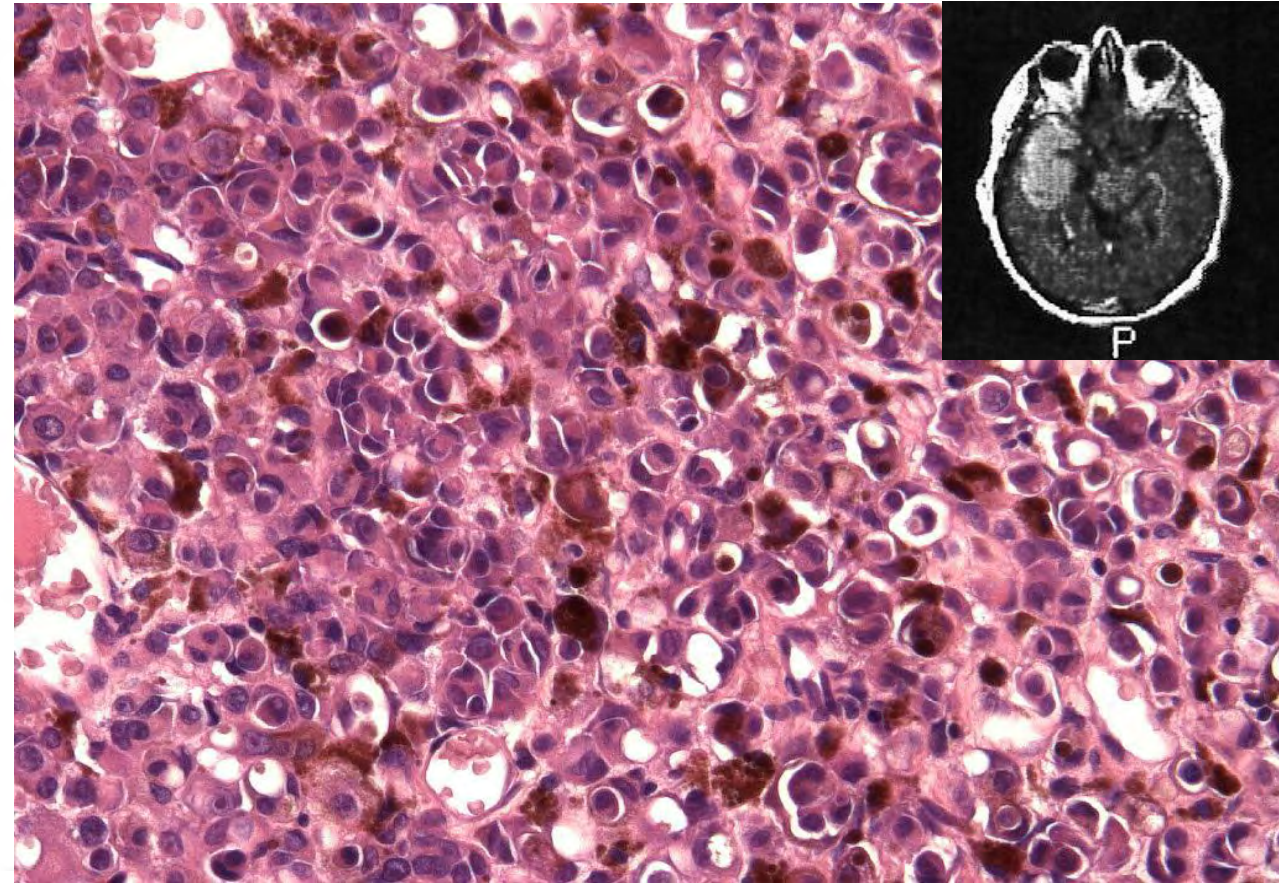
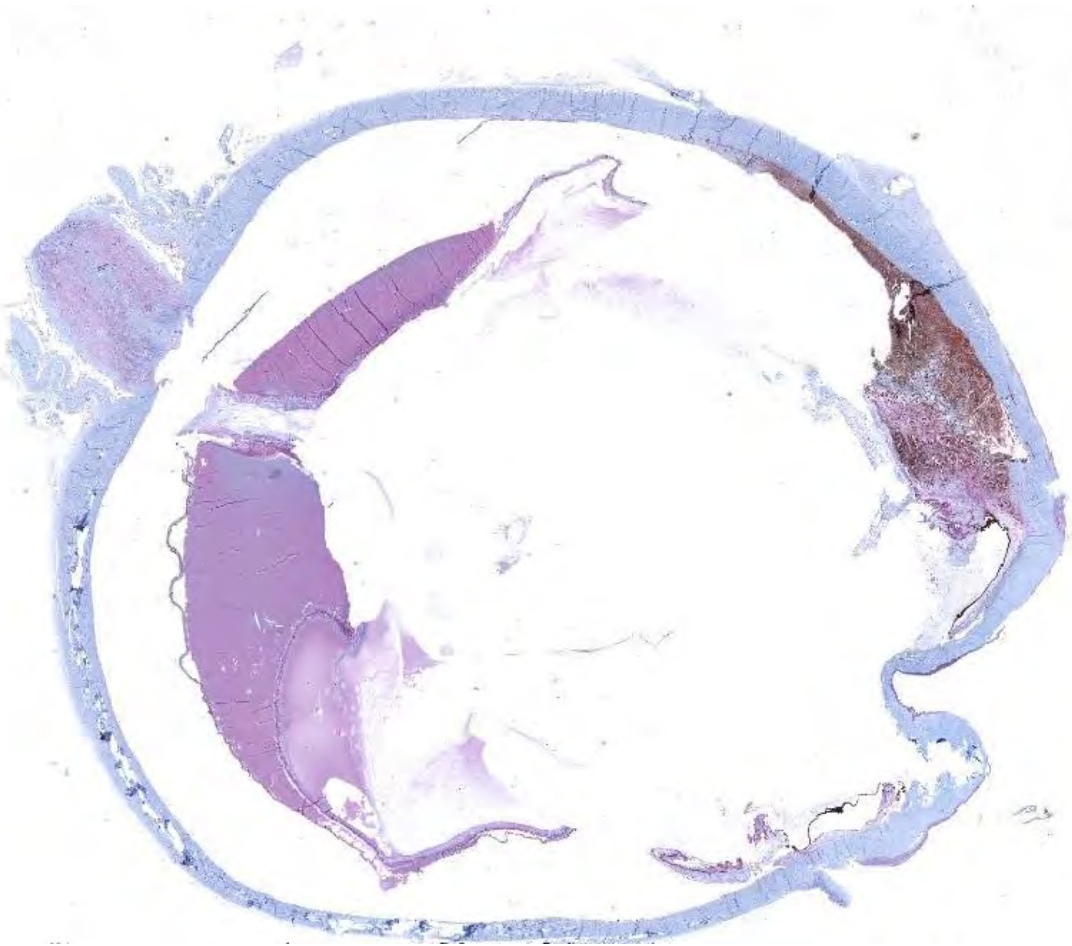
PLCB4

p.D630

PRKCA PRKCB PRKCG gene fusions

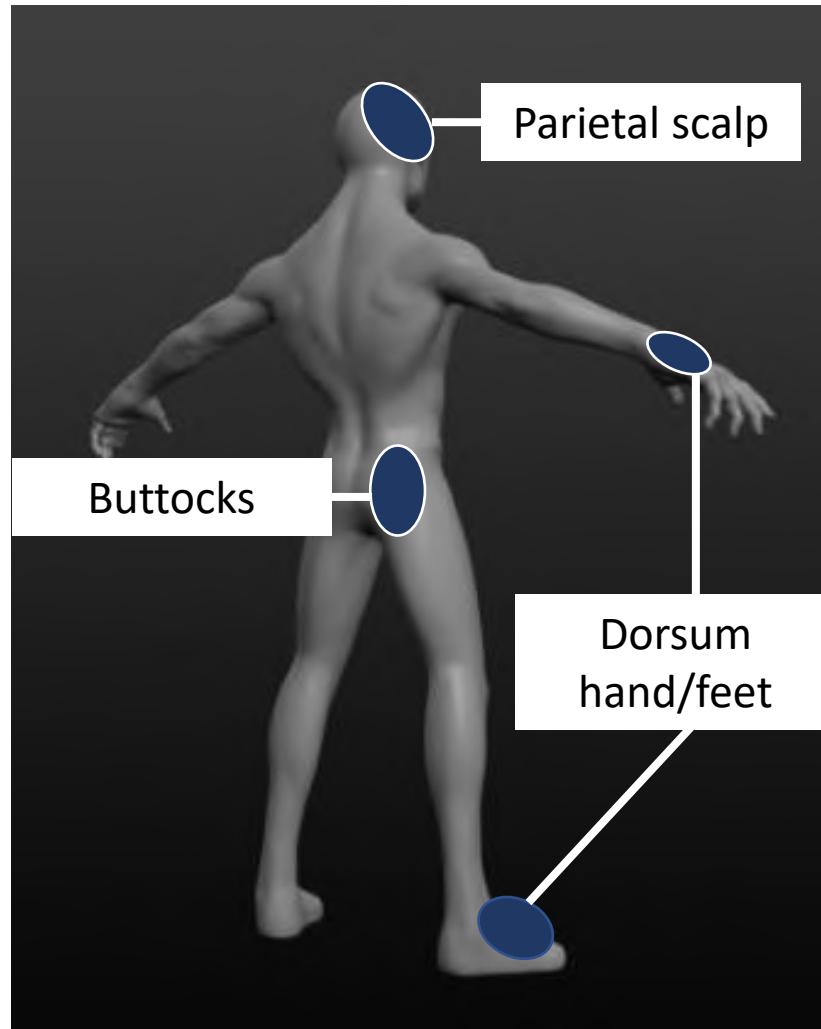


« Blue » melanocytic tumors group



Genetic group with **uveal** and **leptomeningeal** melanocytic lesions

Redundant topography in «Blue» tumors



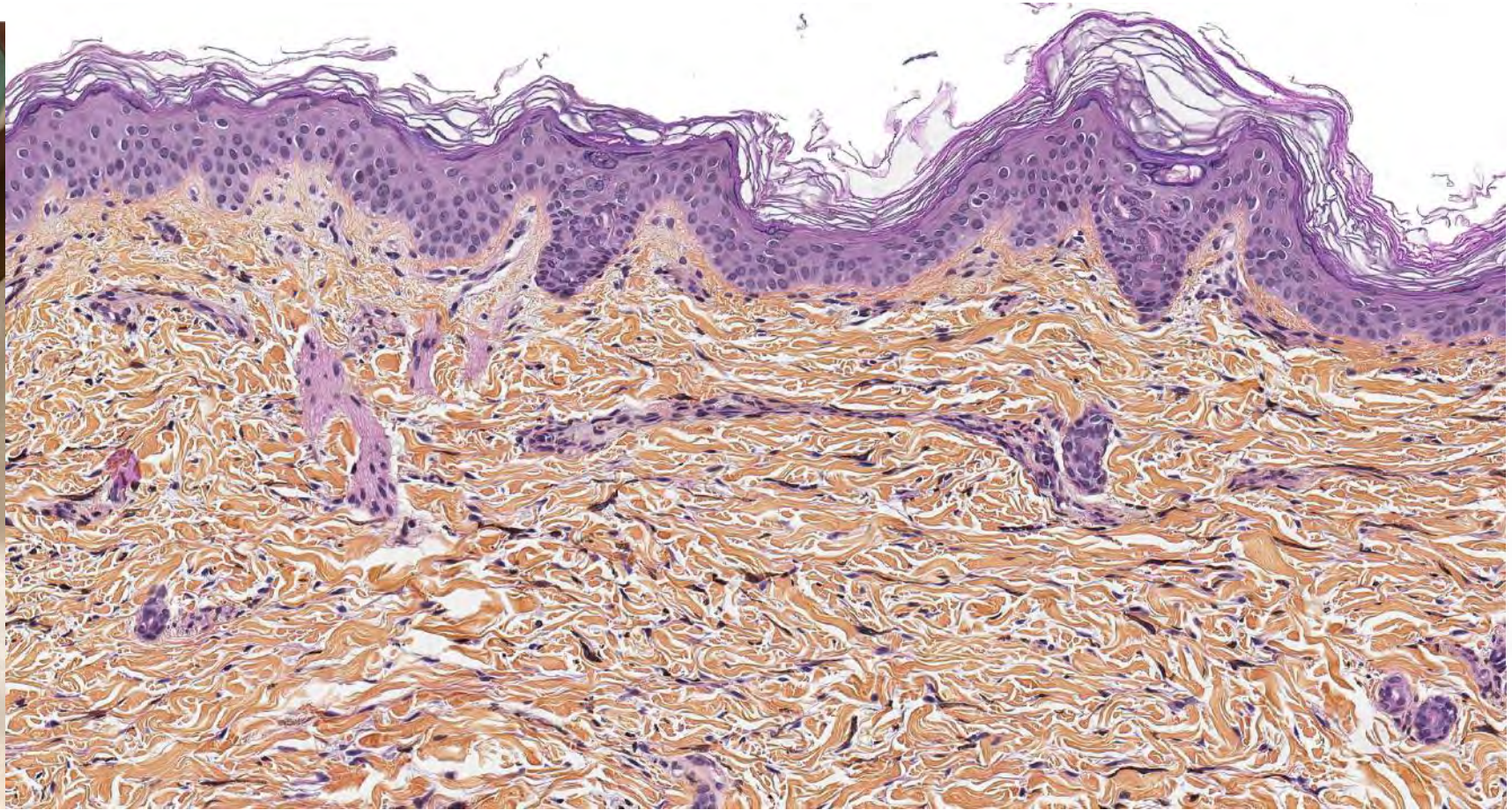
Clinical subtypes

Localized dermal melanosis

- Gluteal or scalp areas
- Progressive fading

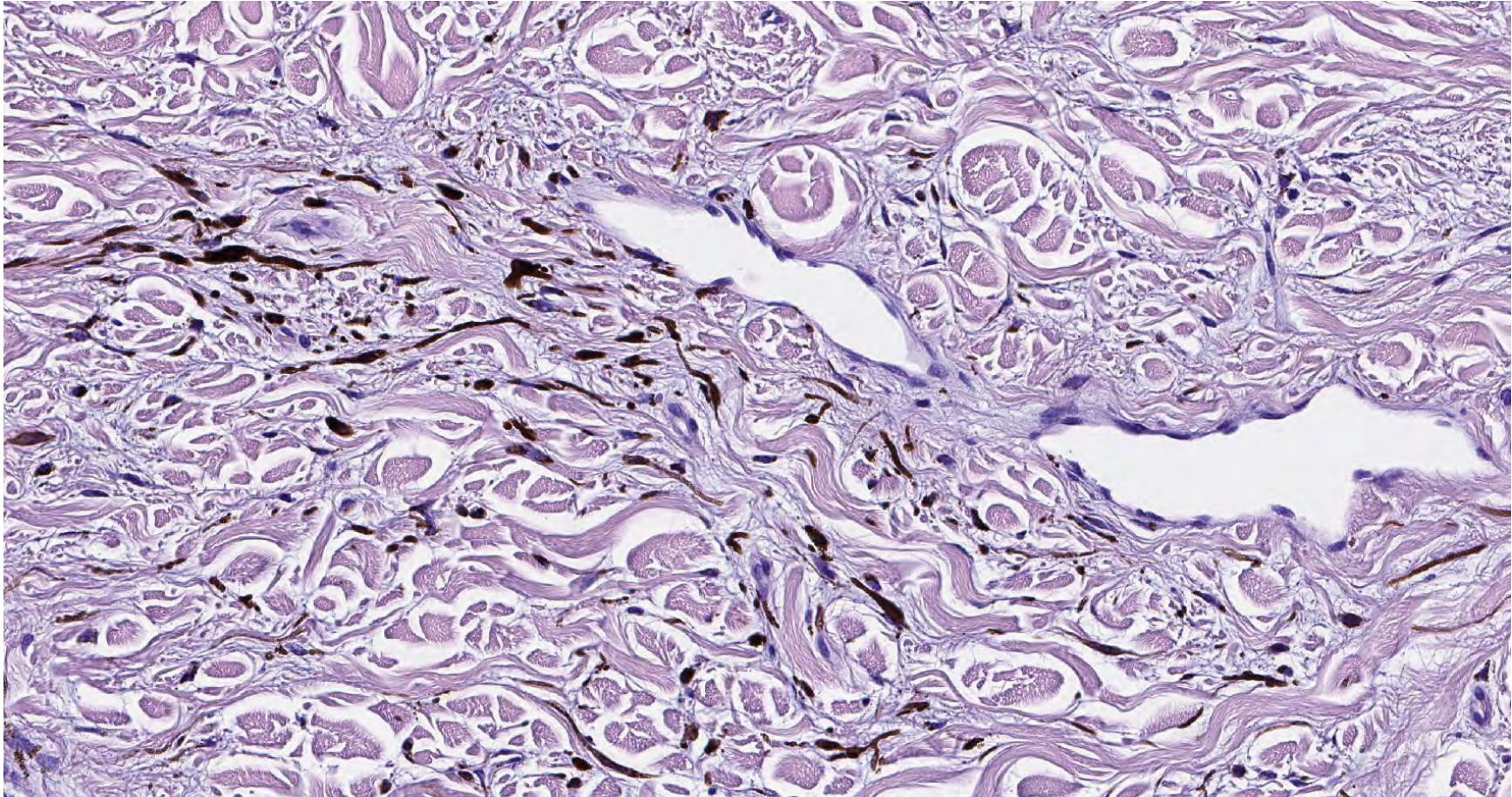


Dermal melanocytosis



Dr James

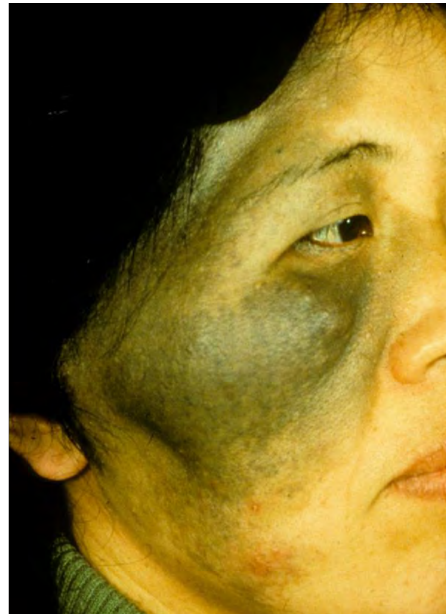
Dermal melanocytosis



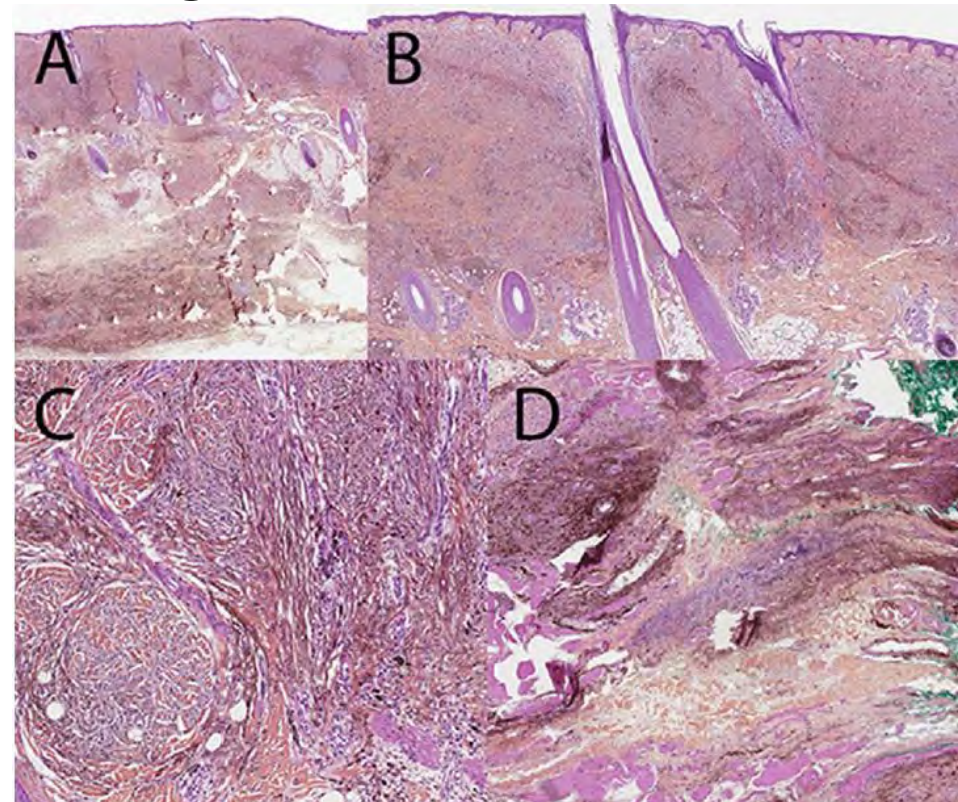
Clinical subtypes

Ota nevus

- Trigeminal/malar region
- Skin, ocular globe, bone and leptomeningial involvement
- +/- hemangioma



WHO book pictures



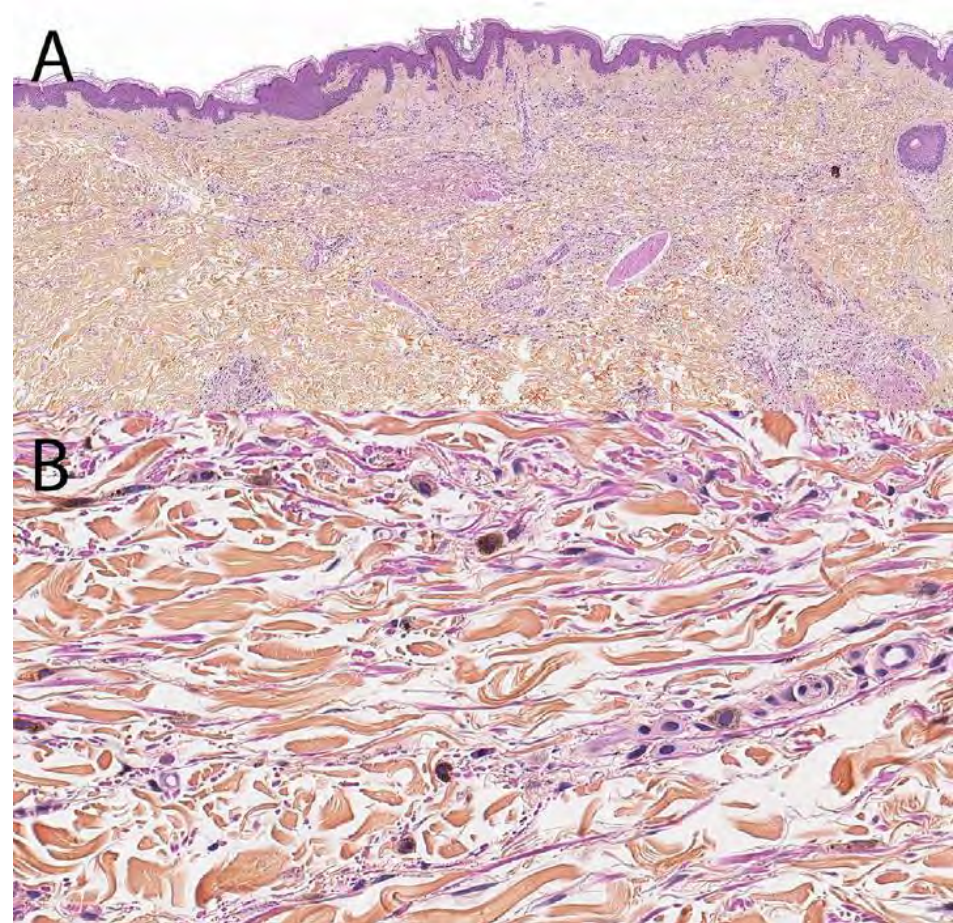
Clinical subtypes

Ito nevus

- Acromio-clavicular patch

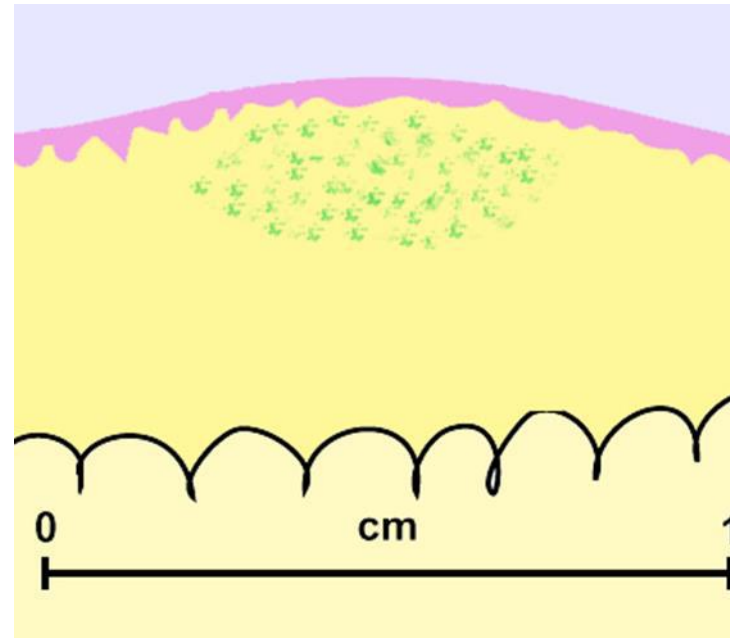


WHO book pictures



Dendritic blue nevus

- Ubiquitous (back of hand and feet)
- Small dome-shaped blue tumor



Clinical subtype Plaque type dendritic blue nevus



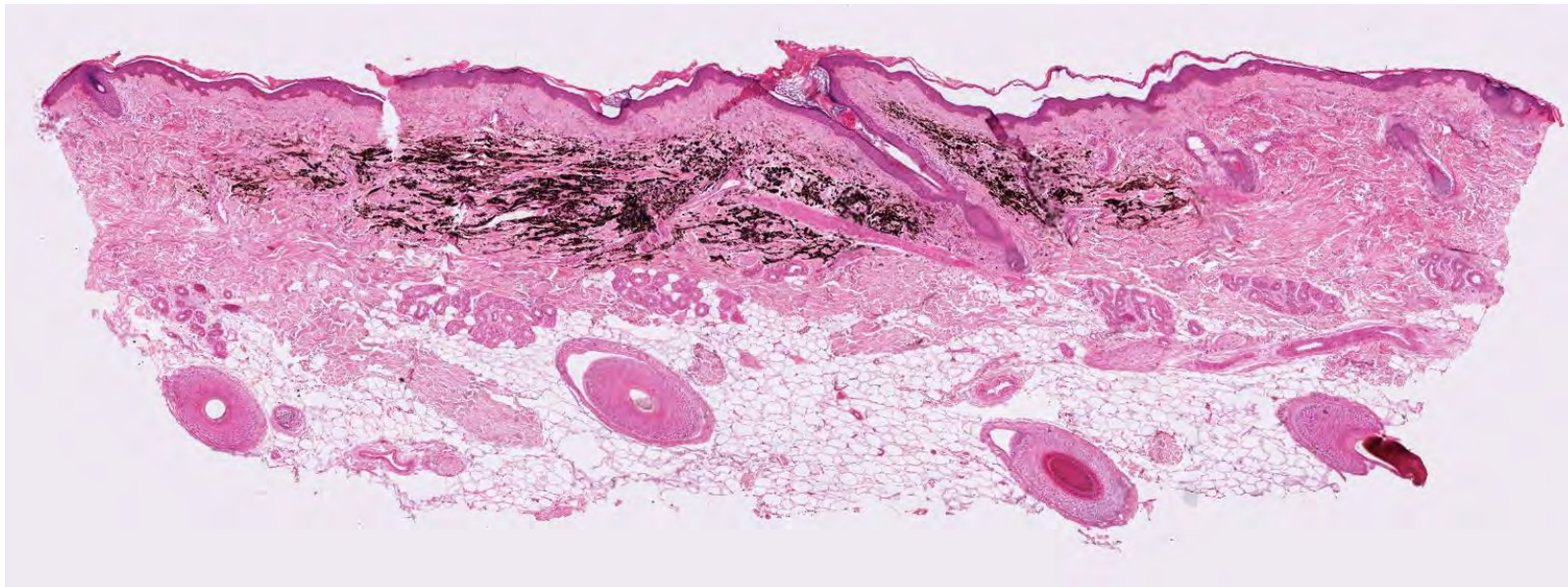
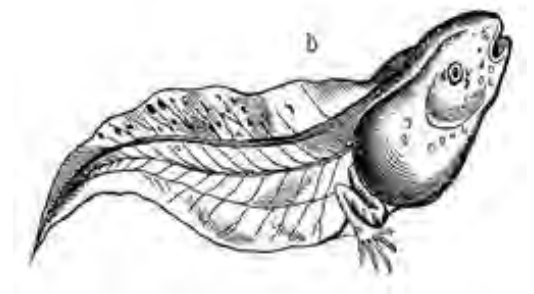
Clinical subtype

Plaque type dendritic blue nevus

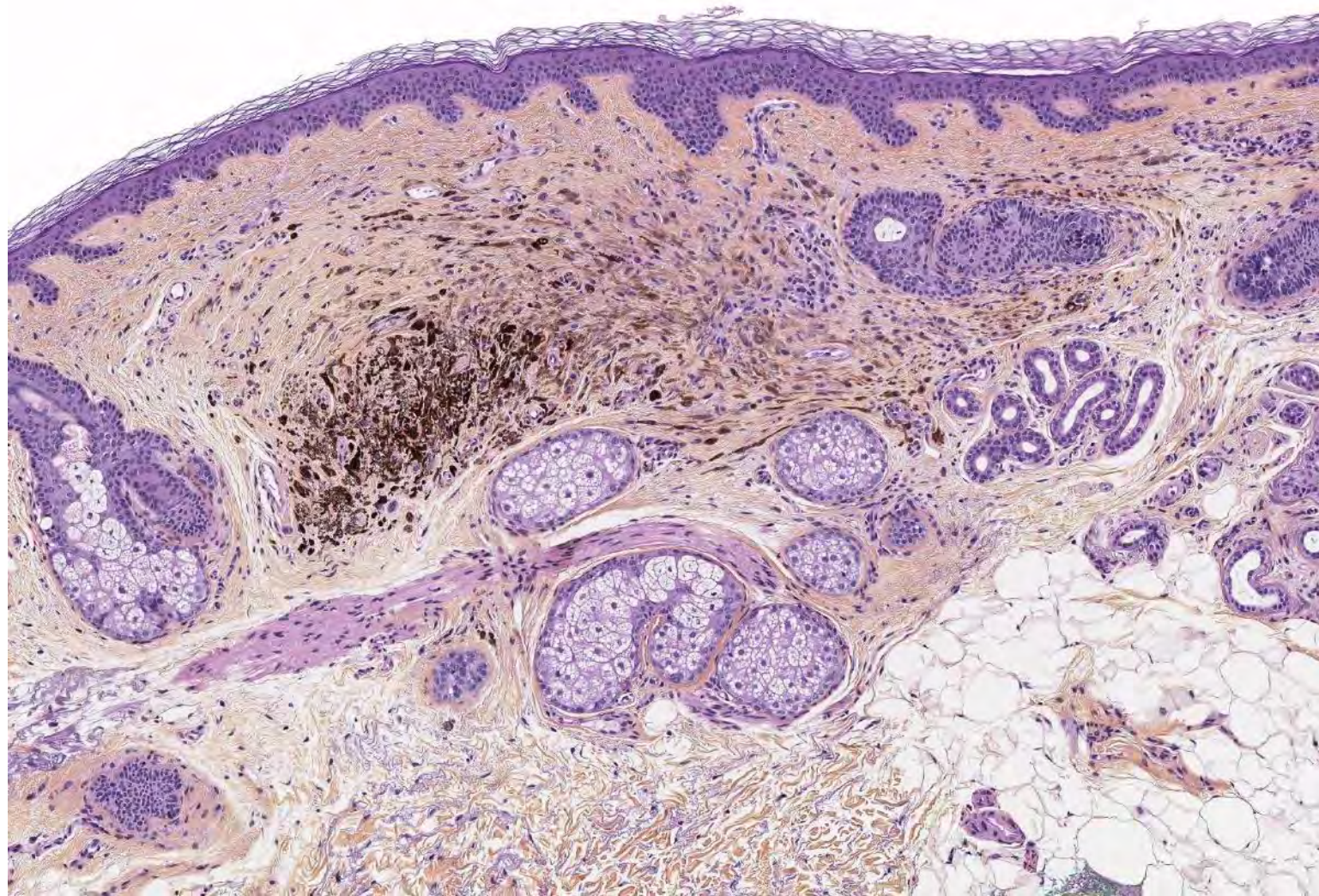


Dendritic blue nevus

- Dispersed dermal dendritic melanocytes
- Fibrous background
- Adnexial/vascular tropism

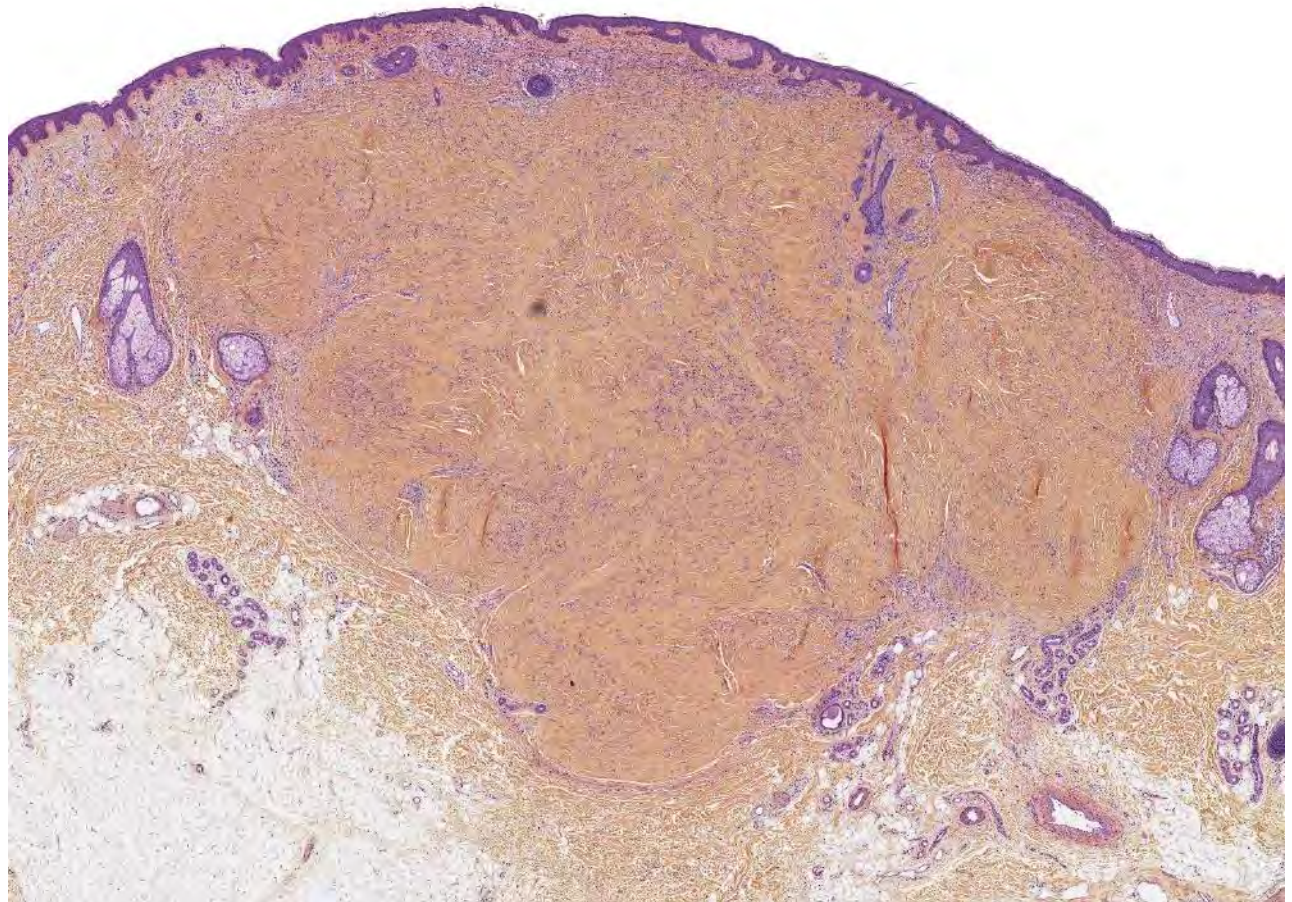


Dendritic blue nevus



Sclerosing blue nevus

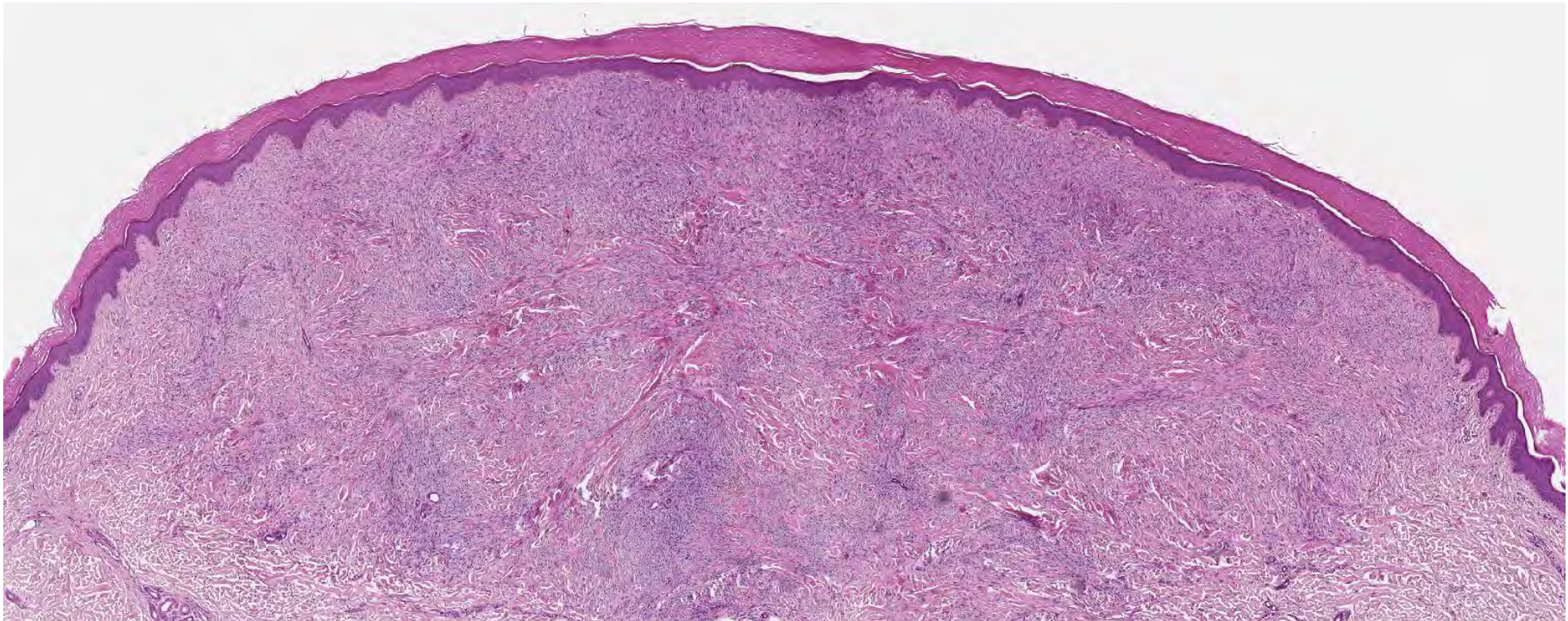
Often scalp/face topography
Adnexial rarefaction



Intermediate subtypes

Blue nevus with hypercellularity

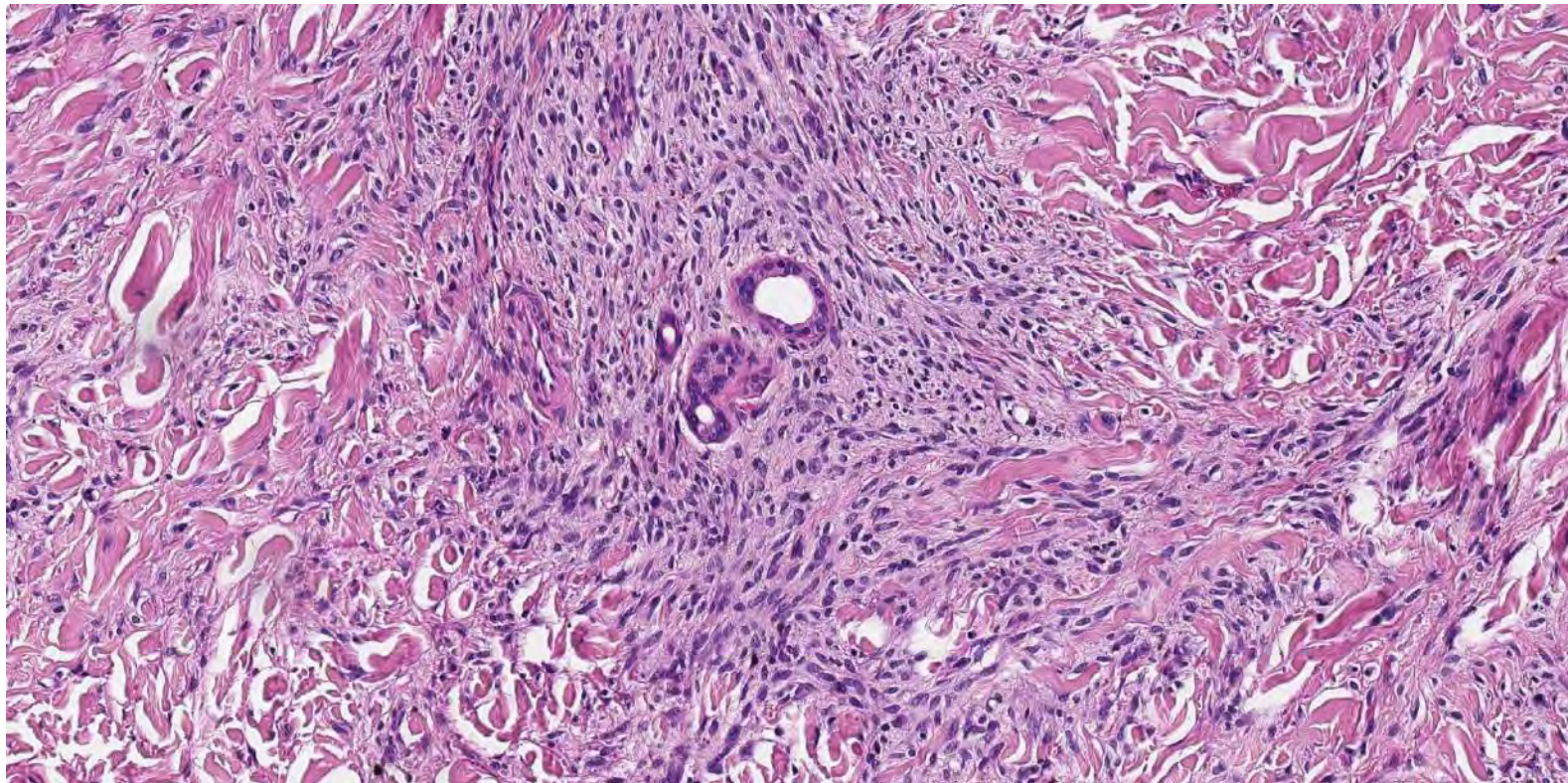
- Superficial/plexiform topography
- Small cellular areas



Intermediate subtypes

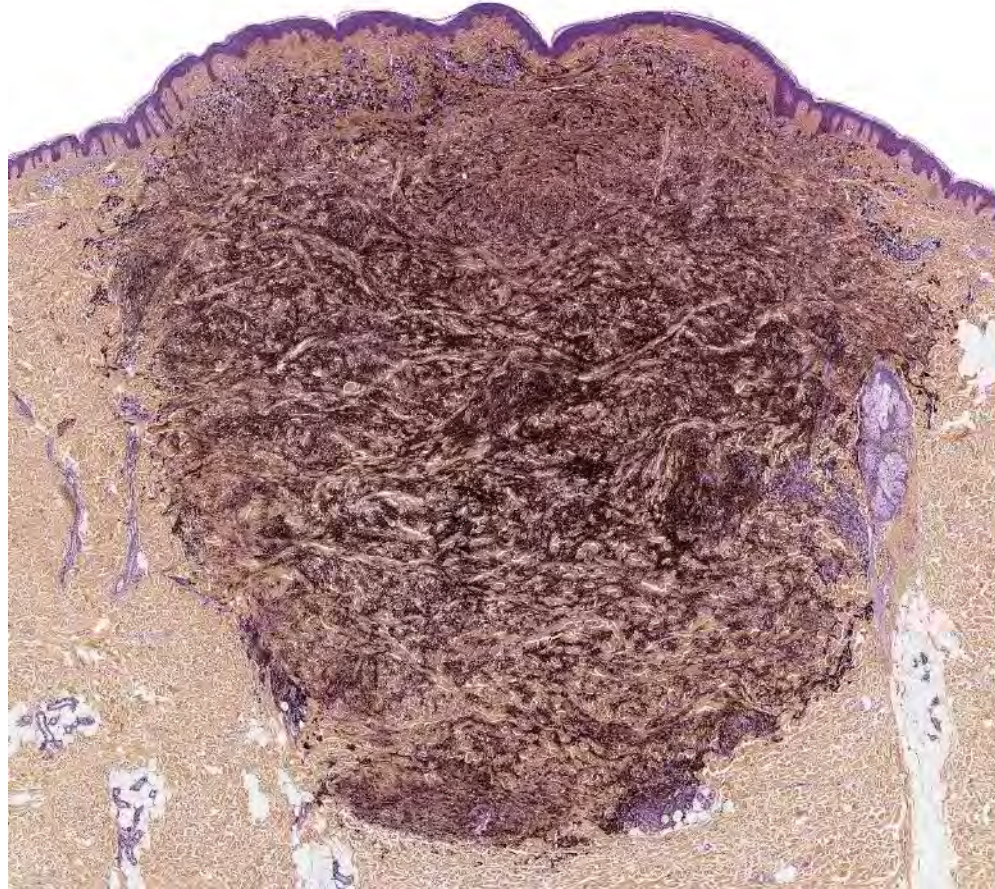
Blue nevus with hypercellularity

- Superficial/plexiform topography
- Small cellular areas



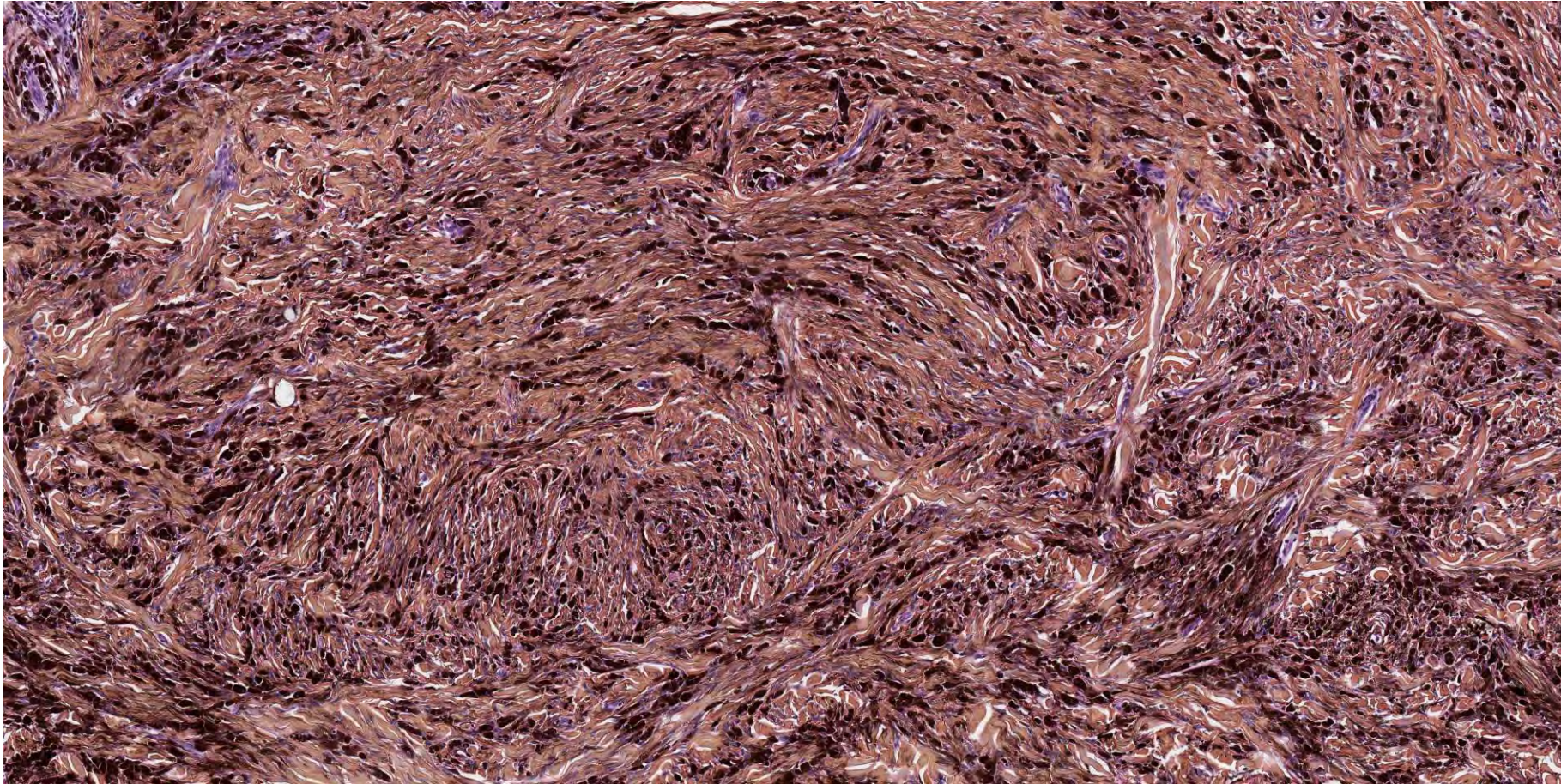
Intermediate subtypes

Blue nevus with hypercellularity



Intermediate subtypes

Blue nevus with hypercellularity



Compound blue nevus Kamino Nevus

Virchows Archiv

<https://doi.org/10.1007/s00428-019-02667-w>

ORIGINAL ARTICLE

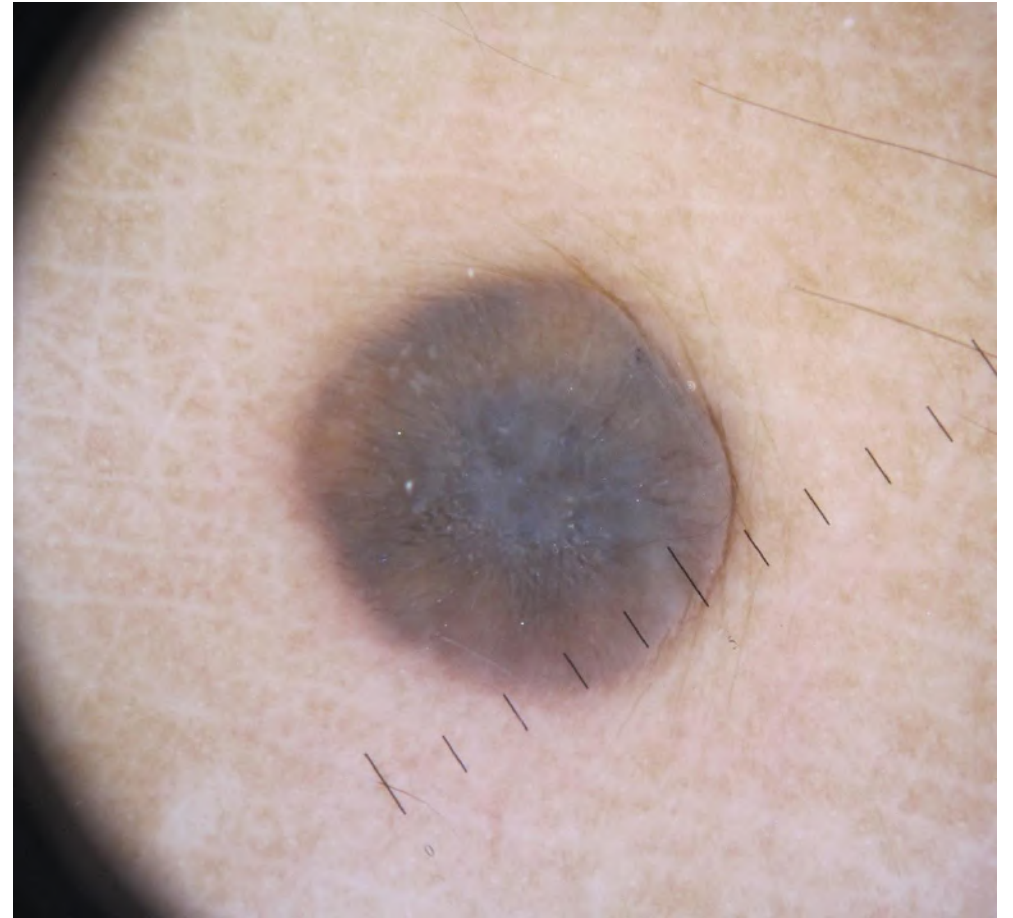
Compound blue nevus: a reappraisal of the concept in the genomic era

Julien Jaquemus¹ • Emilie Perron² • Adrien Buisson¹ • Gerardo Ferrara³ • Veronique Haddad¹ •
Arnaud de la Fouchardiere^{1,4}

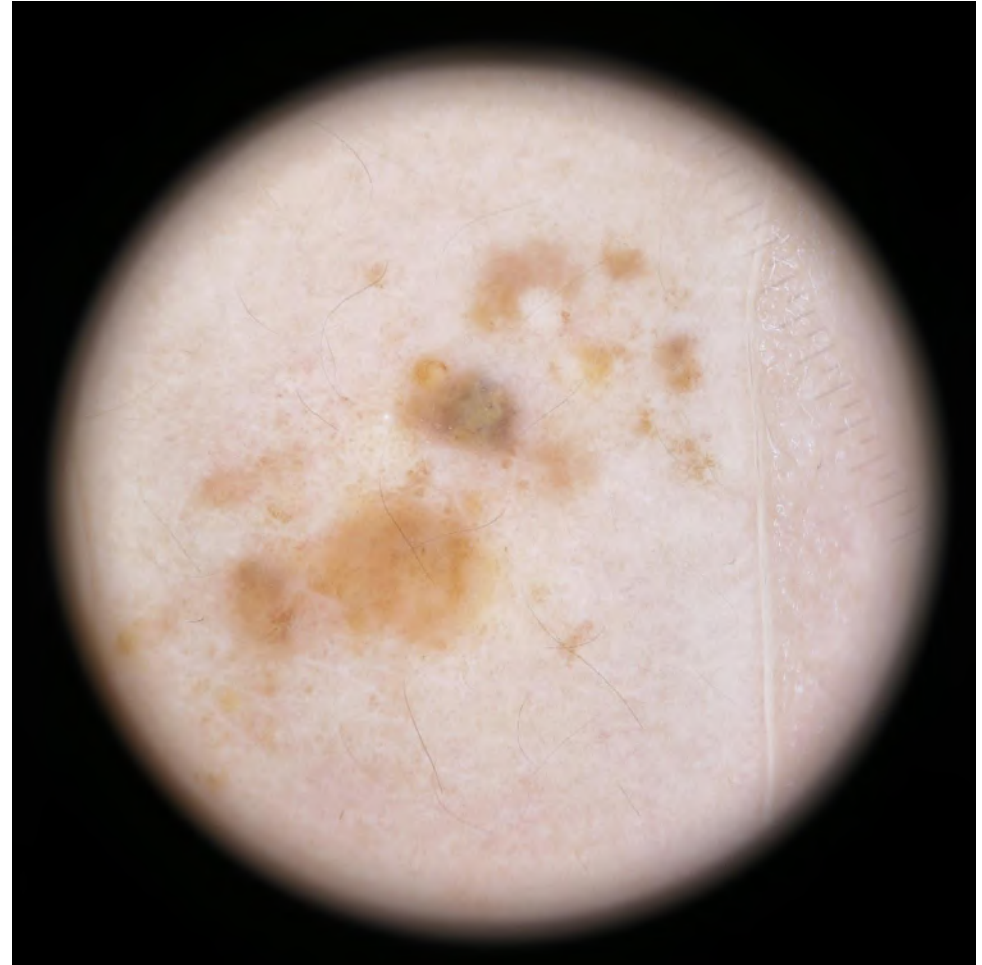
Received: 16 July 2019 / Revised: 4 September 2019 / Accepted: 10 September 2019

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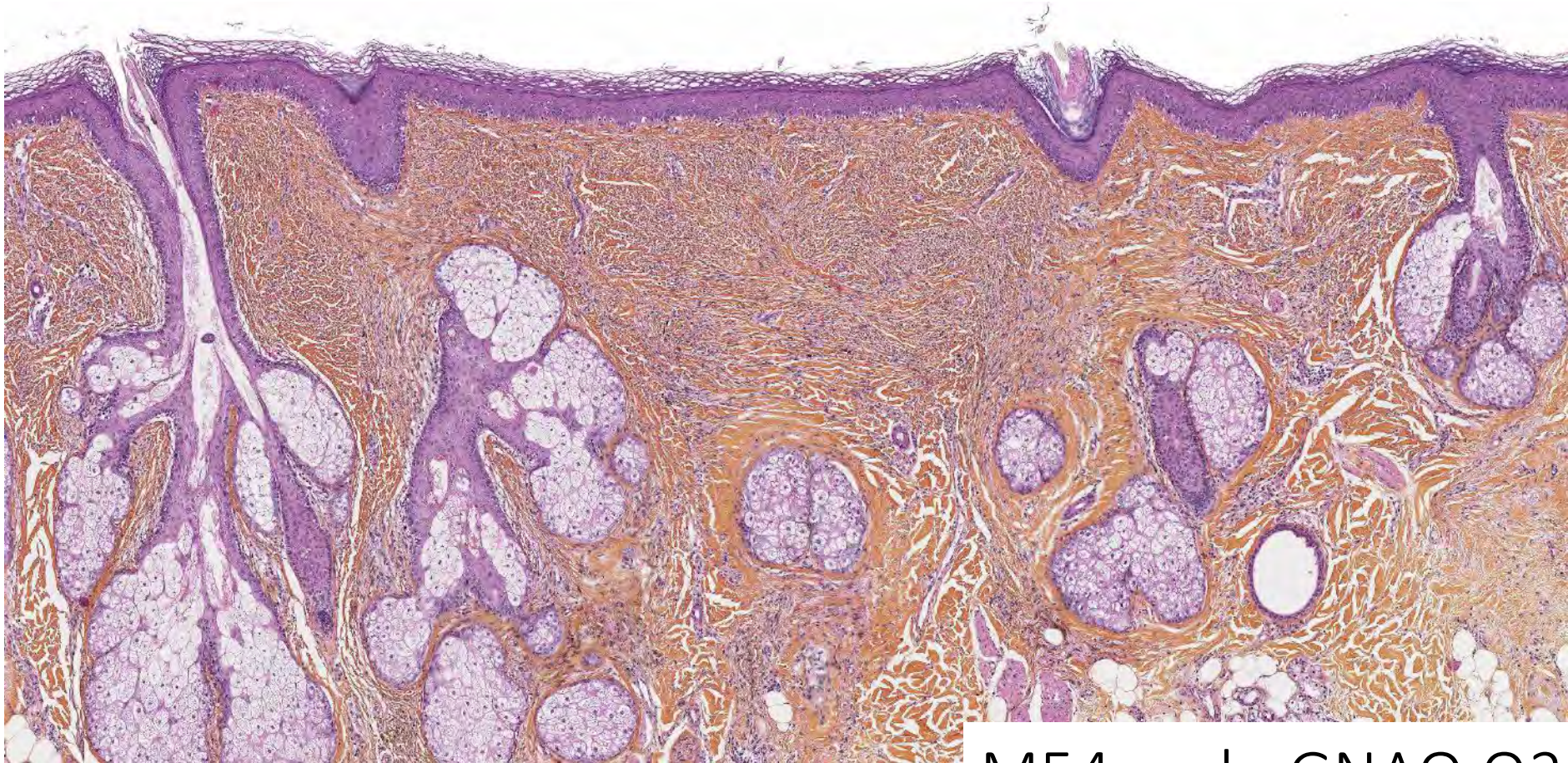
Compound blue nevus: clinical features



Plaque-type compound blue nevus (GNAQ Q209P mutation)

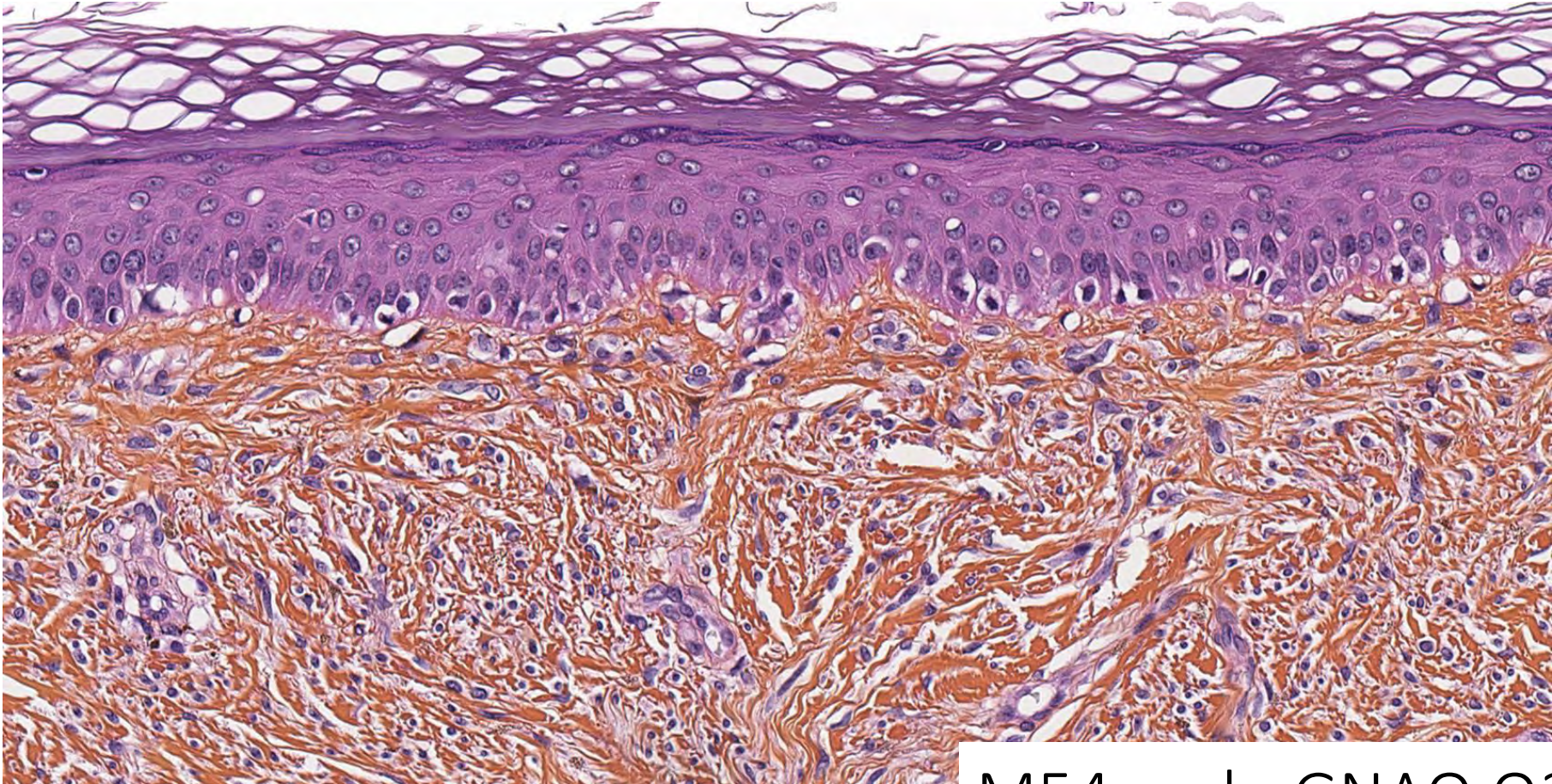


Compound blue nevus Dendritic junctional component



M54 scalp GNAQ Q209L

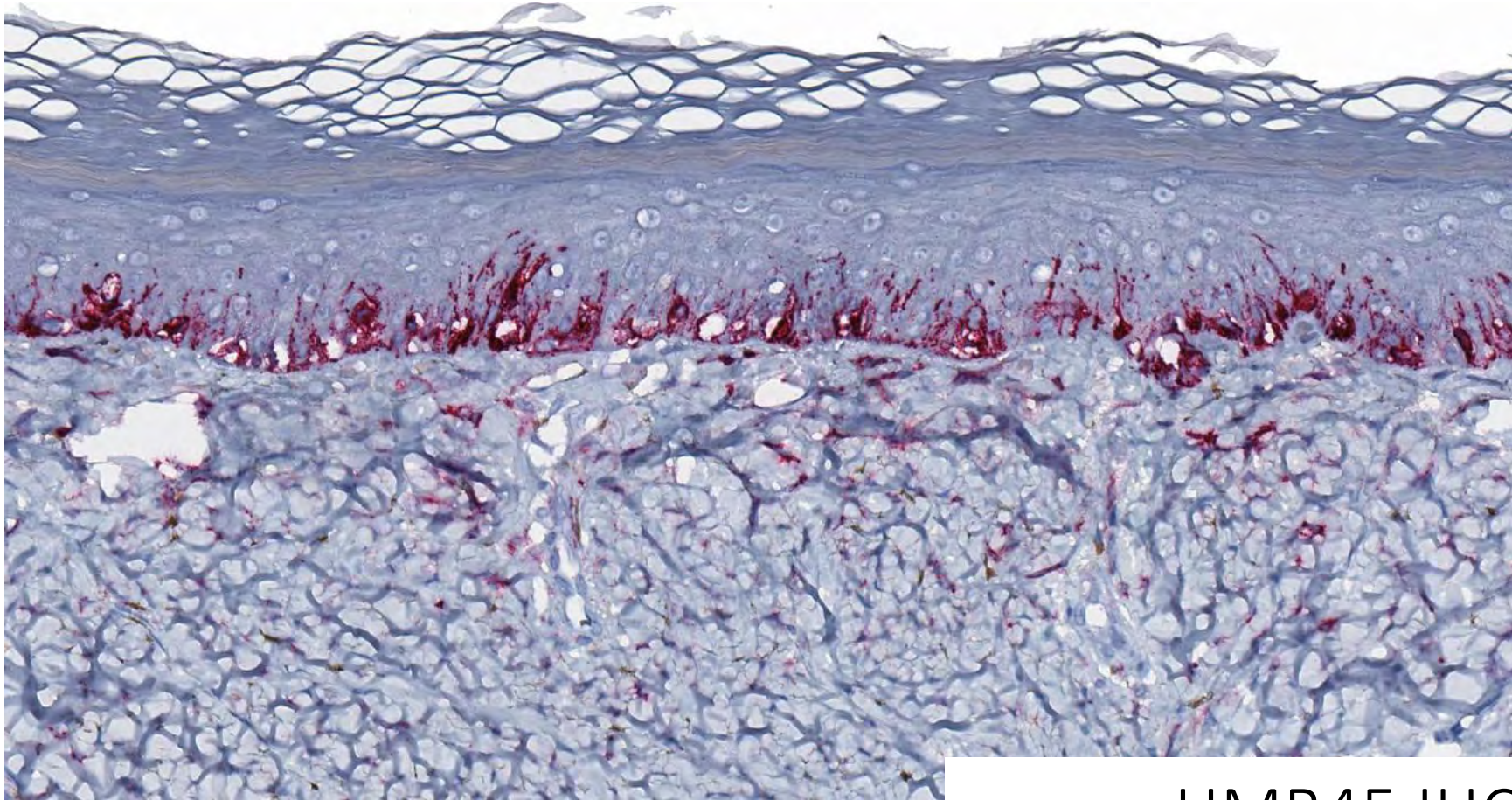
Compound blue nevus Dendritic junctional component



M54 scalp GNAQ Q209L

Compound blue nevus

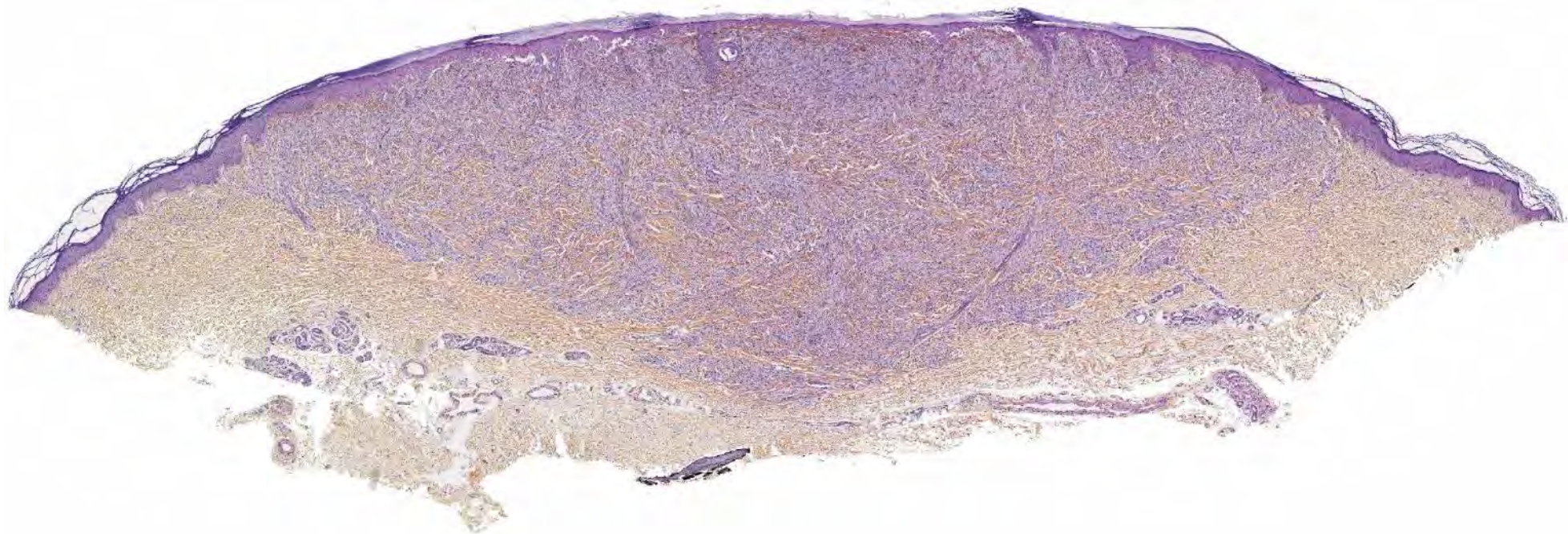
Dendritic junctional component



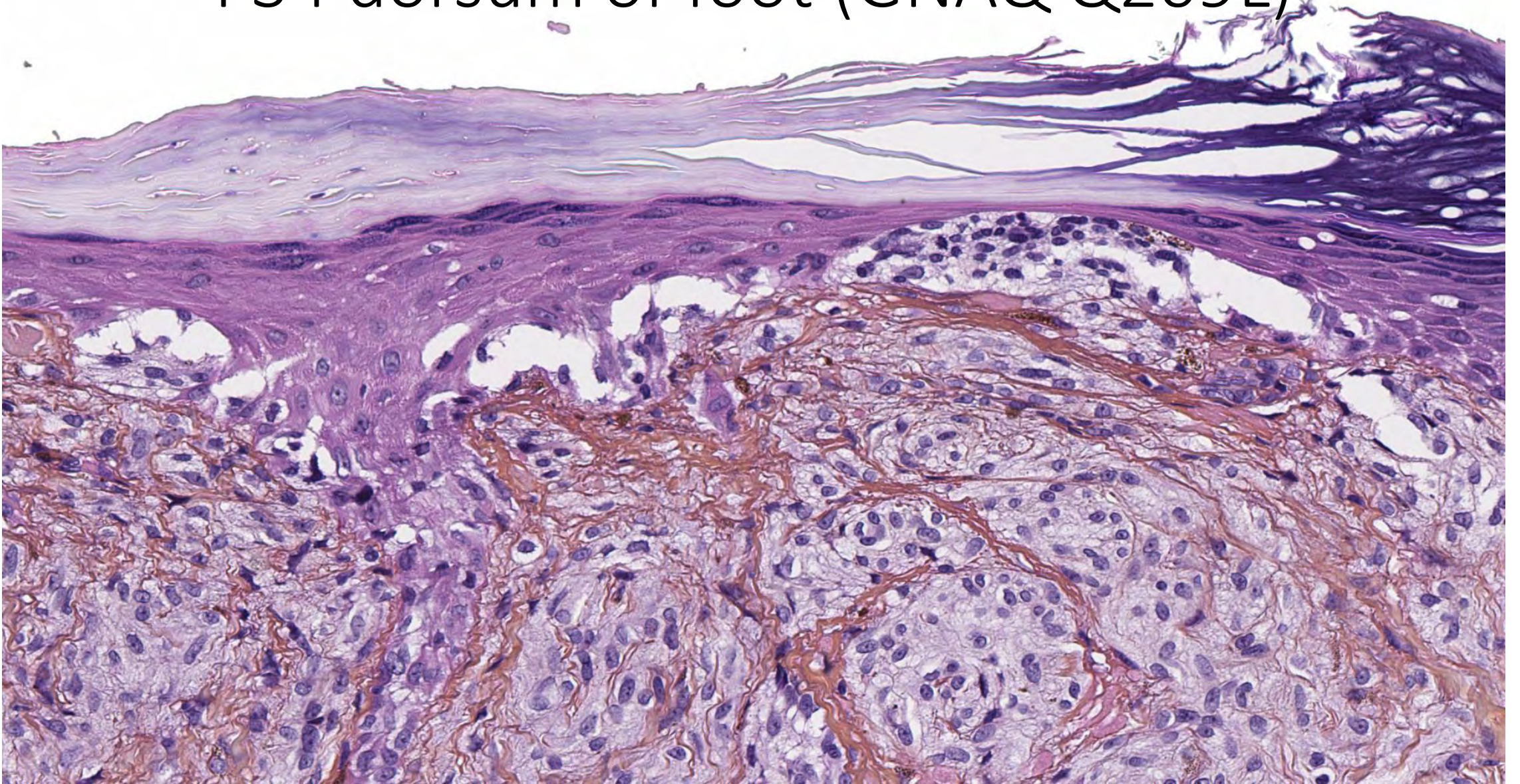
HMB45 IHC

Compound blue nevus Kamino Nevus

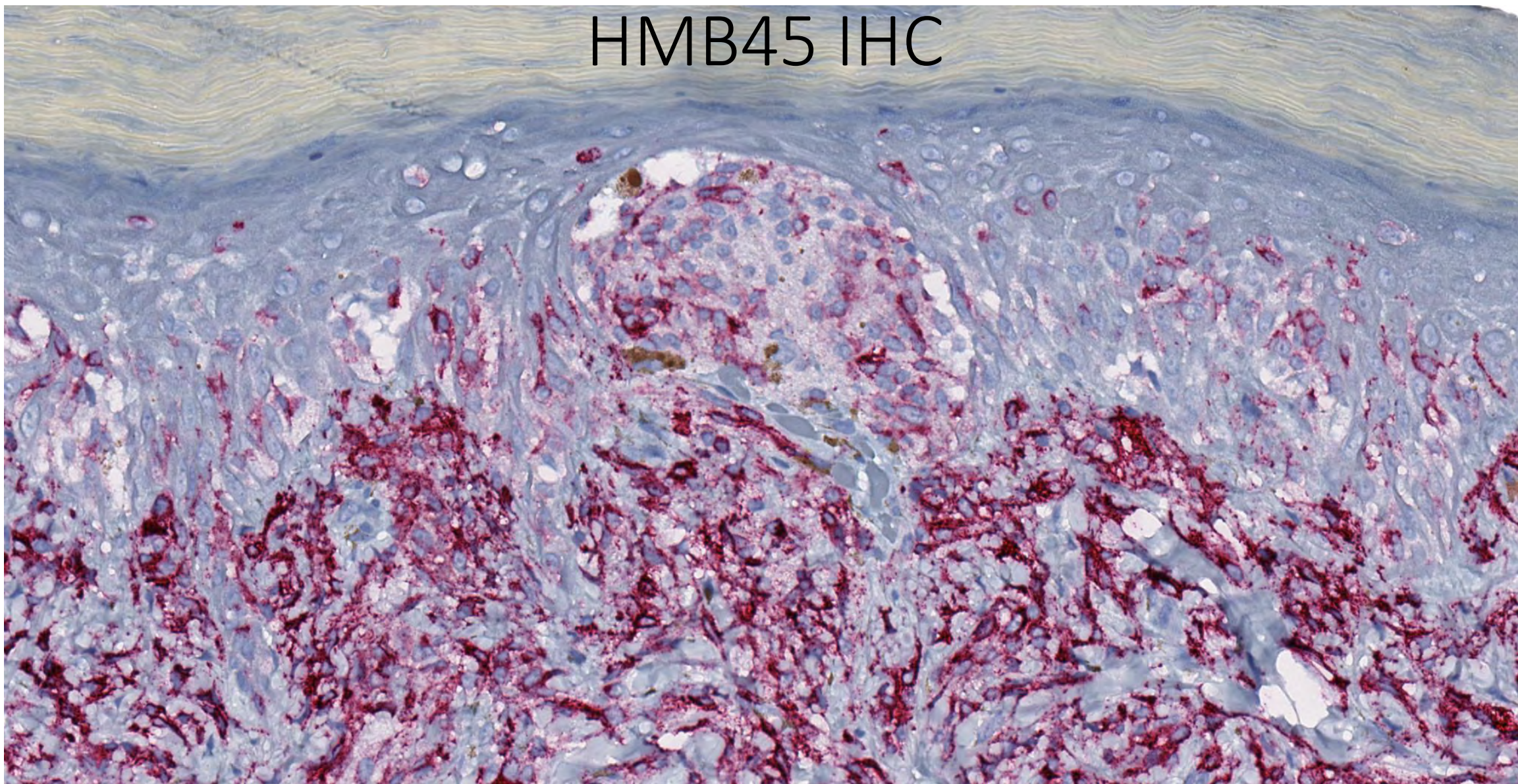
- Dorsum of foot +++
- Central nevocytoid nests with a symmetrical lentiginous lateral fading



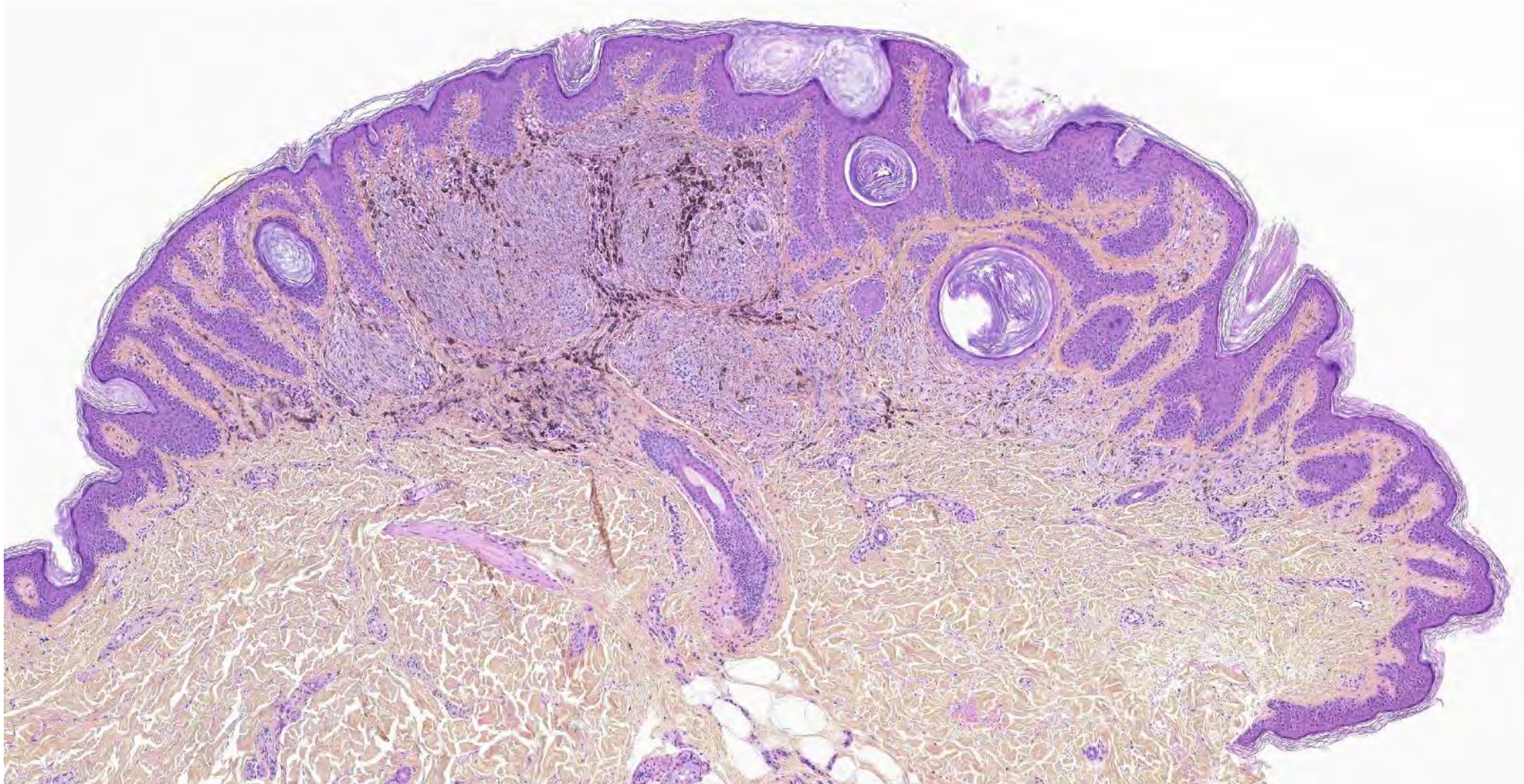
F34 dorsum of foot (GNAQ Q209L)



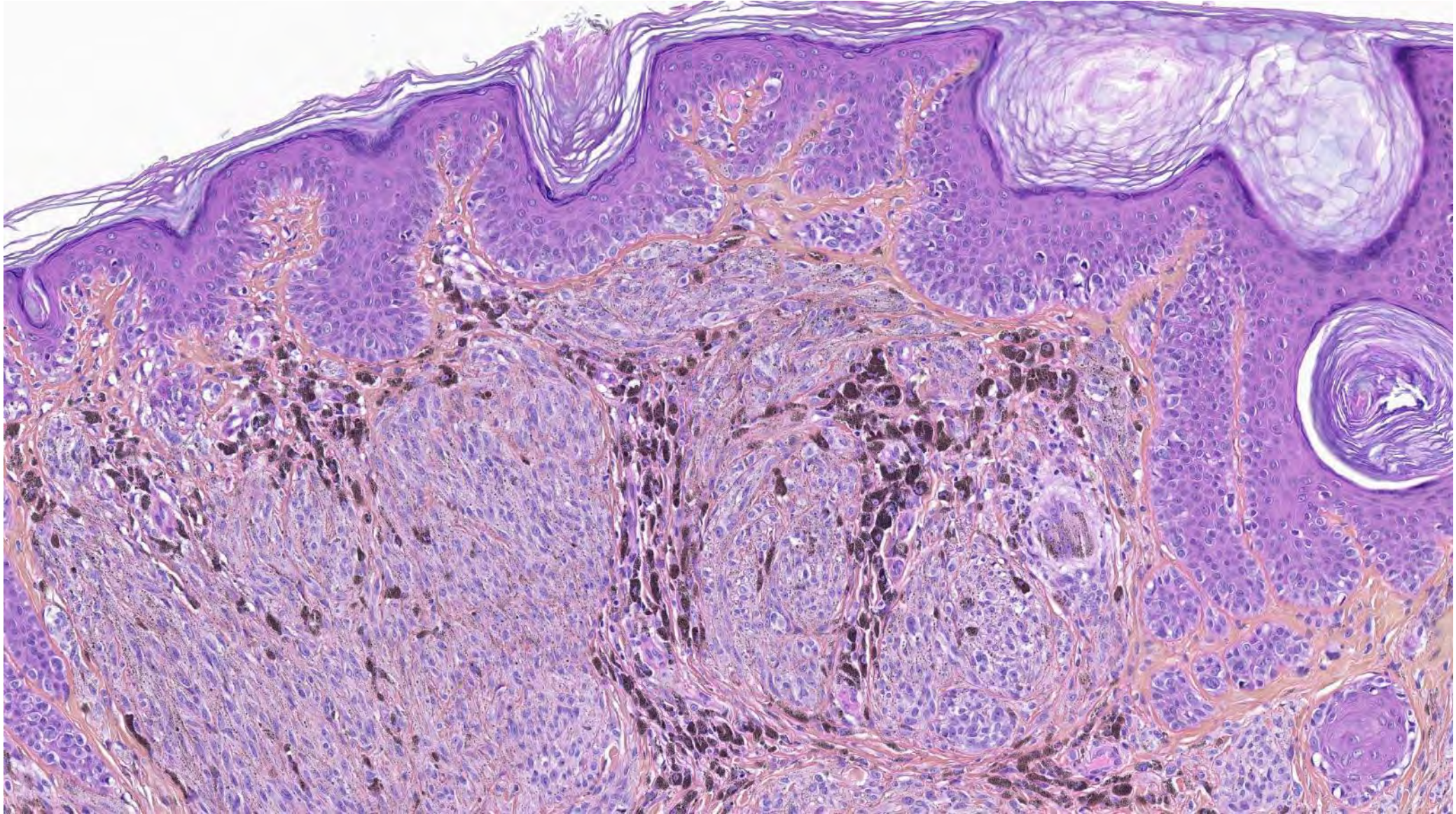
HMB45 IHC



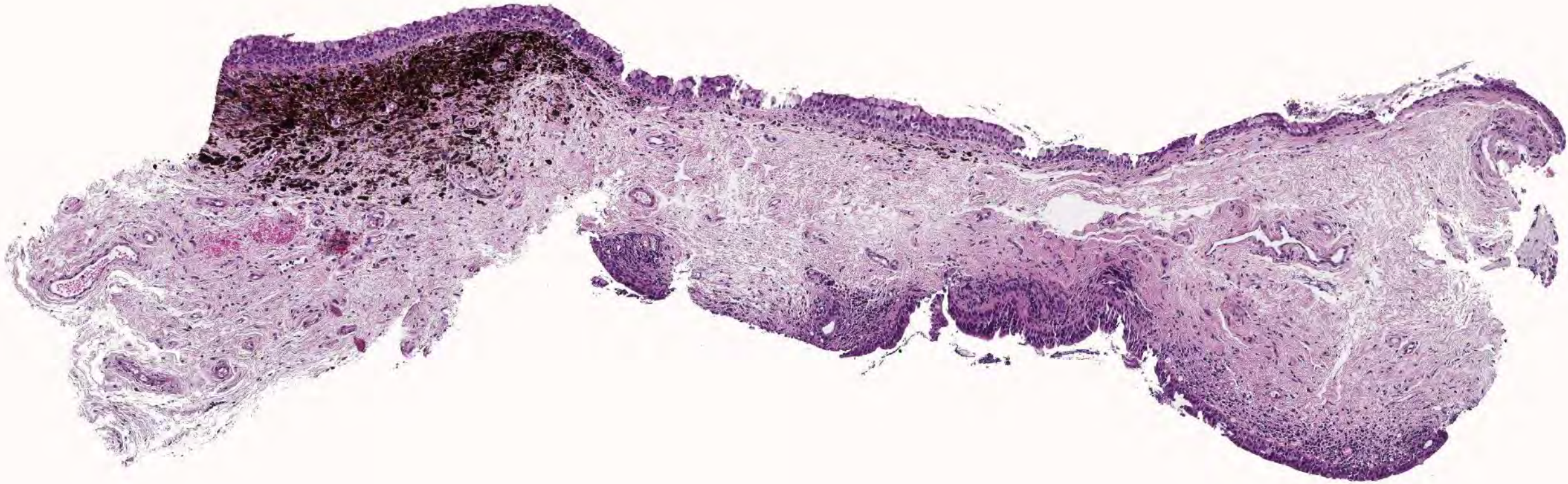
Compound blue nevus (*GNAQ* mutation)

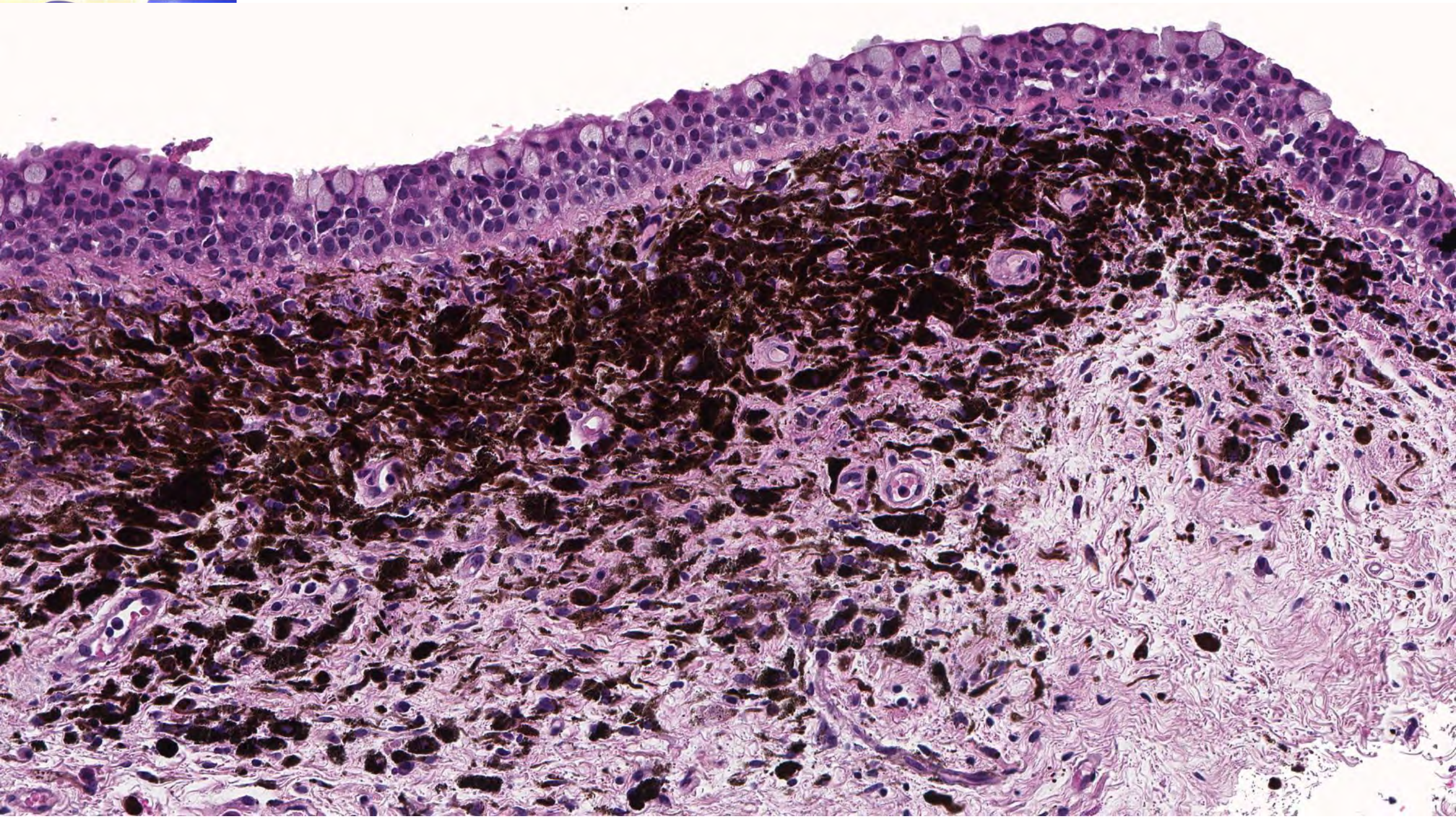


Compound blue nevus (*GNAQ* mutation)

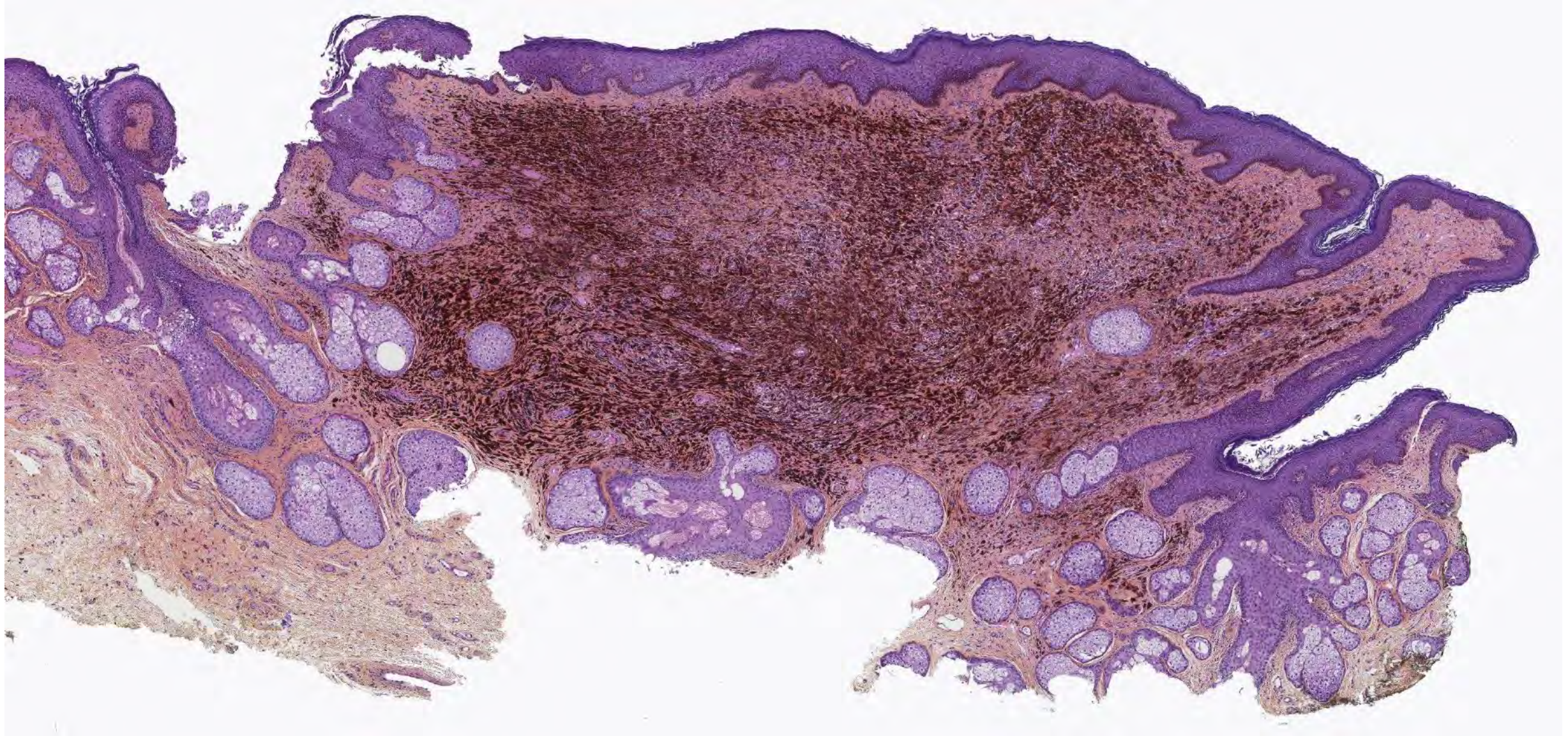


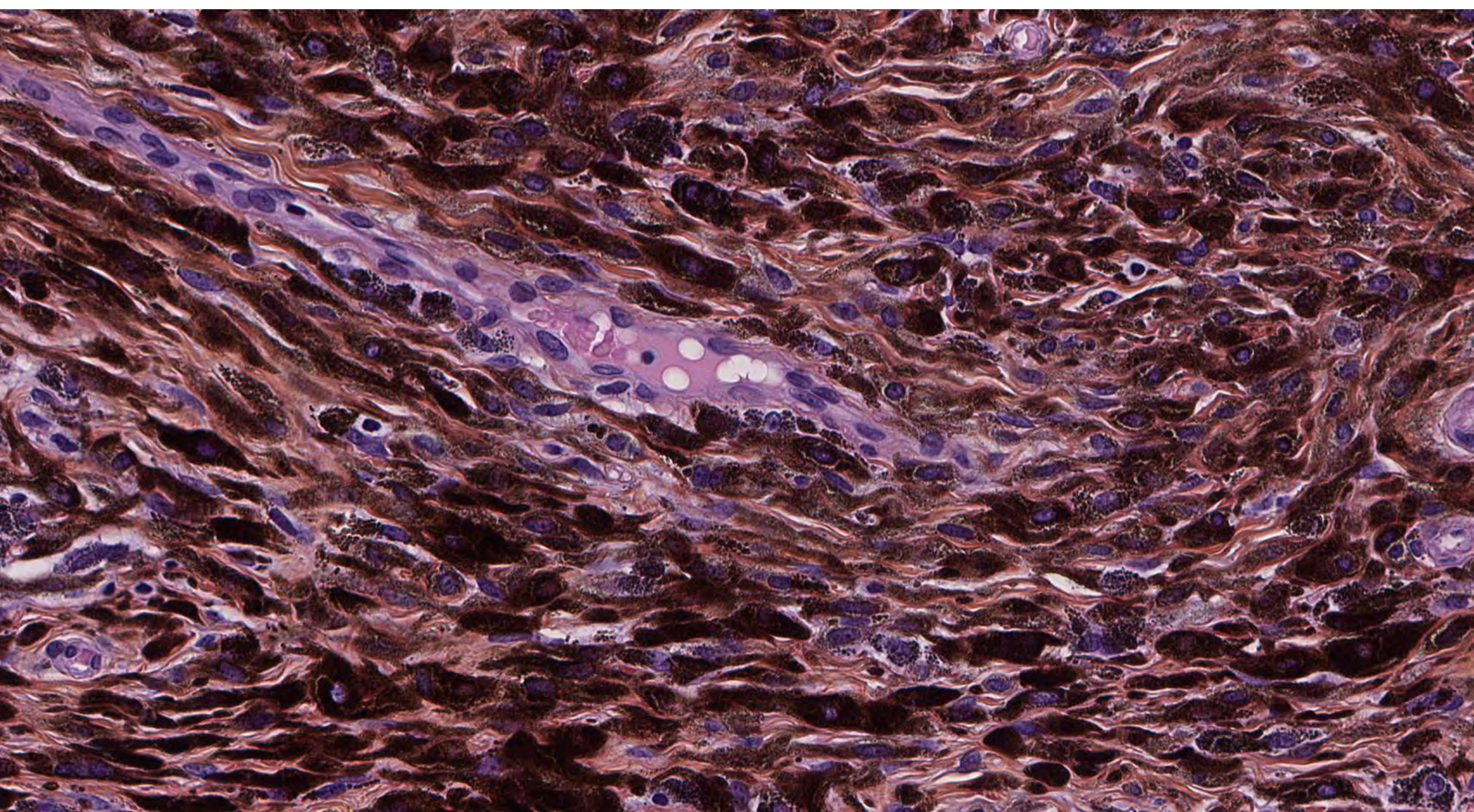
Conjunctival dendritic blue nevus



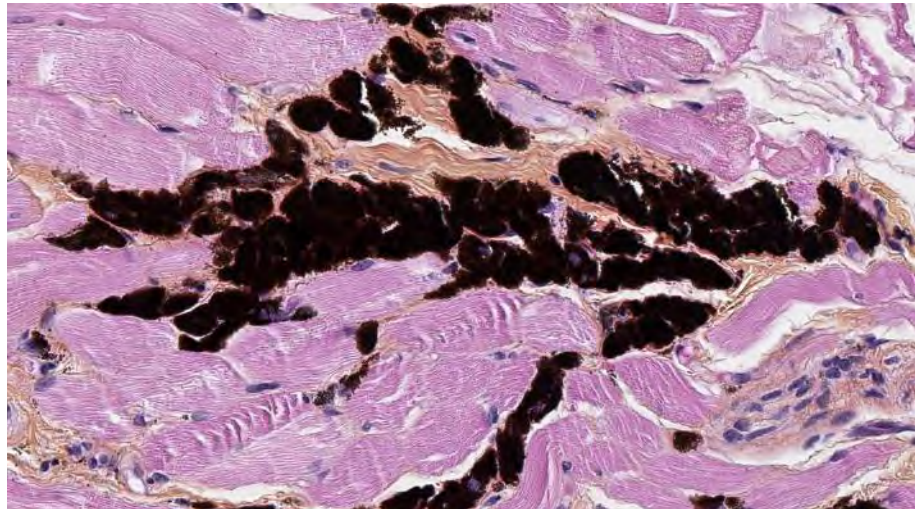


Genital dendritic blue nevus



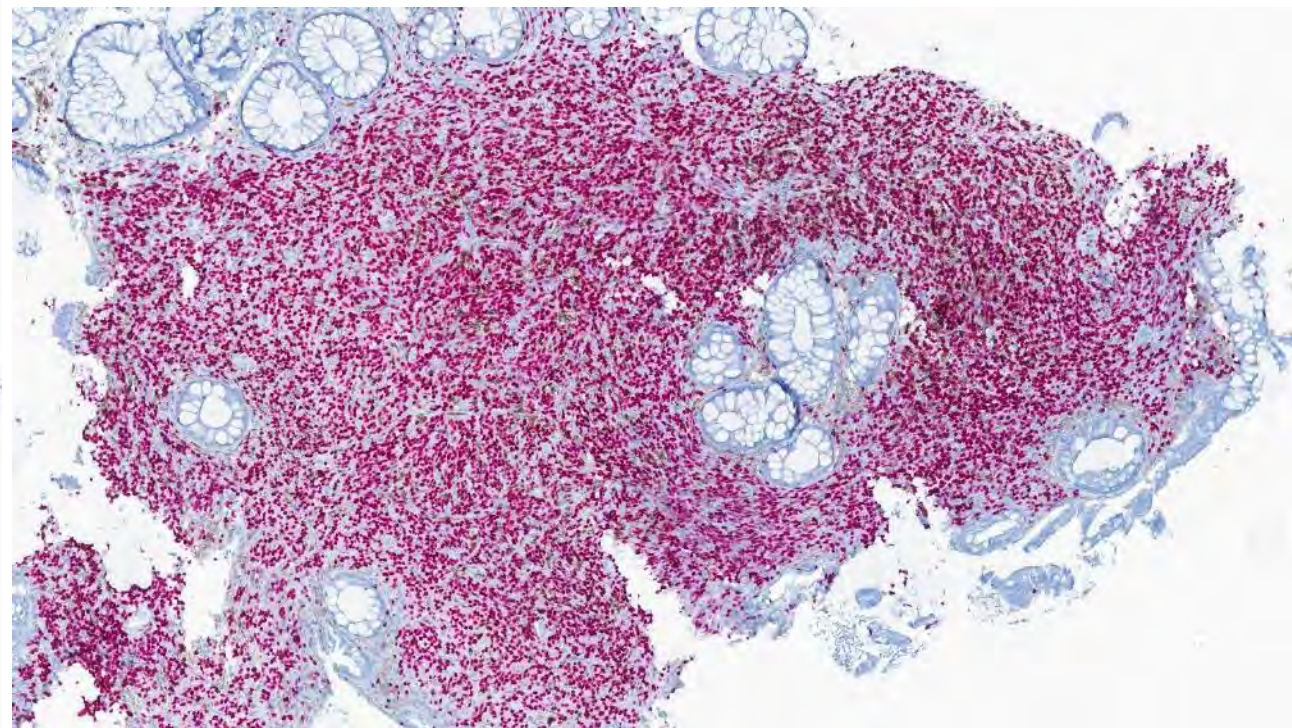
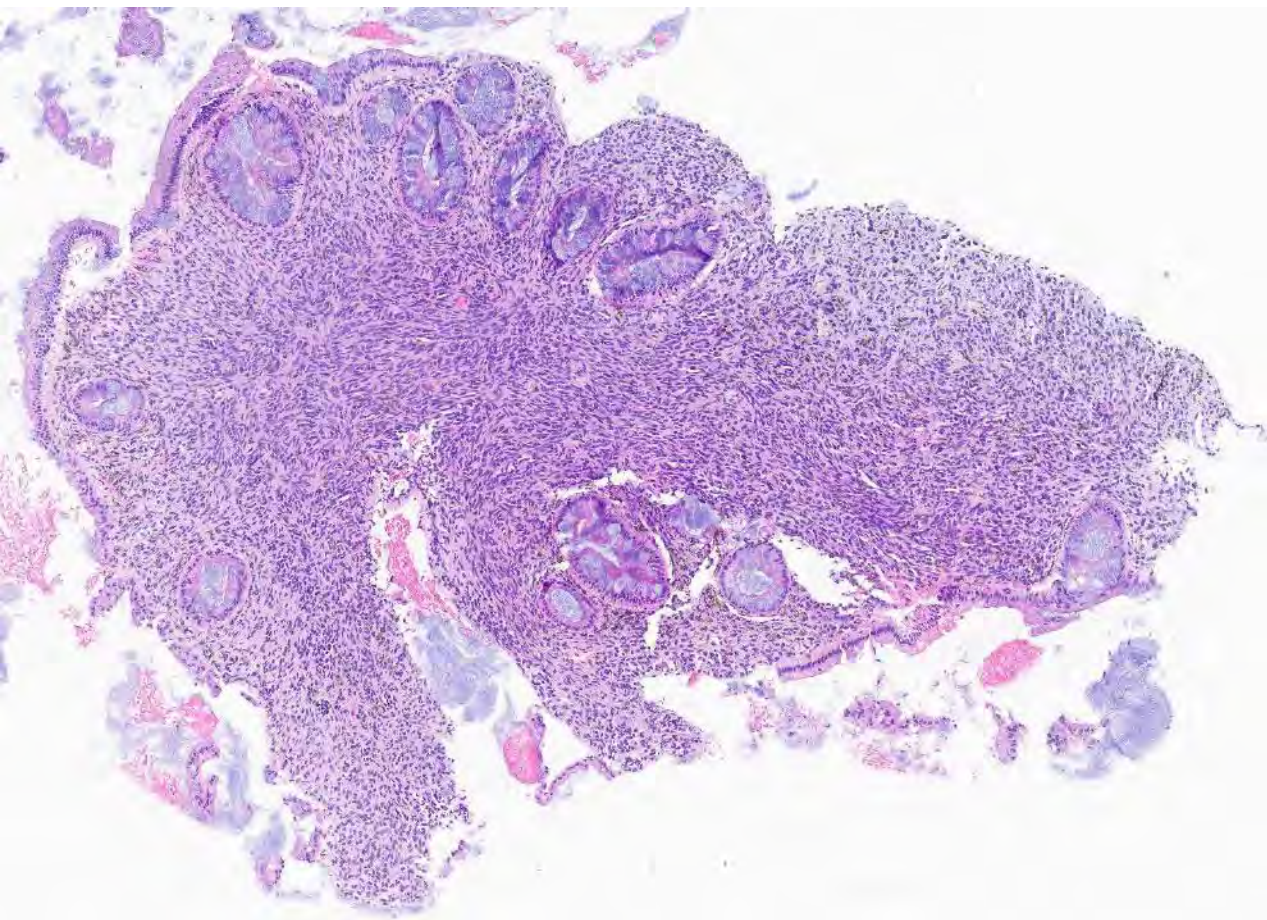


Dendritic mucosal Plaque-type



Visceral blue nevus

Rectal blue nevus



Sox10

Cellular blue nevus

- Mainly located on buttocks, back hand/feet
- Large lesions (15mm)

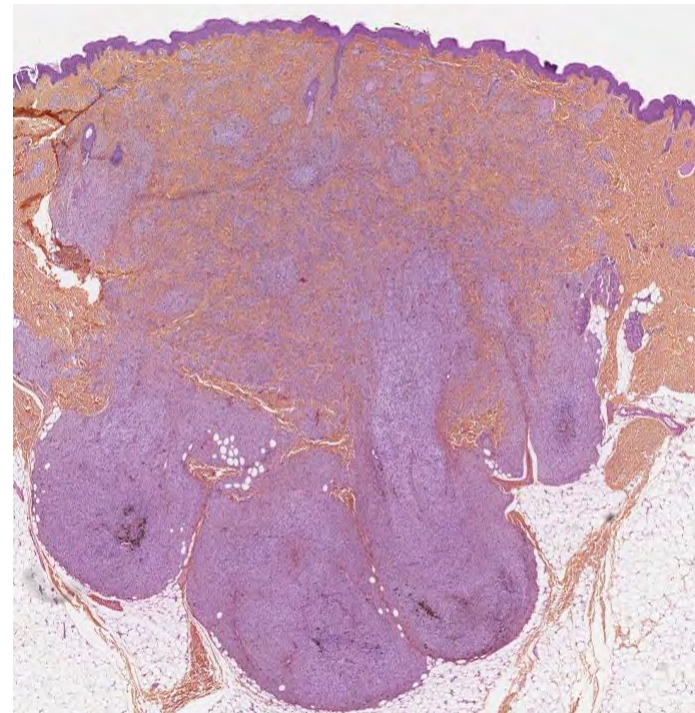
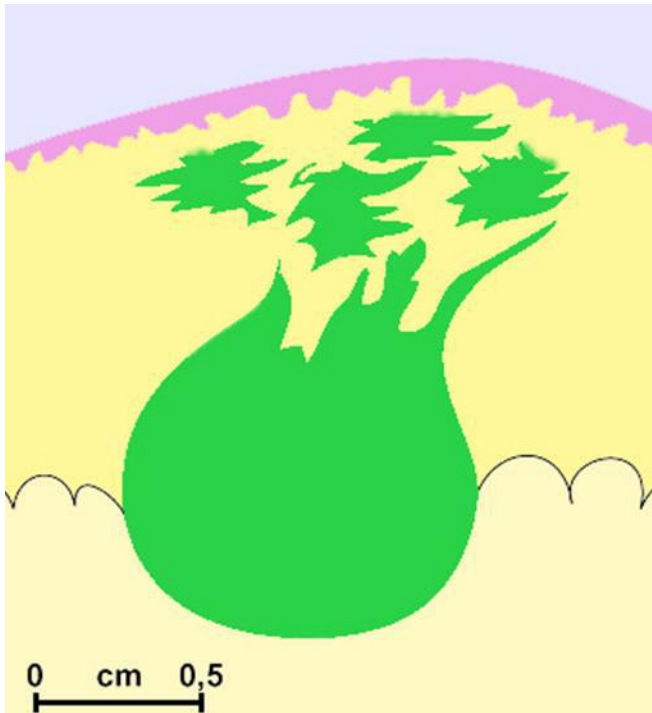


Dr Samira Ahbib

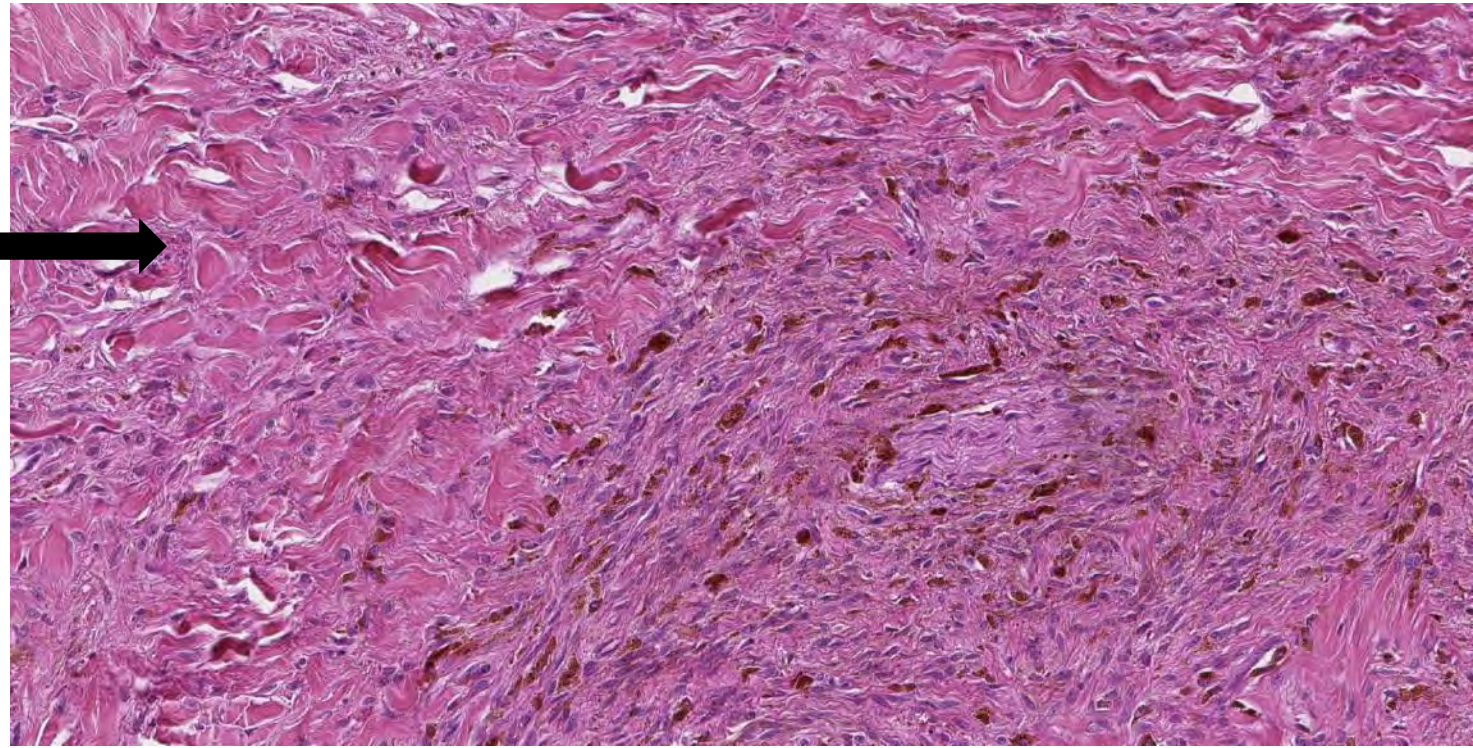
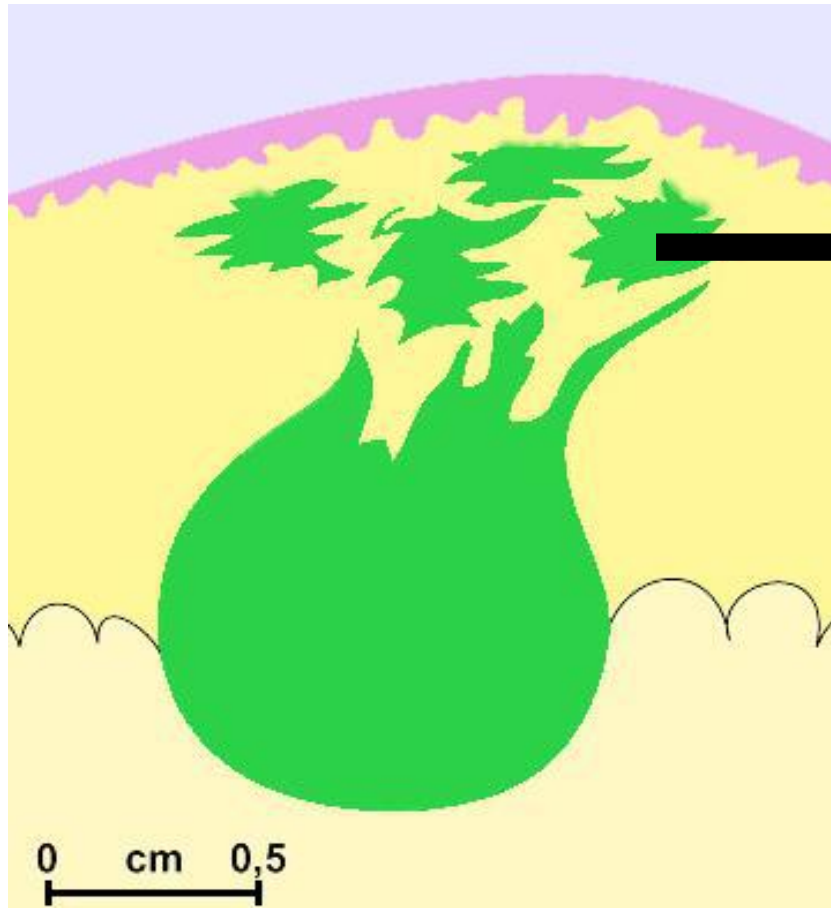


Cellular blue nevus

- Biphasic architecture : dendritic blue and cellular expansions

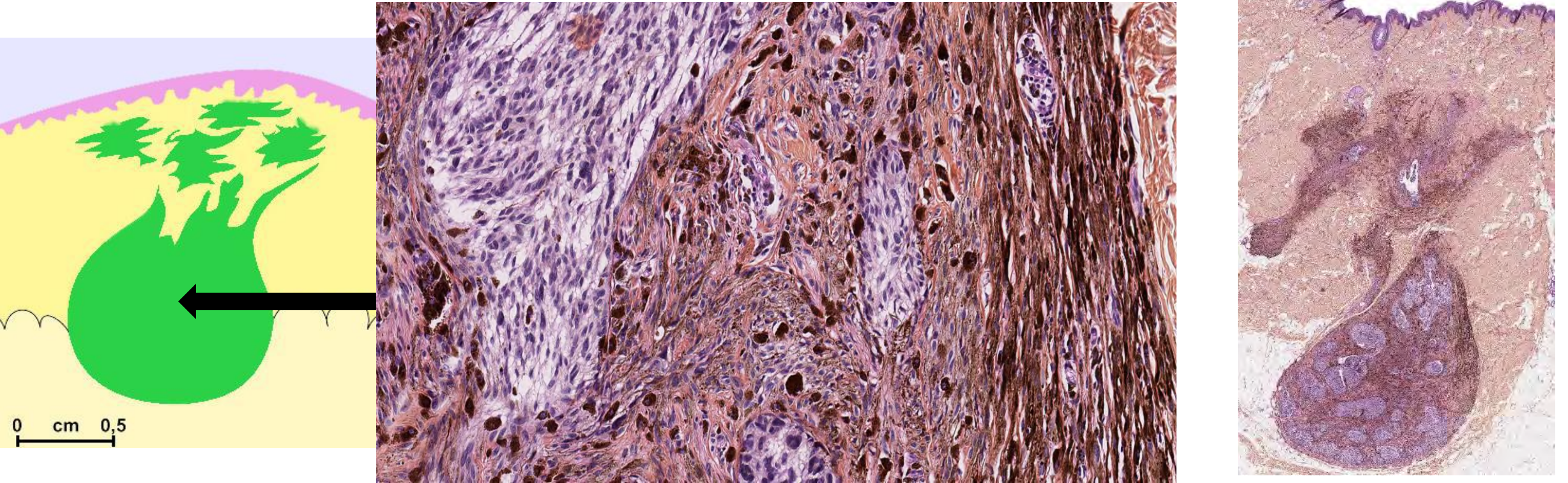


CBN biphasic pattern

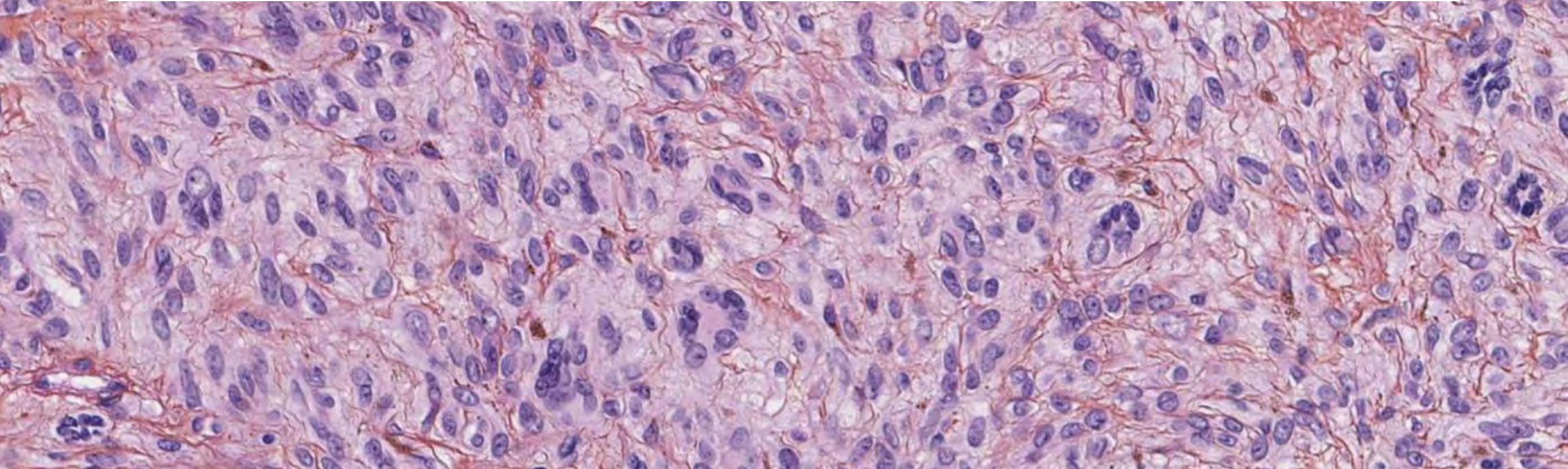


Cellular blue nevus

Bland cytology in cellular areas



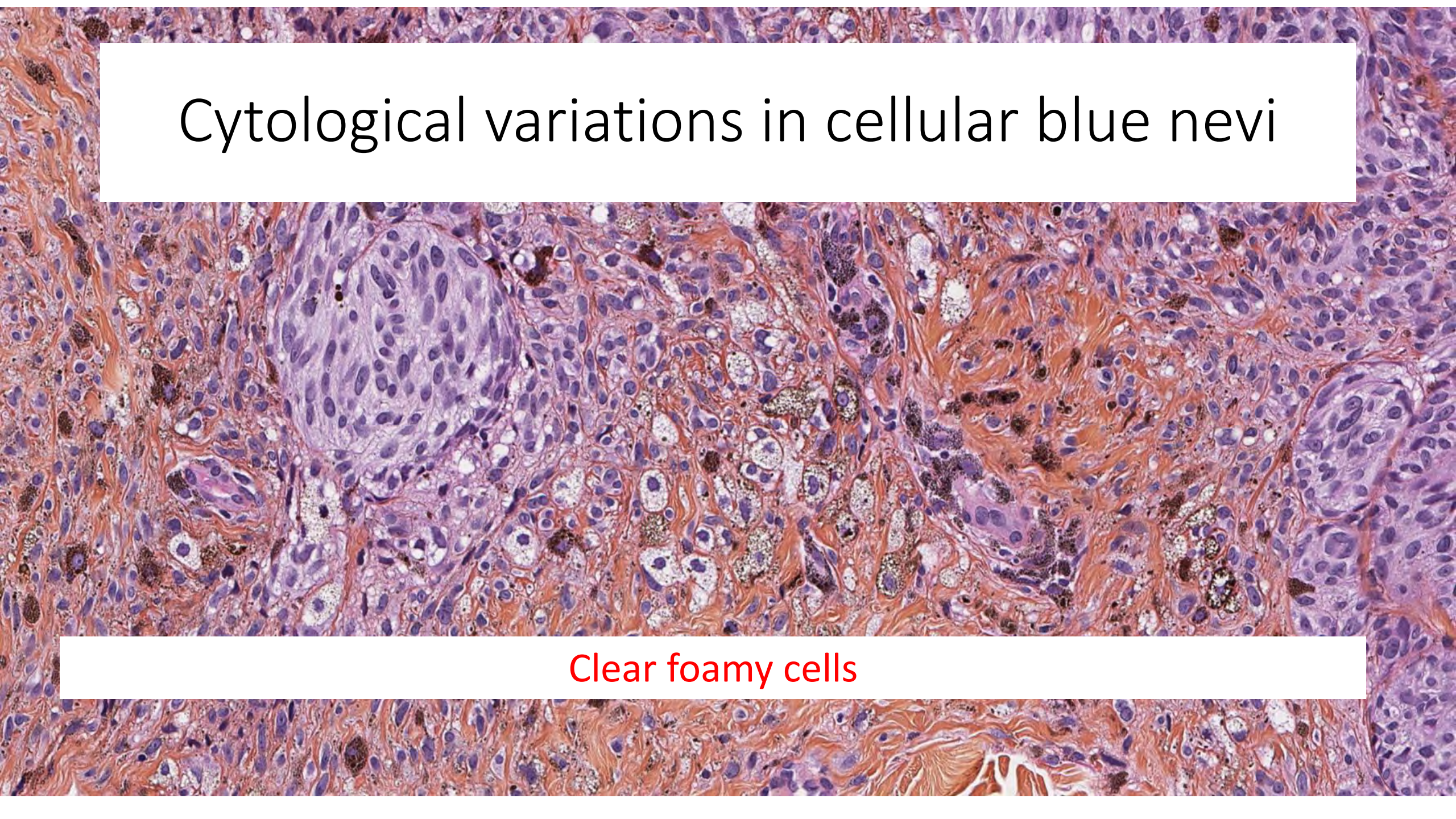
Cytological variations in cellular blue nevi



Multinucleated cells

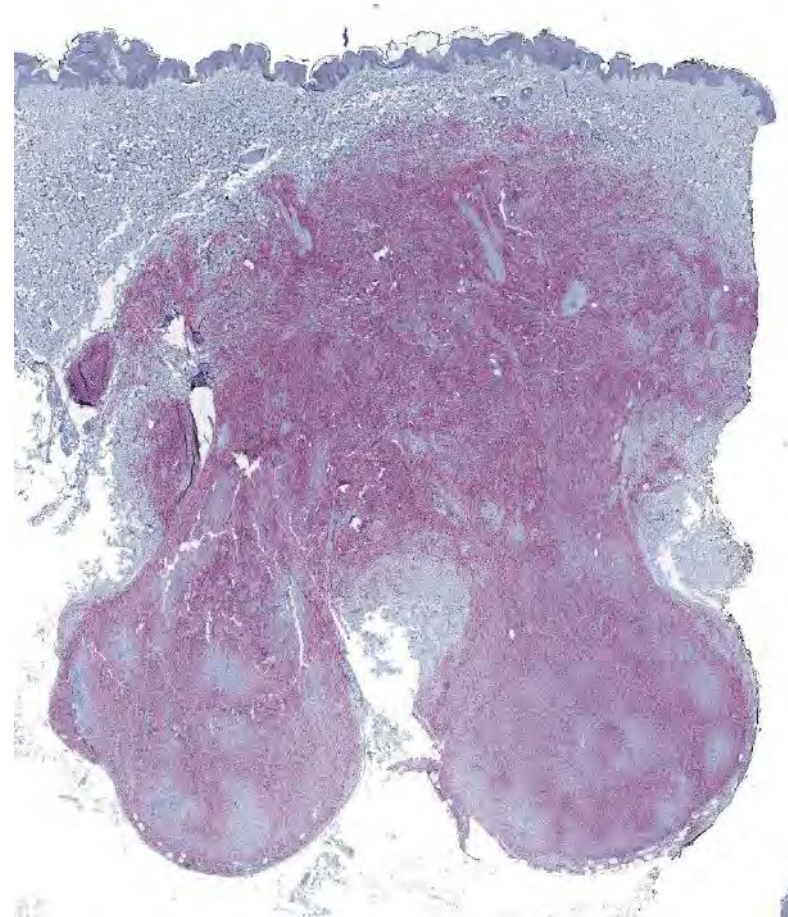
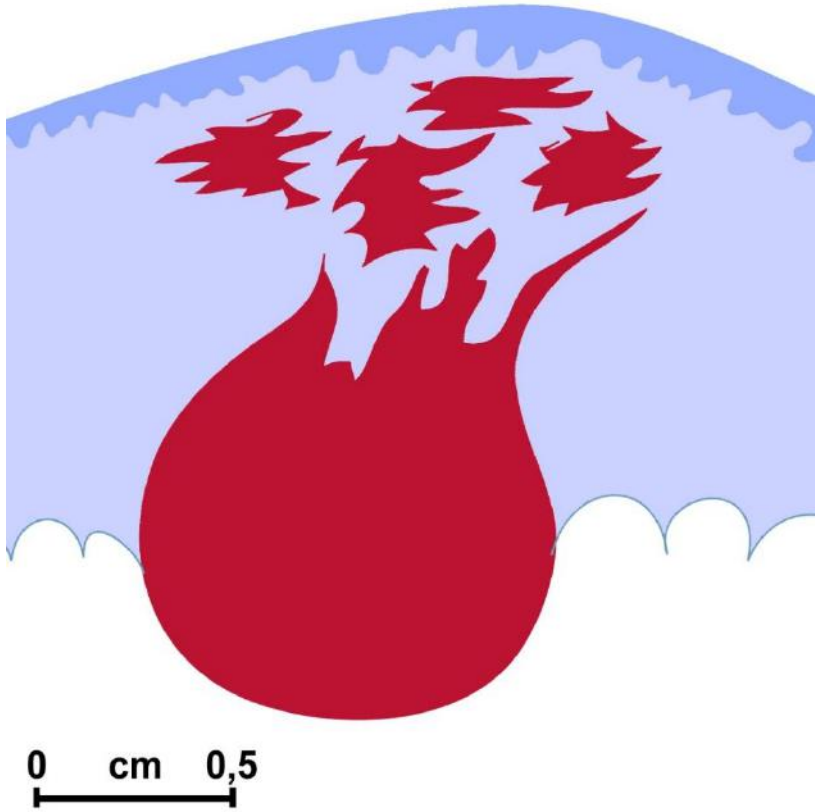
Cytological variations in cellular blue nevi

Clear foamy cells



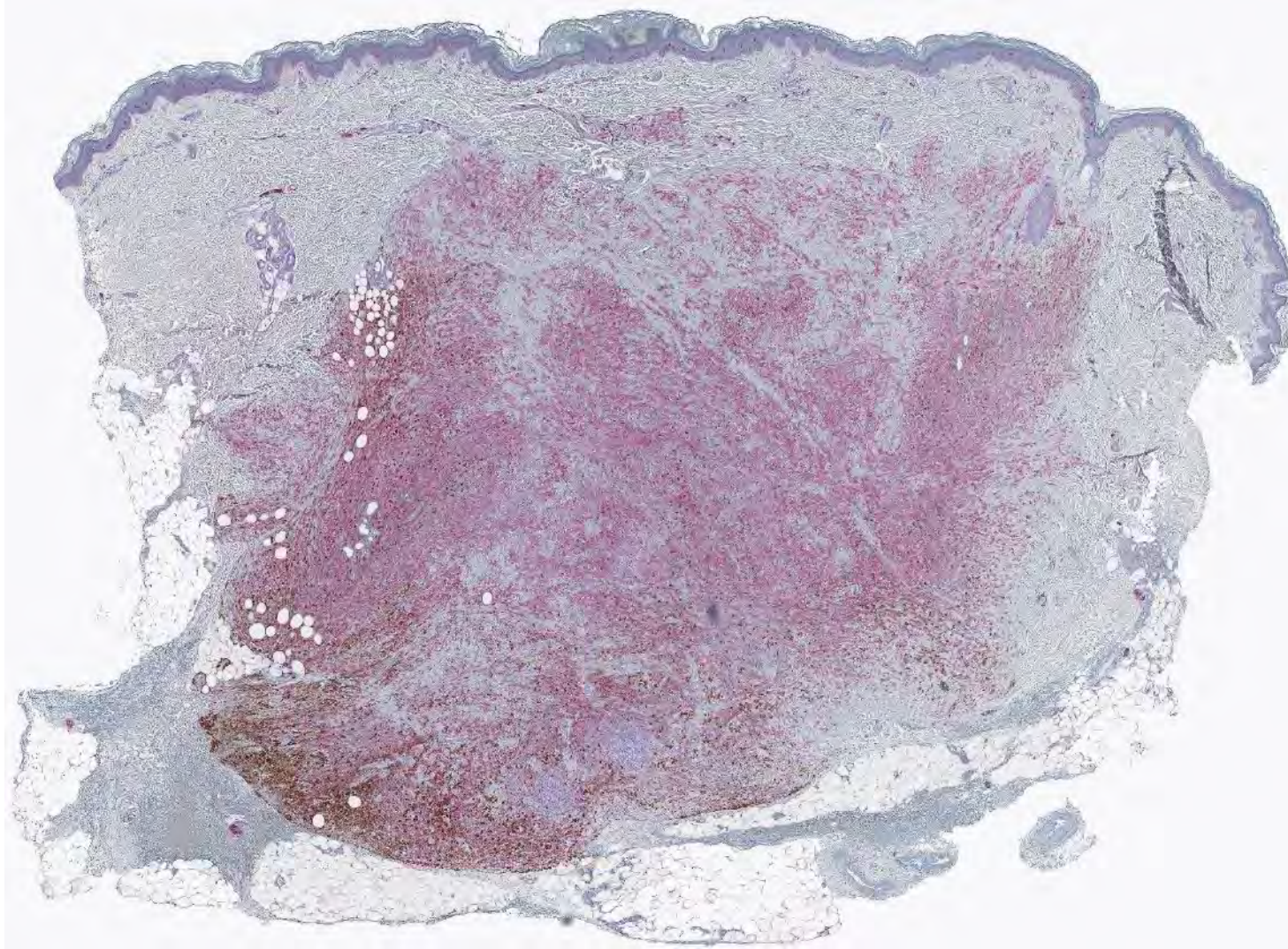
Cellular blue nevus

HMB45 expression



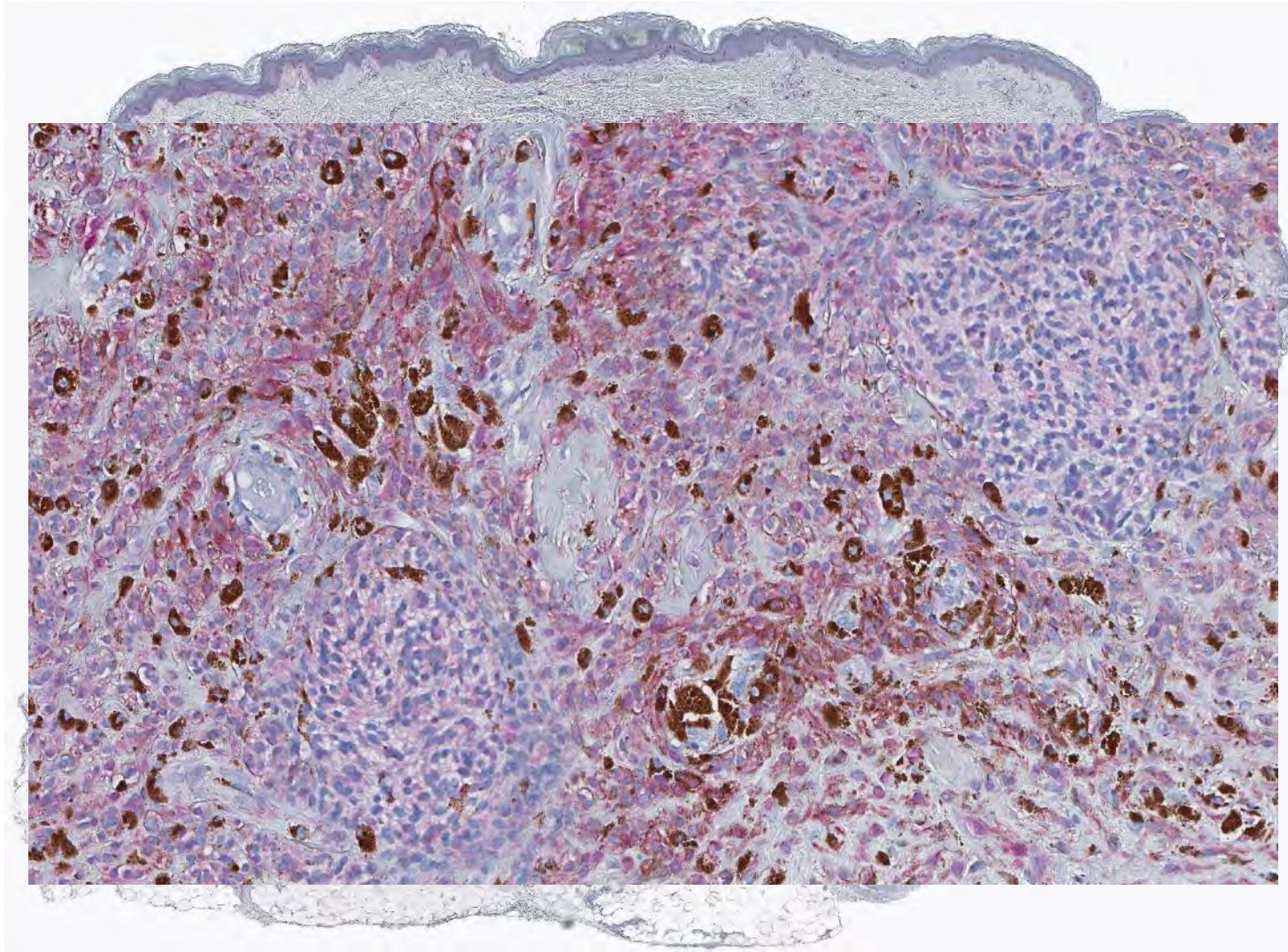
Cellular blue nevus

Mild or absence of PS100 expression



Cellular blue nevus

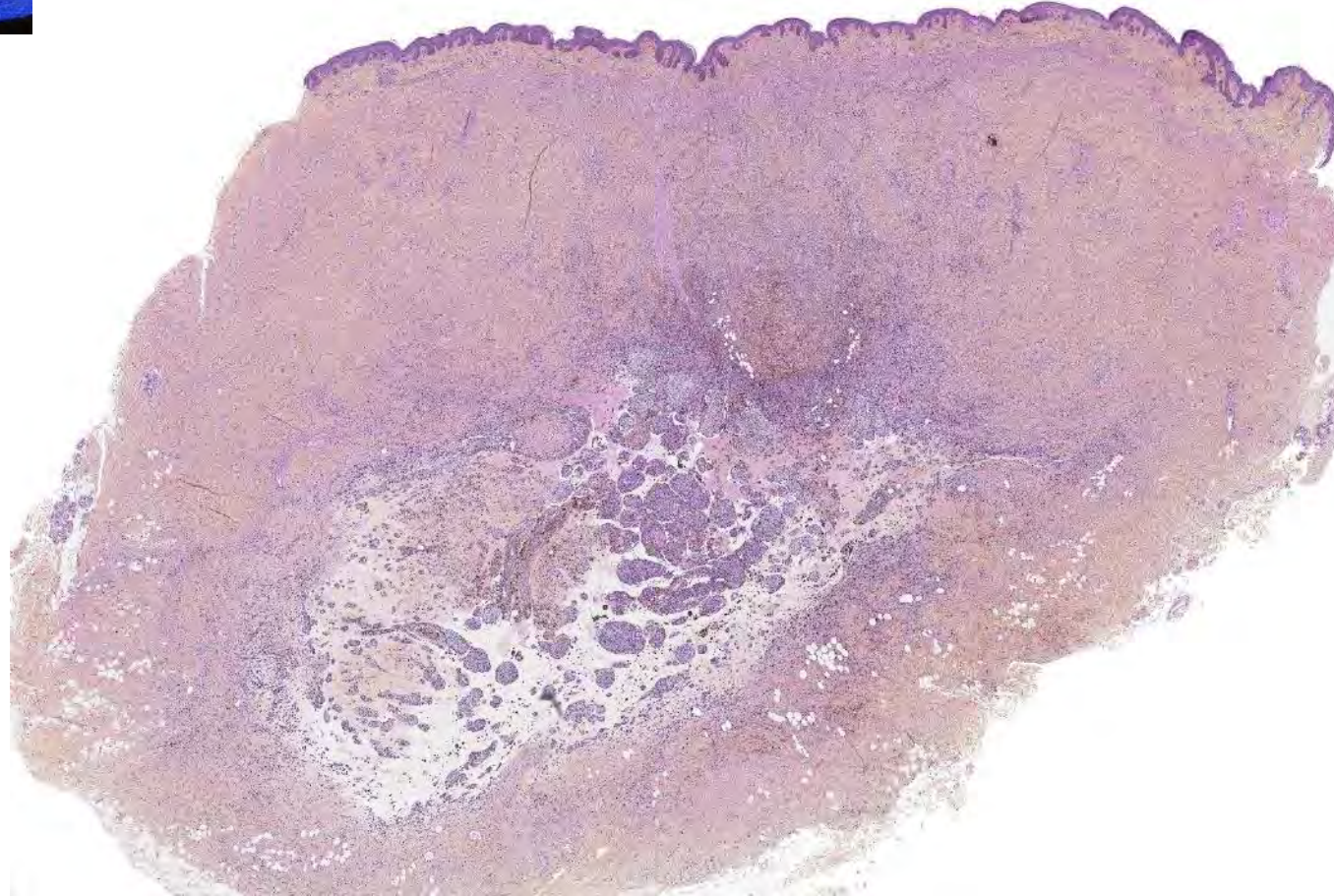
Mild or absence of PS100 expression





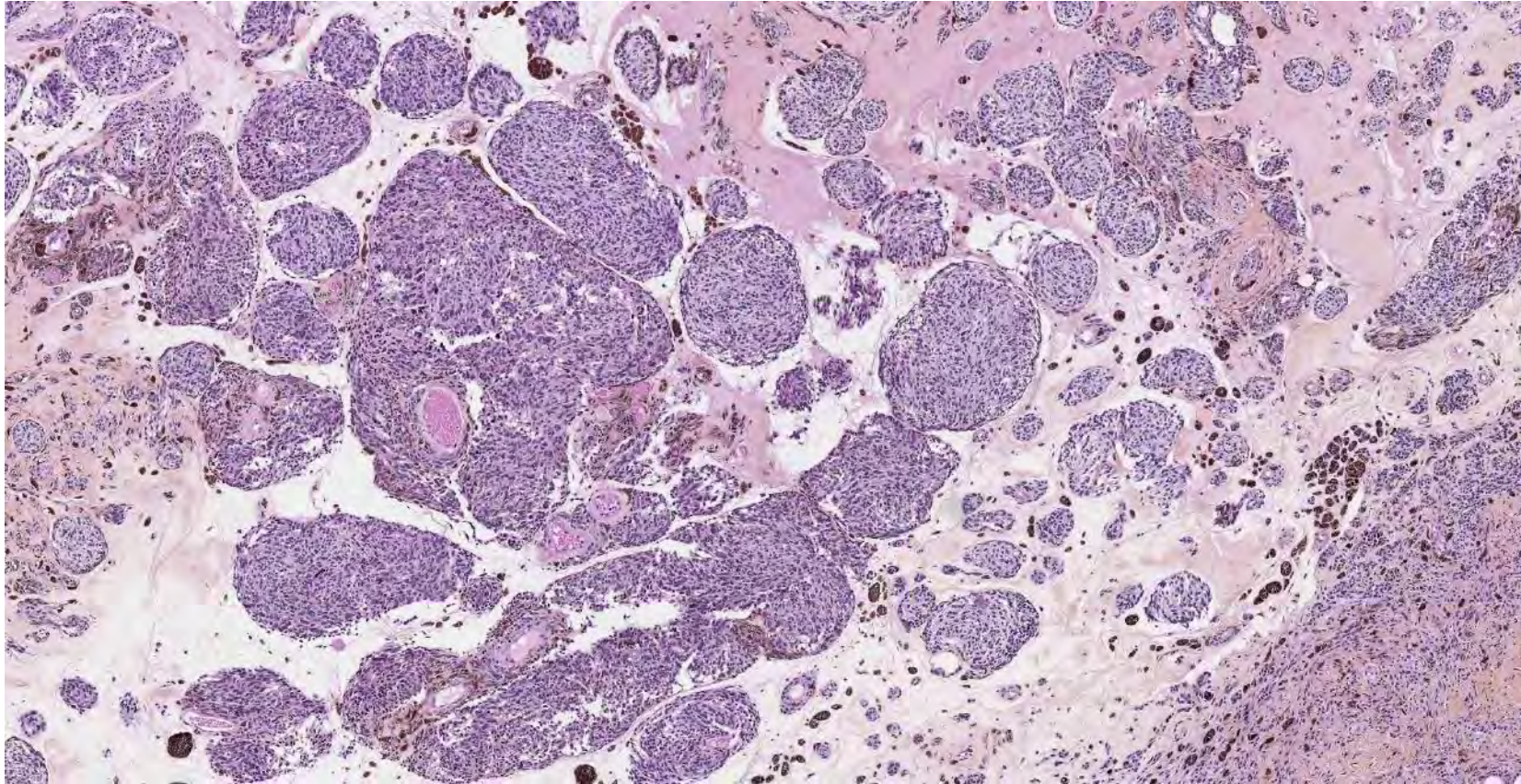
CBN subtypes

Myxoid/cystic CBN

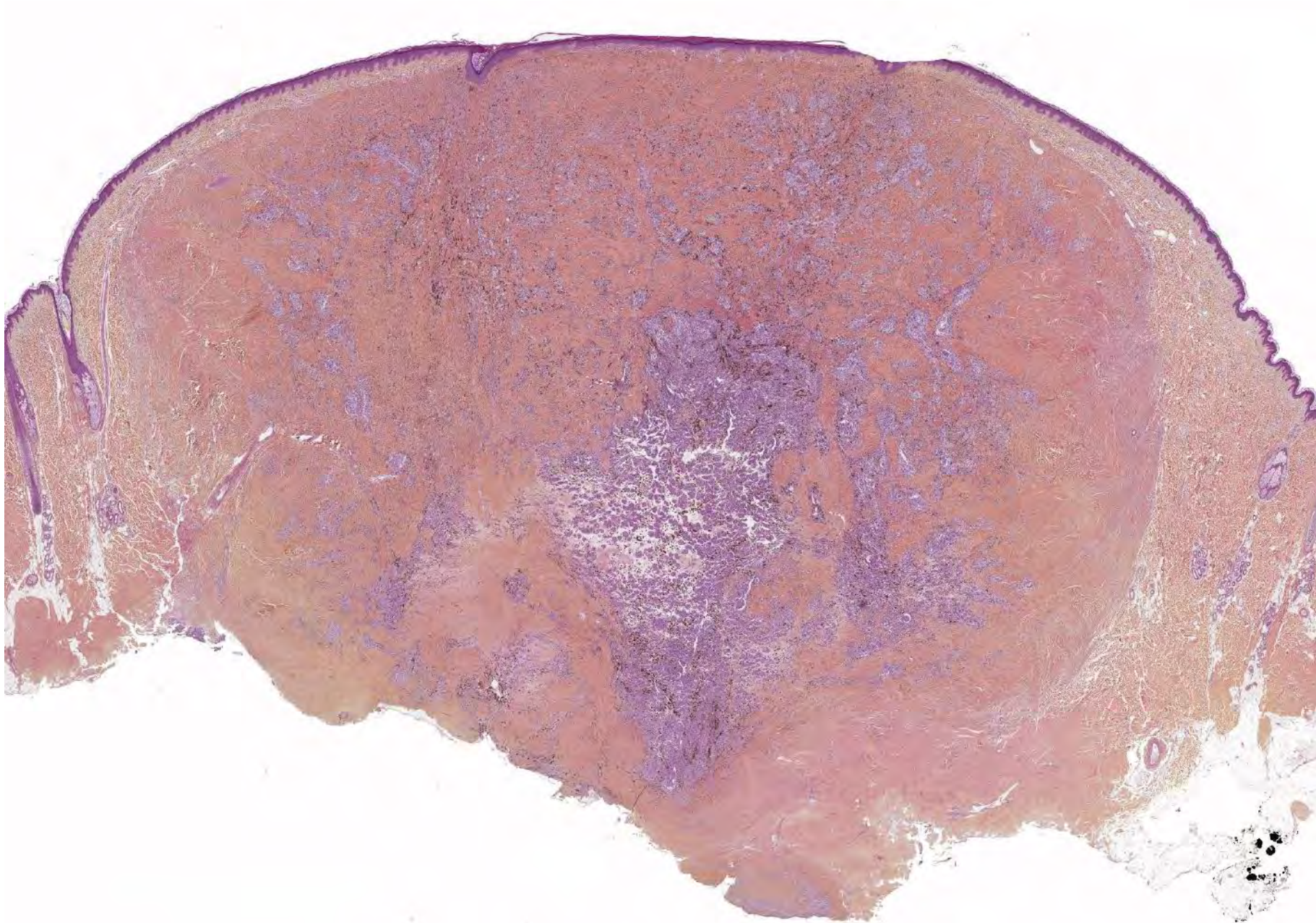


CBN subtypes

Myxoid/cystic CBN

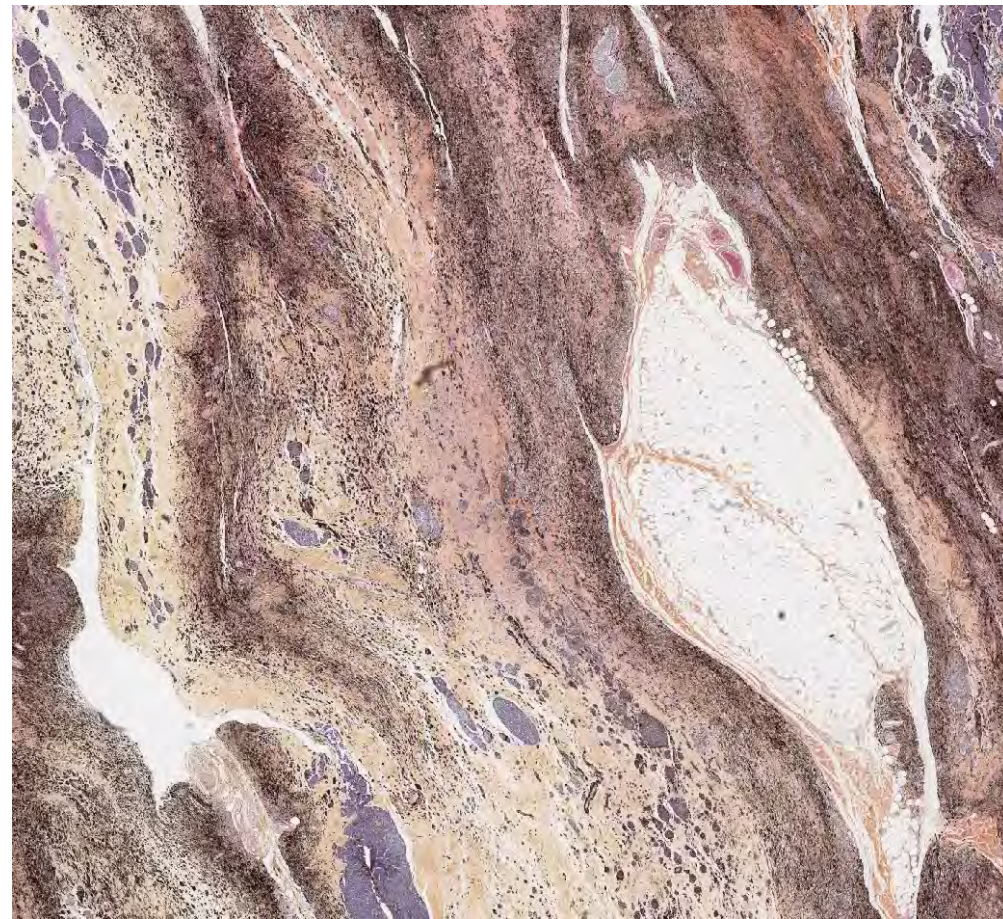


CBN combination of subtypes



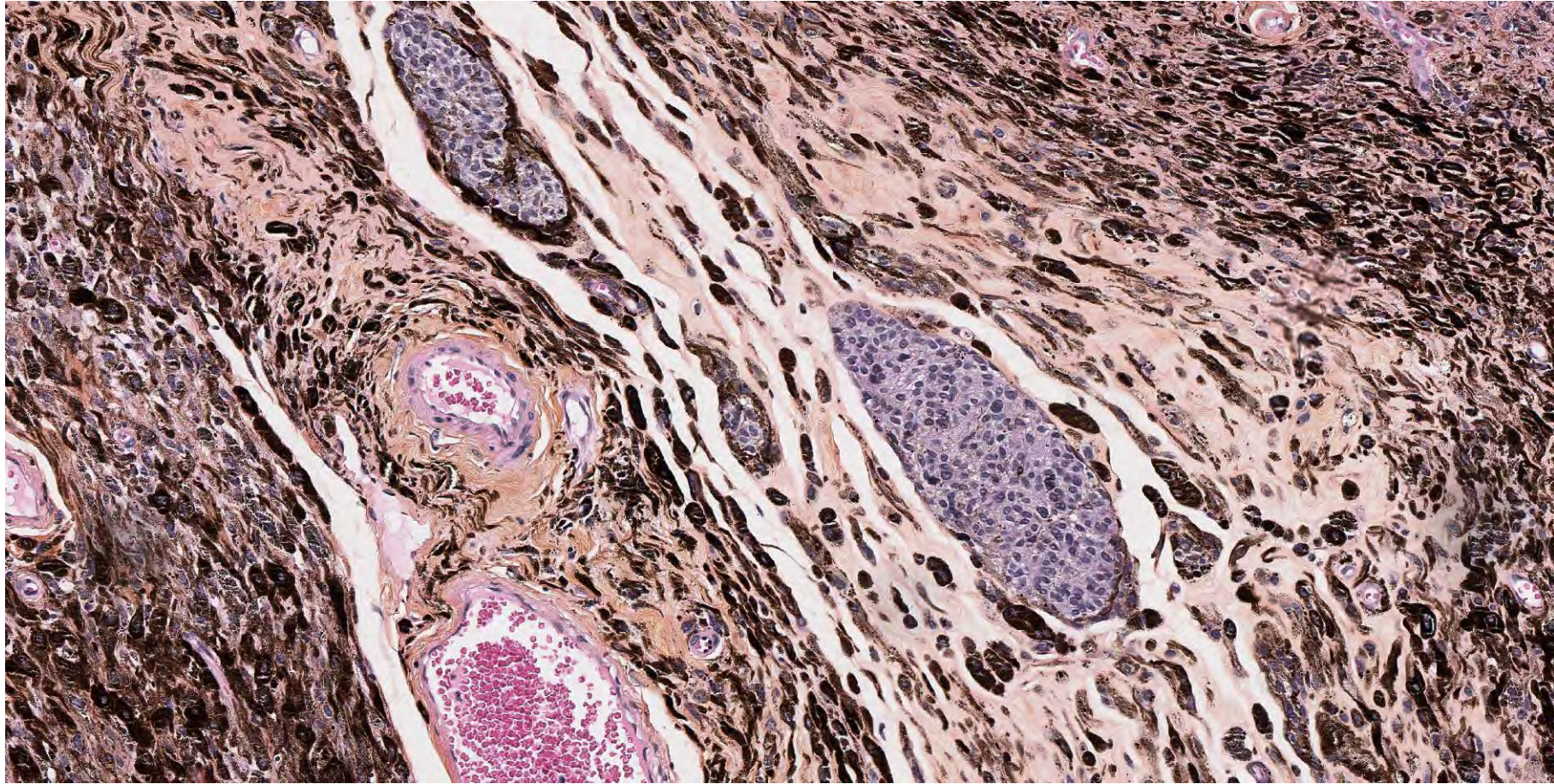
Blue nevus subtypes

Cellular plaque type



Blue nevus subtypes

Cellular plaque type



CYSLTR2-mutated blue lesions

Am J Surg Pathol. 2019 Oct;43(10):1368-1376. doi: 10.1097/PAS.0000000000001299.

CYSLTR2-mutant Cutaneous Melanocytic Neoplasms Frequently Simulate "Pigmented Epithelioid Melanocytoma," Expanding the Morphologic Spectrum of Blue Tumors: A Clinicopathologic Study of 7 Cases.

Goto K^{1,2,3,4,5}, Pissaloux D^{6,7}, Paindavoine S⁶, Tirode F⁷, de la Fouchardière A^{6,7}.

Author information

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- 5 Department of Dermatology, Hyogo Cancer Center, Akashi, Japan.
- 6 Department of Biopathology, Center Le[Combining Acute Accent]on Be[Combining Acute Accent]rard, Lyon, France.
- 7 University of Lyon, Claude Bernard Lyon1 University, INSERM 1052, CNRS 5286, Léon Bérard Cancer Care Center, Cancer Research Center of Lyon, Ligue Contre Le Cancer Labellised Team, Lyon, France.

Activating cysteinyl leukotriene receptor 2 (CYSLTR2) mutations in blue nevi.

Möller I¹, Murali R², Müller H³, Wiesner T⁴, Jackett LA^{5,6,7}, Scholz SL⁸, Cosgarea I¹, van de Nes JA⁹, Sucker A¹, Hillen U¹, Schilling B¹, Paschen A¹, Kutzner H³, Rütten A³, Böckers M¹⁰, Scolyer RA^{5,6,7}, Schadendorf D¹, Griewank KG^{1,10}.

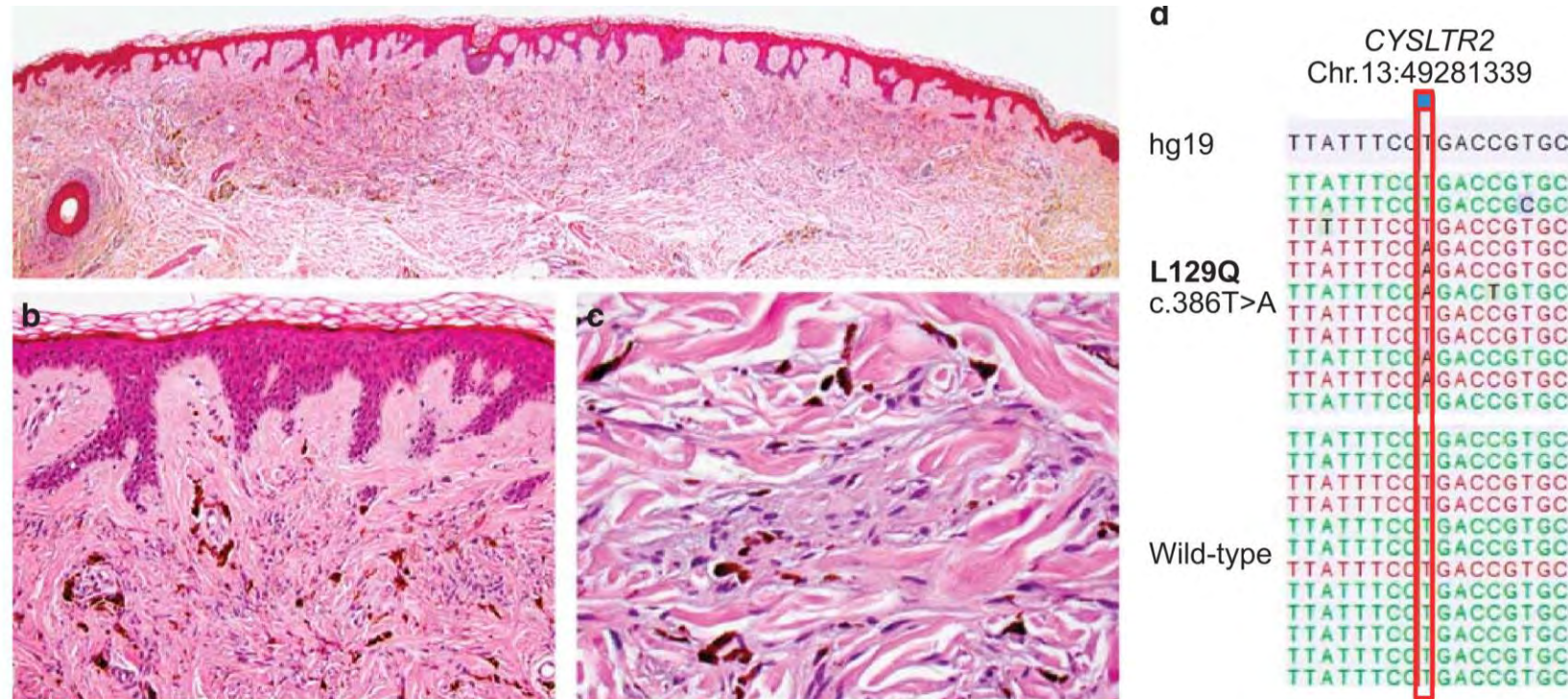
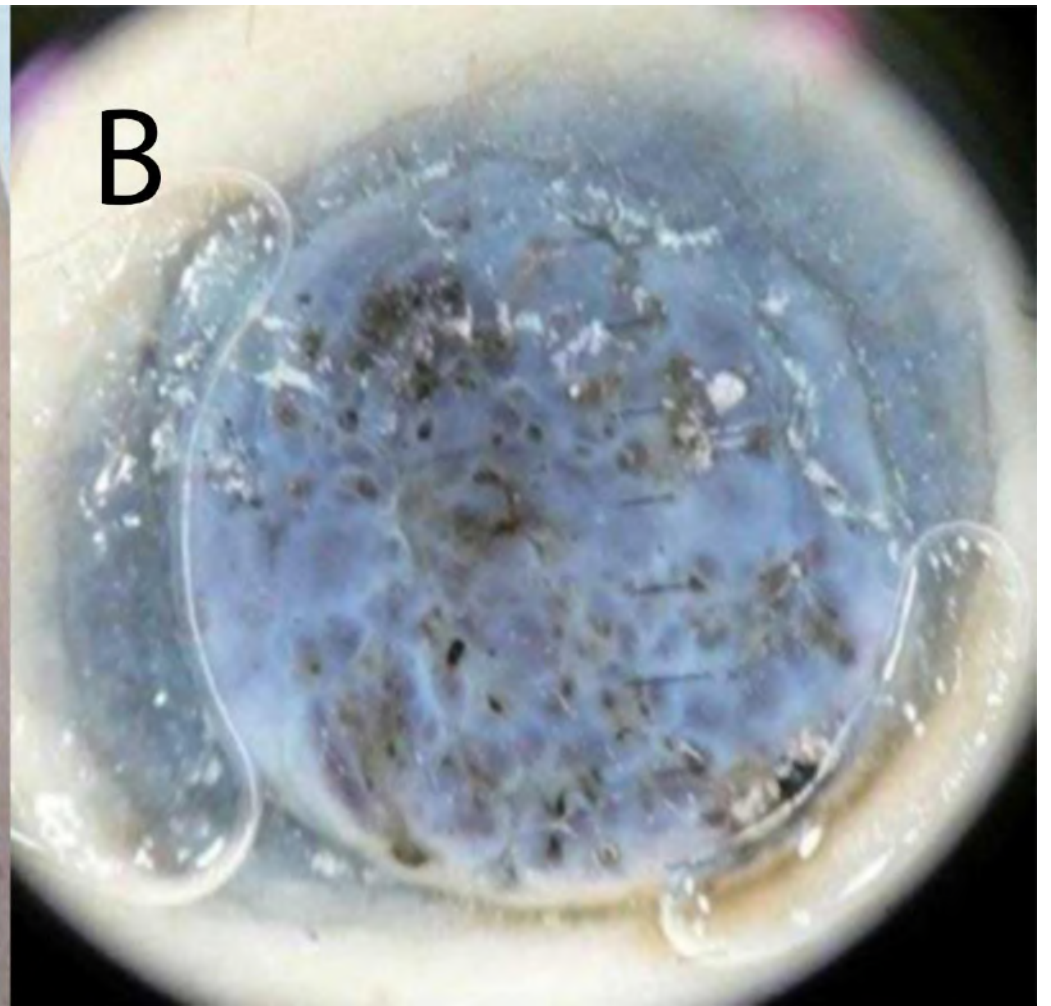
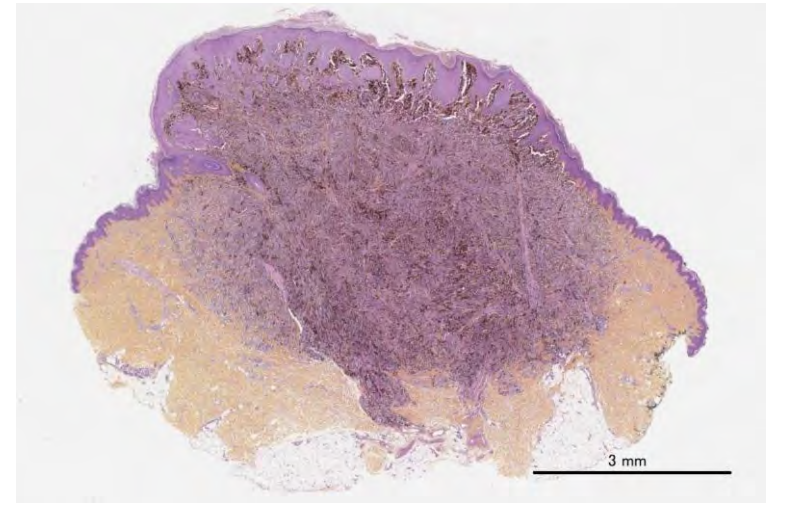
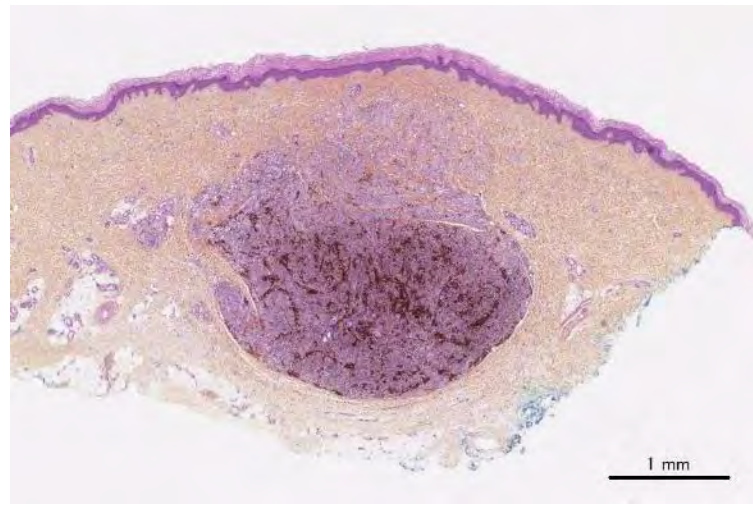
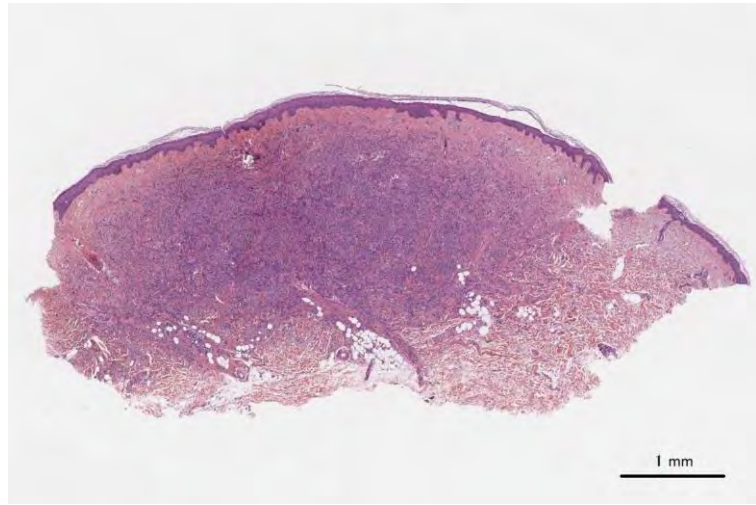
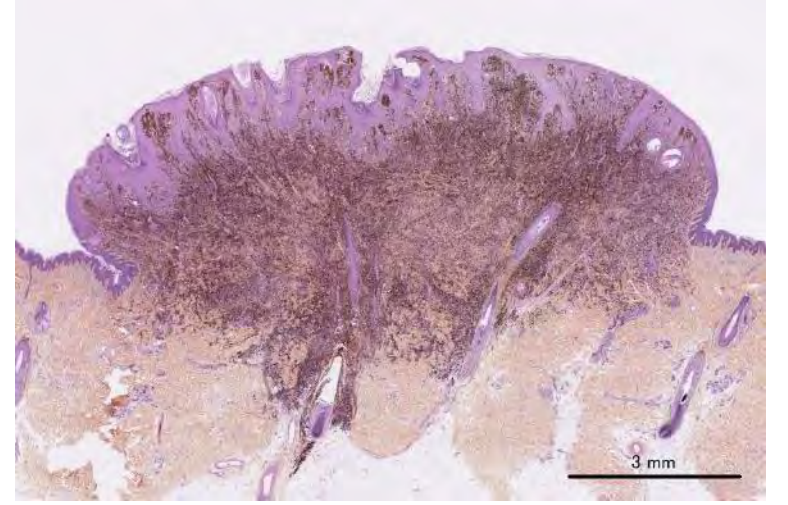
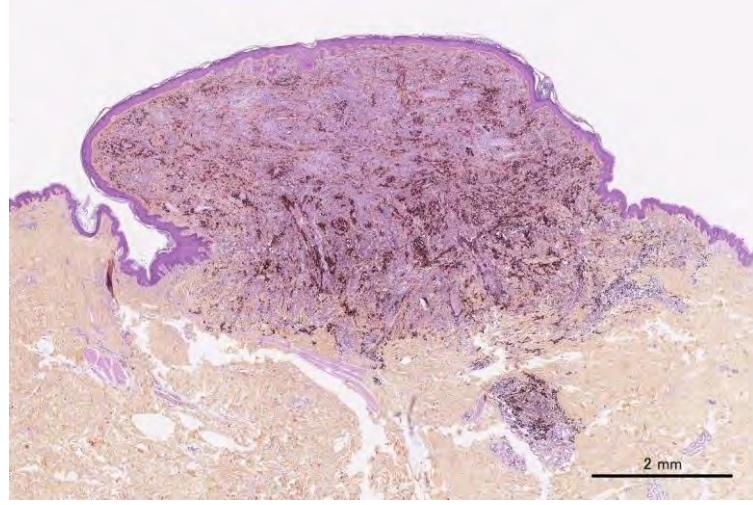
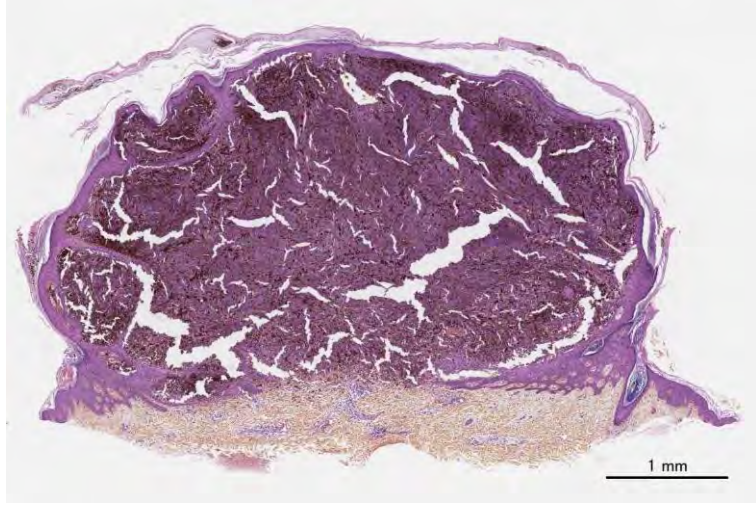
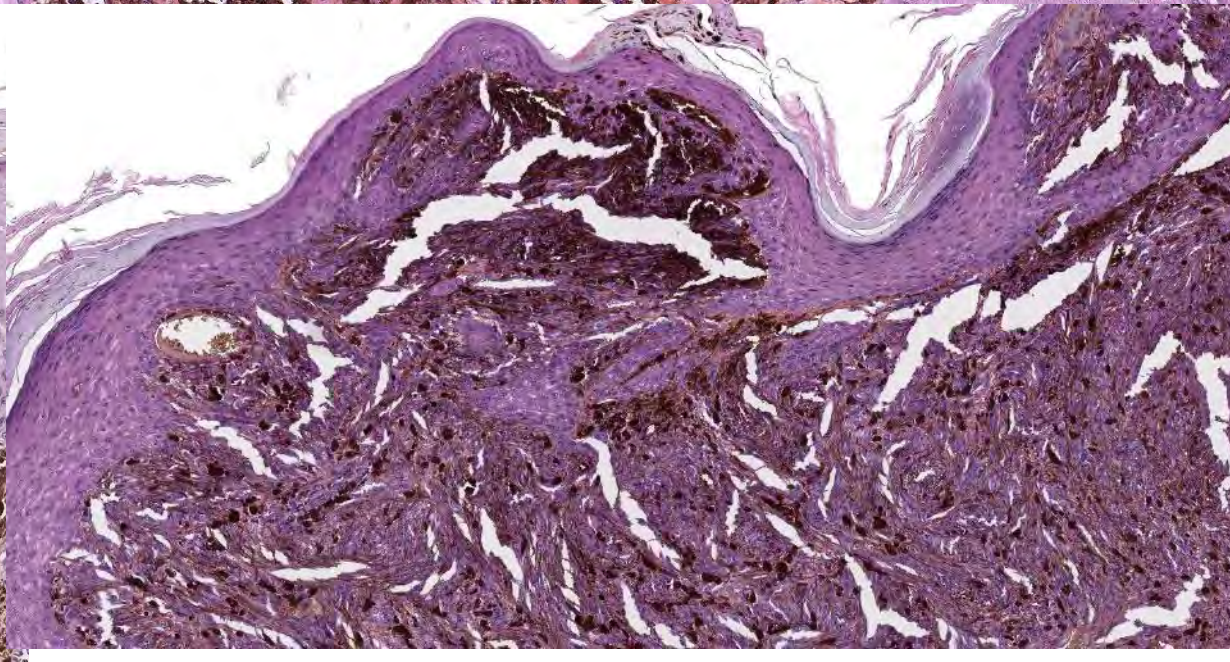
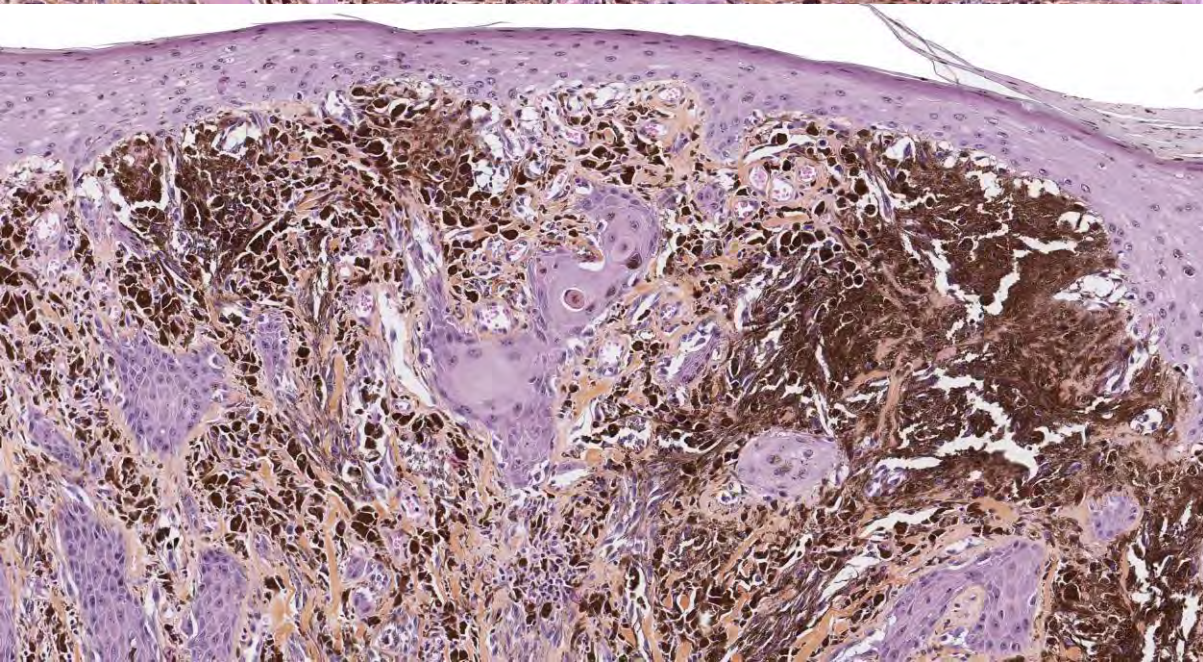
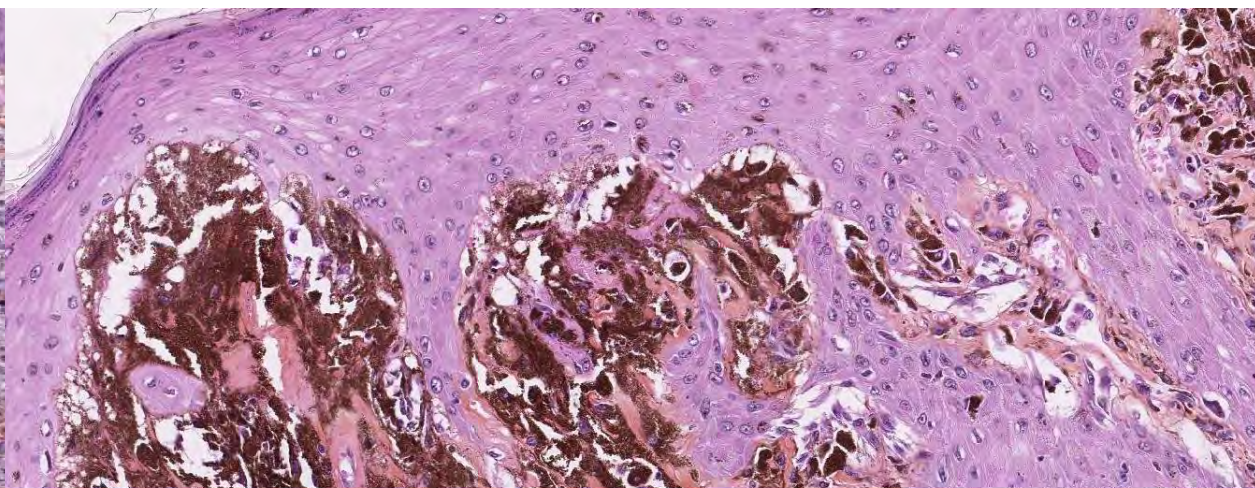
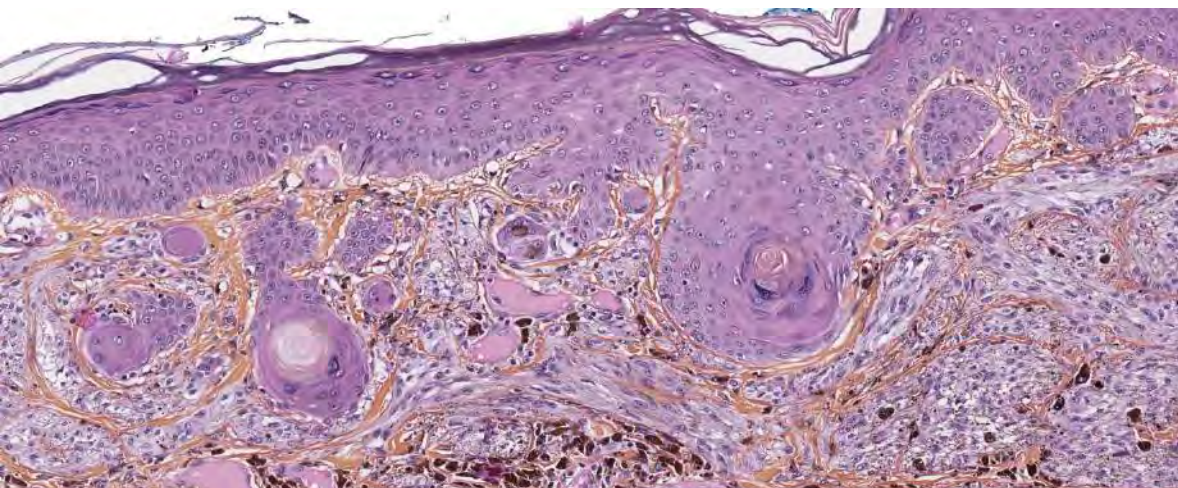


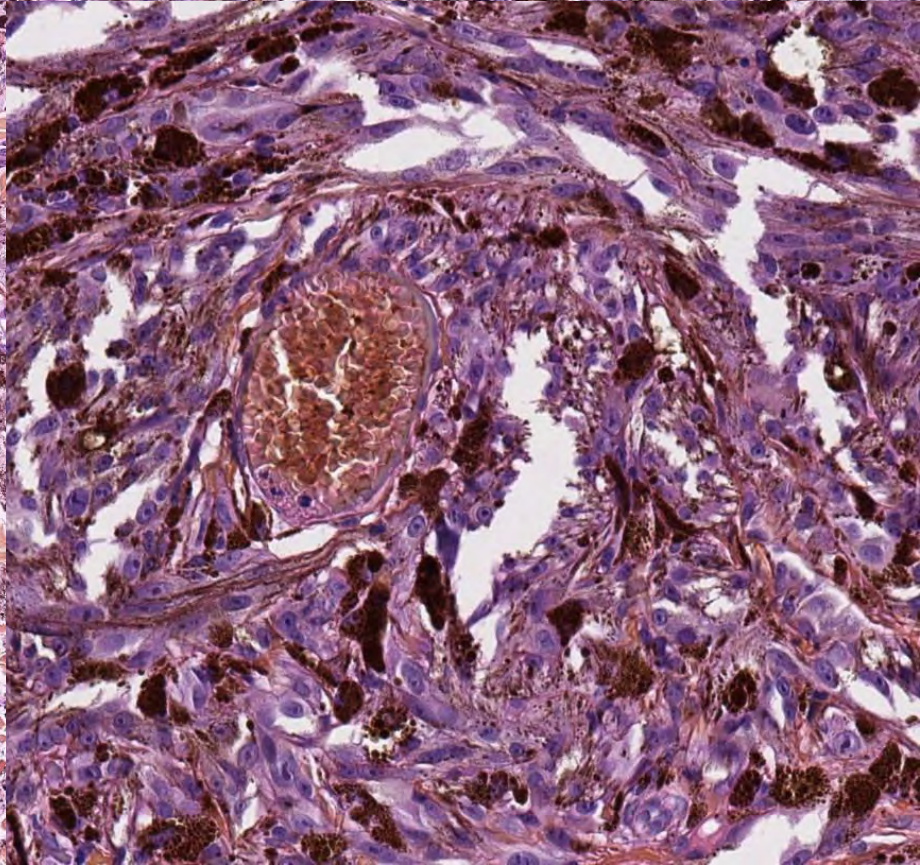
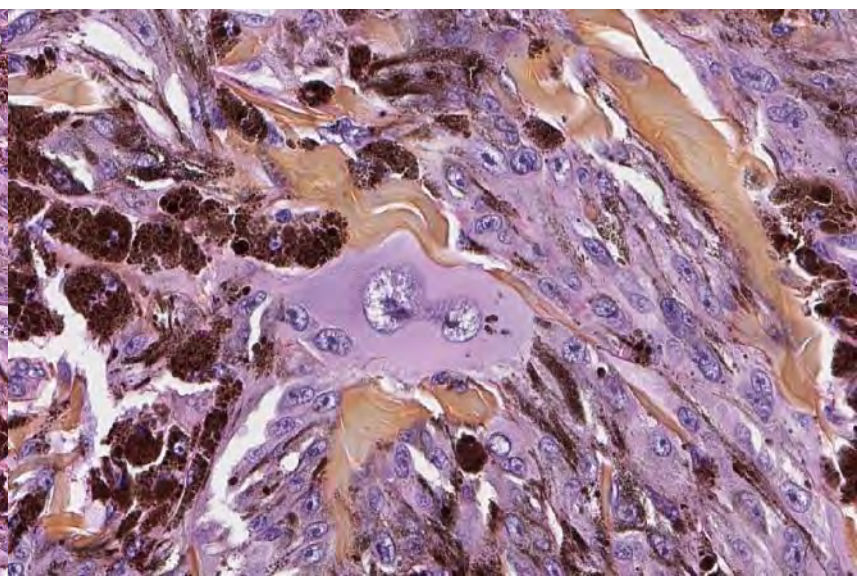
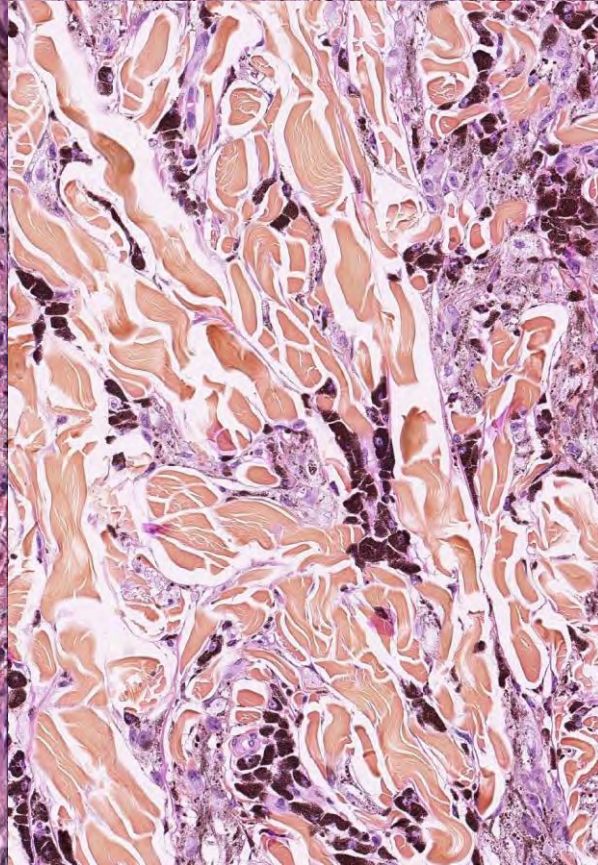
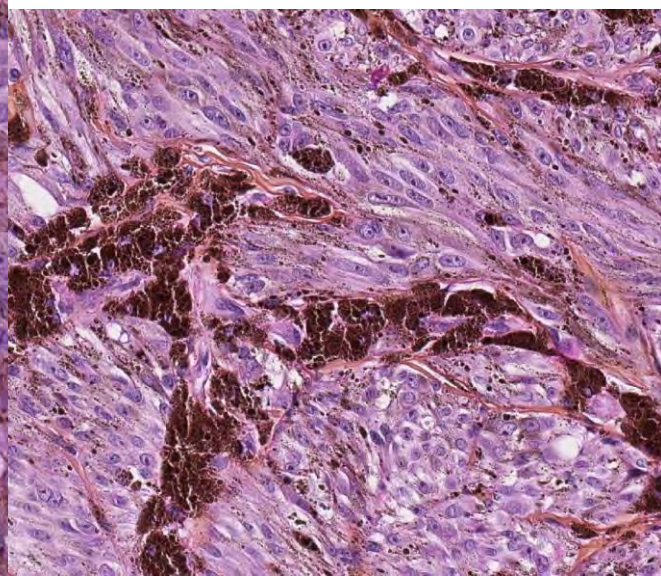
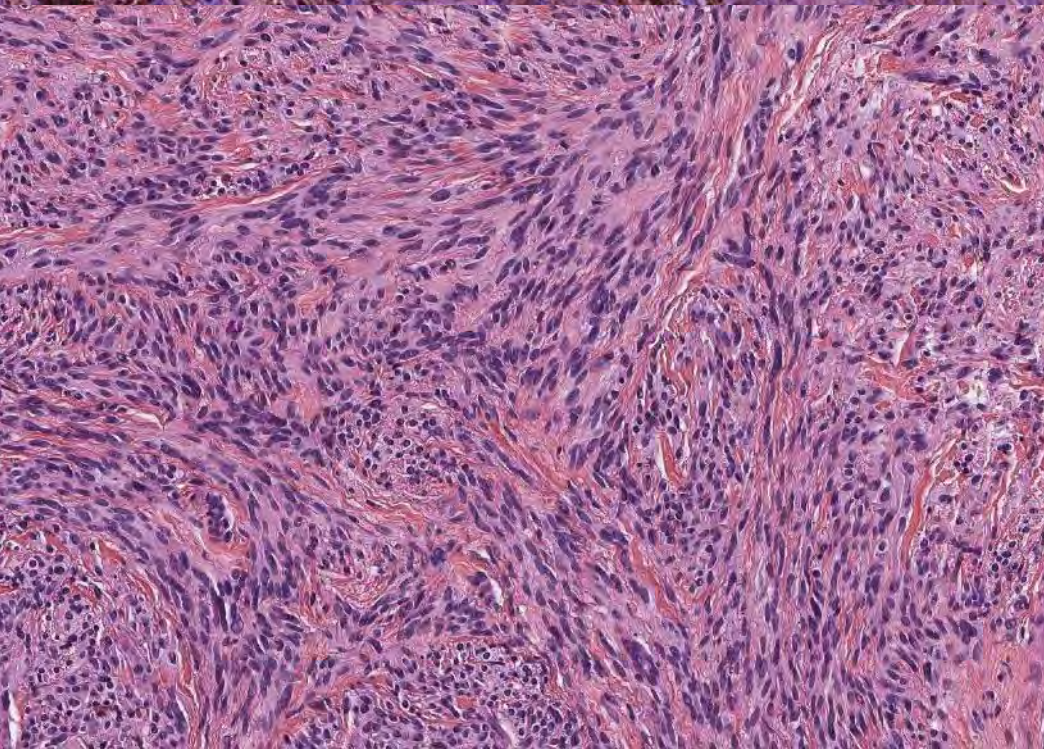
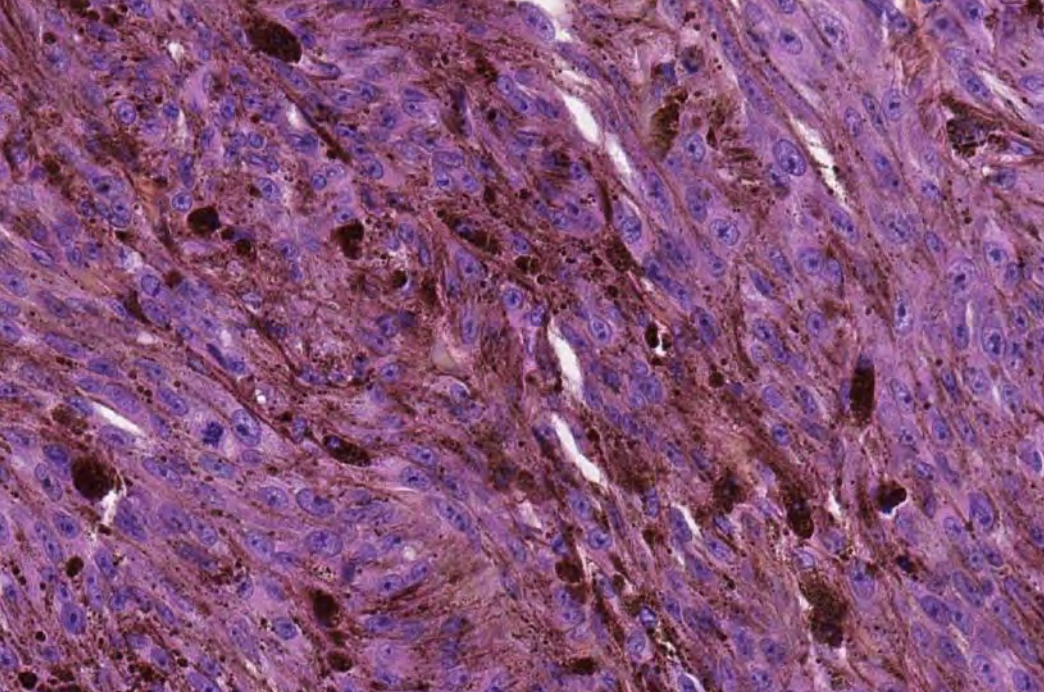
Figure 3 Activating *CYSLTR2* mutation in a superficial common blue nevus. (a–c) Histological pictures of a common blue nevus harboring an activating *CYSLTR2* mutation, showing the characteristic proliferation of bland pigmented spindle cells in the dermis with no epidermal involvement ((a) x20, (b) x200, and (c) x400 magnification). The tumor was removed from the upper right arm of a 78-year-old male. (d) The *CYSLTR2* c.386T>A mutation identified in the tumor with a wild-type sequence for comparison shown underneath. Annotation according to human genome assembly 19 (hg19).





Junctional component





CYSLTR2-mutated cutaneous blue lesions

Take home messages

- Nevi have a common blue nevi morphology
- Larger lesions have an unusual architecture
 - Exophytic
 - Fasciculated
 - PEM-like
- Cytology is most often large pigmented spindled melanocytes

Atypical cellular blue nevus

- **Diagnosis of exclusion**
- Currently not well defined
- More atypia than a CBN
- Not enough for a malignant Blue Melanoma

Atypical CBN

Ancillary techniques

- Protein G mutations *GNAQ>GNA11*
- Heterogeneous HMB45/MelanA expression
- BAP1 expression retained
- aCGH flat or whole chromosomal gains

Atypical Cellular Blue Nevus

Clinical atypia

- Large size
- Ulceration
- Growing mass

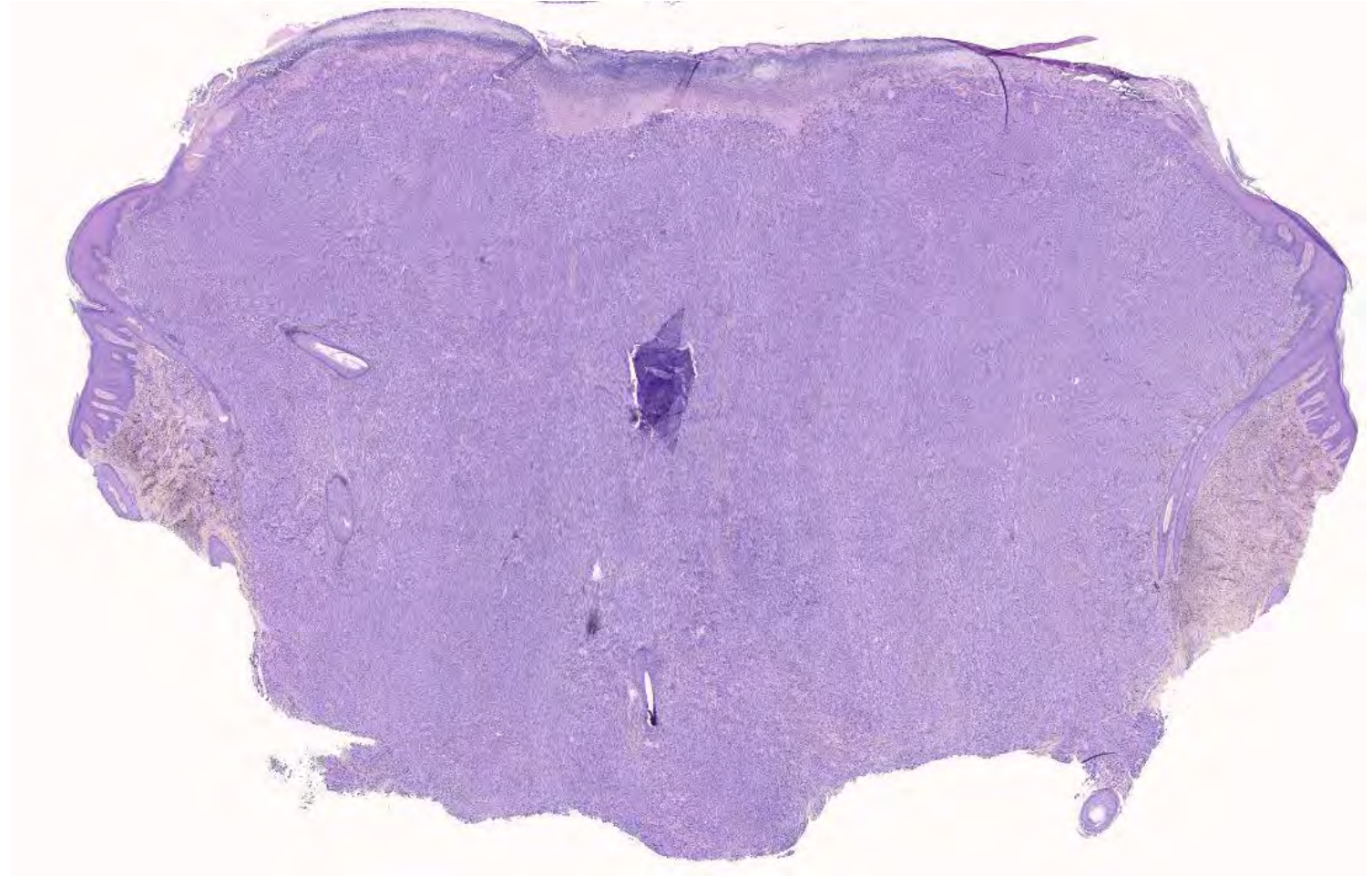


F24, melanocytosis + nodule

Atypical Cellular Blue Nevus

Morphological atypia

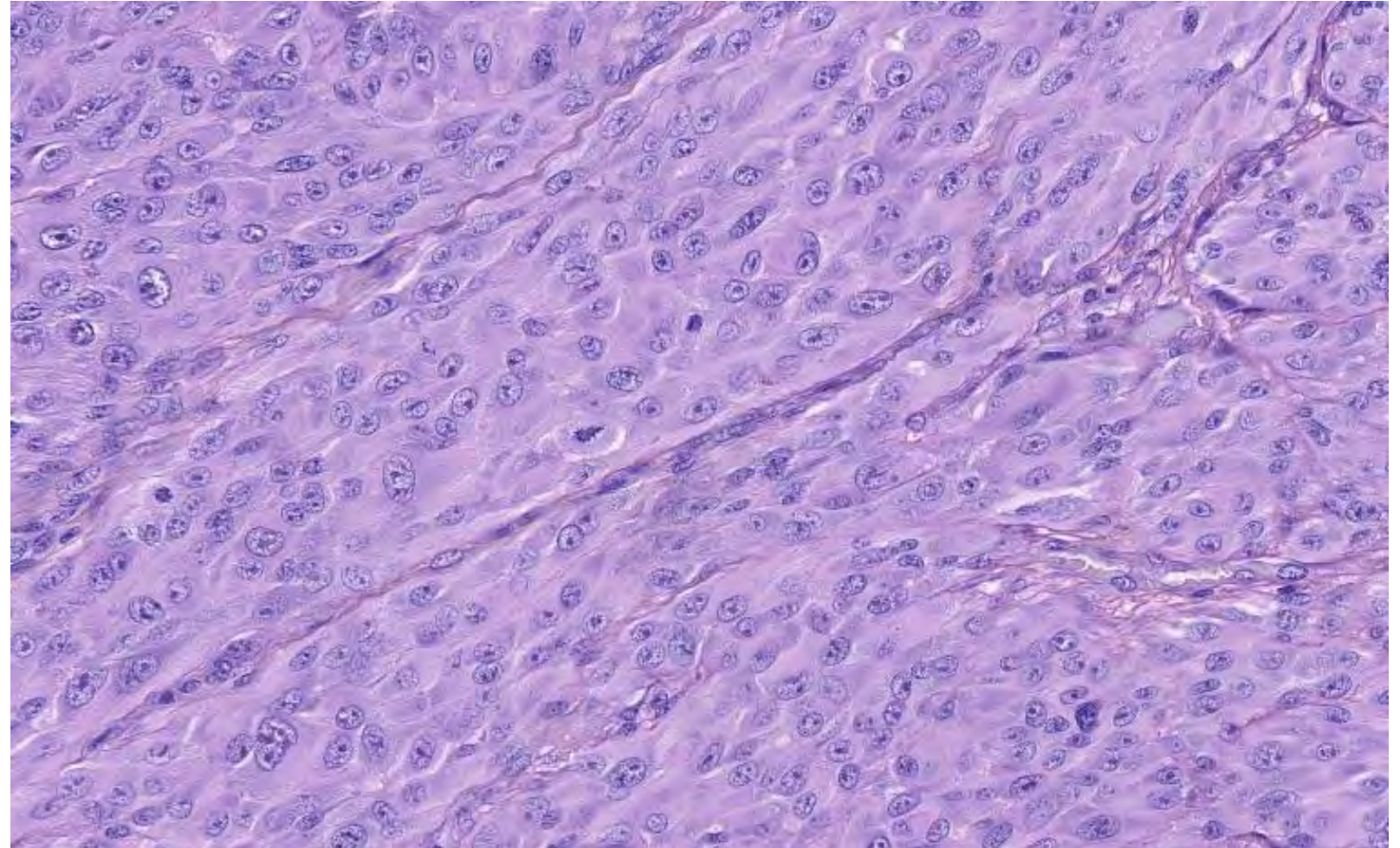
- Large size
- Ulceration
- High cellularity



Atypical Cellular Blue Nevus

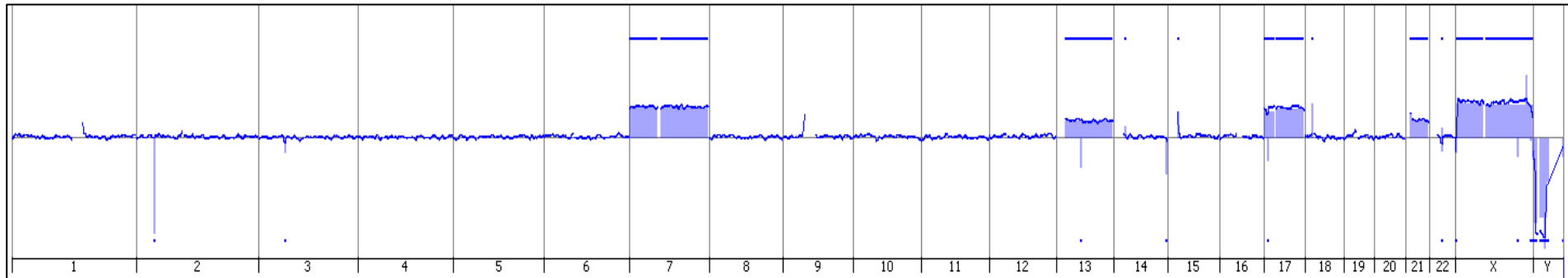
Morphological atypia

- Large size
- Ulceration
- High cellularity
- Pleomorphism
- Mitotic figures



Molecular study

- *CYSLTR2* p.L129Q
- Retained BAP1 Expression
- Whole chromosome gains on array-CGH

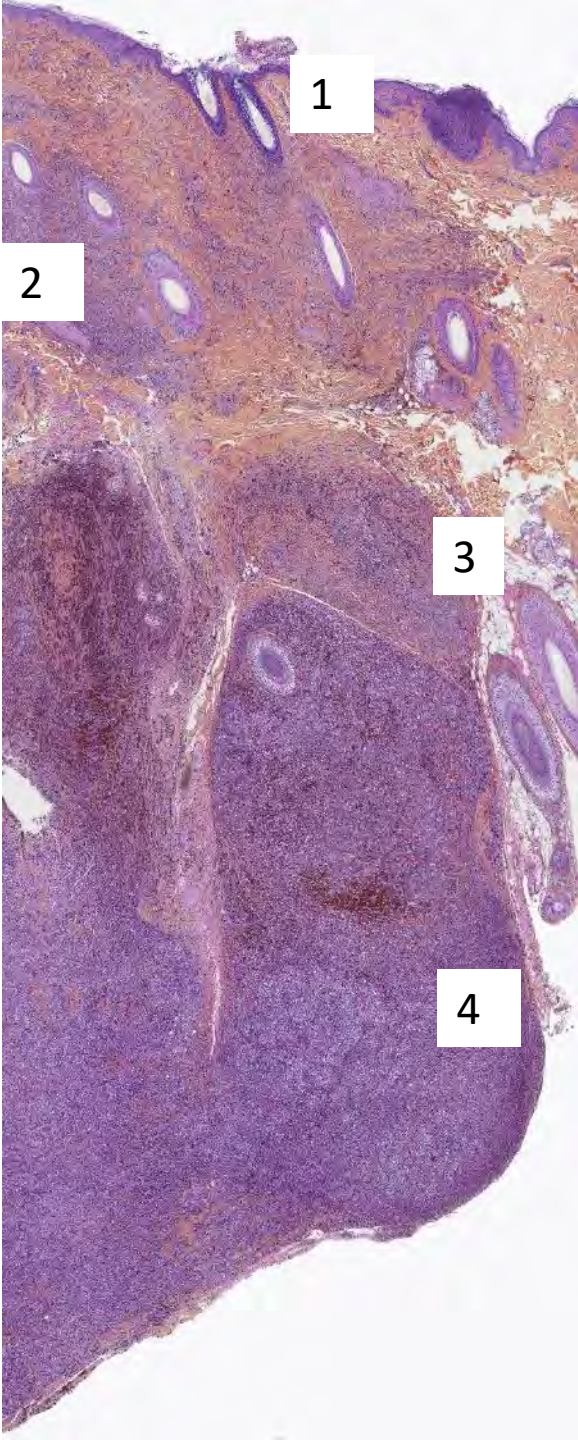


Atypical CBN

Atypical Cellular Blue Nevus

Outcome

- Low risk in early transformation
- Higher risk afterwards
- Complete removal can be problematic:
 - decapitation of dumbbell structures
 - plaque –type lesions



Malignant progression from blue nevi

*GNAQ, GNA11, PLCB4, CYSLTR2,
GRM1, PKC fused*

Blue nevus

Cellular blue nevus

Atypical blue nevus

Blue-type melanoma

Melanoma arising from a blue nevus

- Rare type of melanoma
- Adults, often >50 y
- Scalp, mostly parietal area
- Fast growing, >1cm

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

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

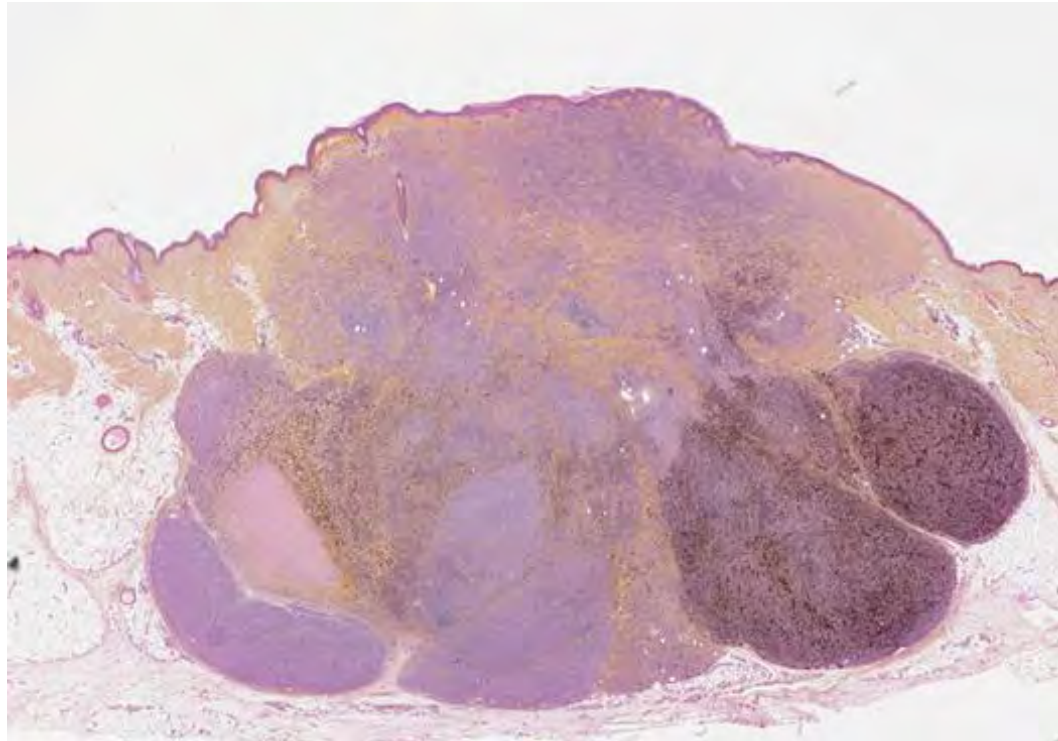
Author Information

The American Journal of Surgical Pathology: March 2016 - Volume 40 - Issue 3 - p 368-377
doi: 10.1097/PAS.0000000000000568



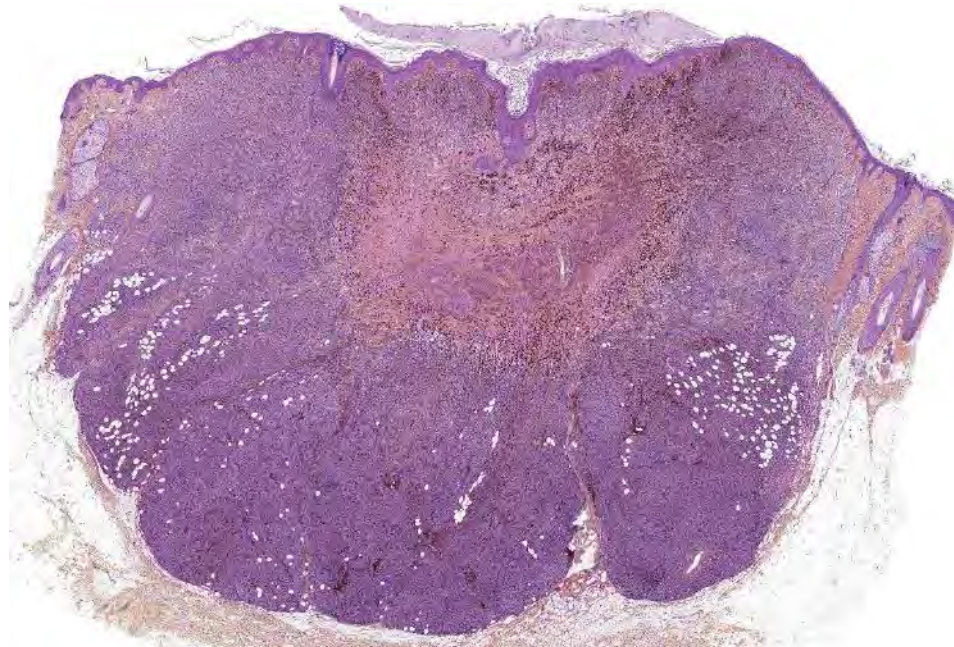
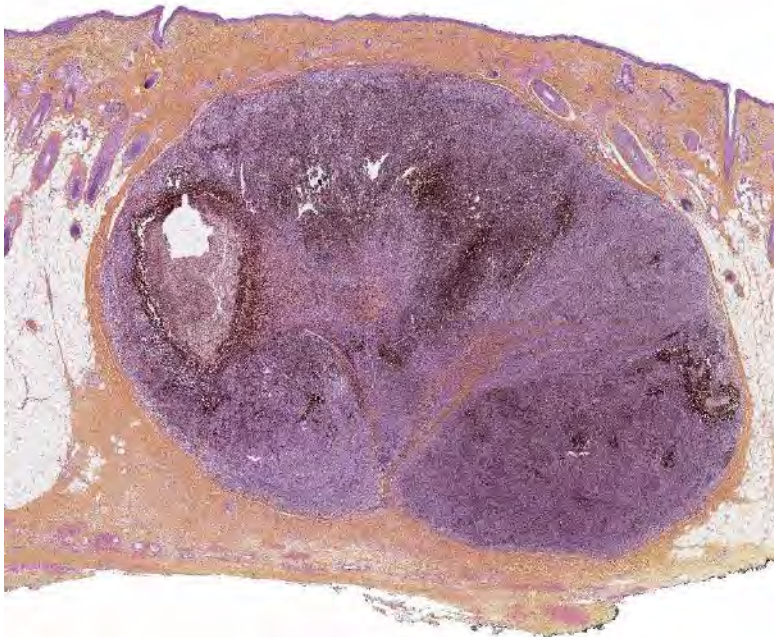
Melanoma arising from a blue nevus

- Diagnostic of malignancy is easy but classification is difficult.



Melanoma arising from a blue nevus

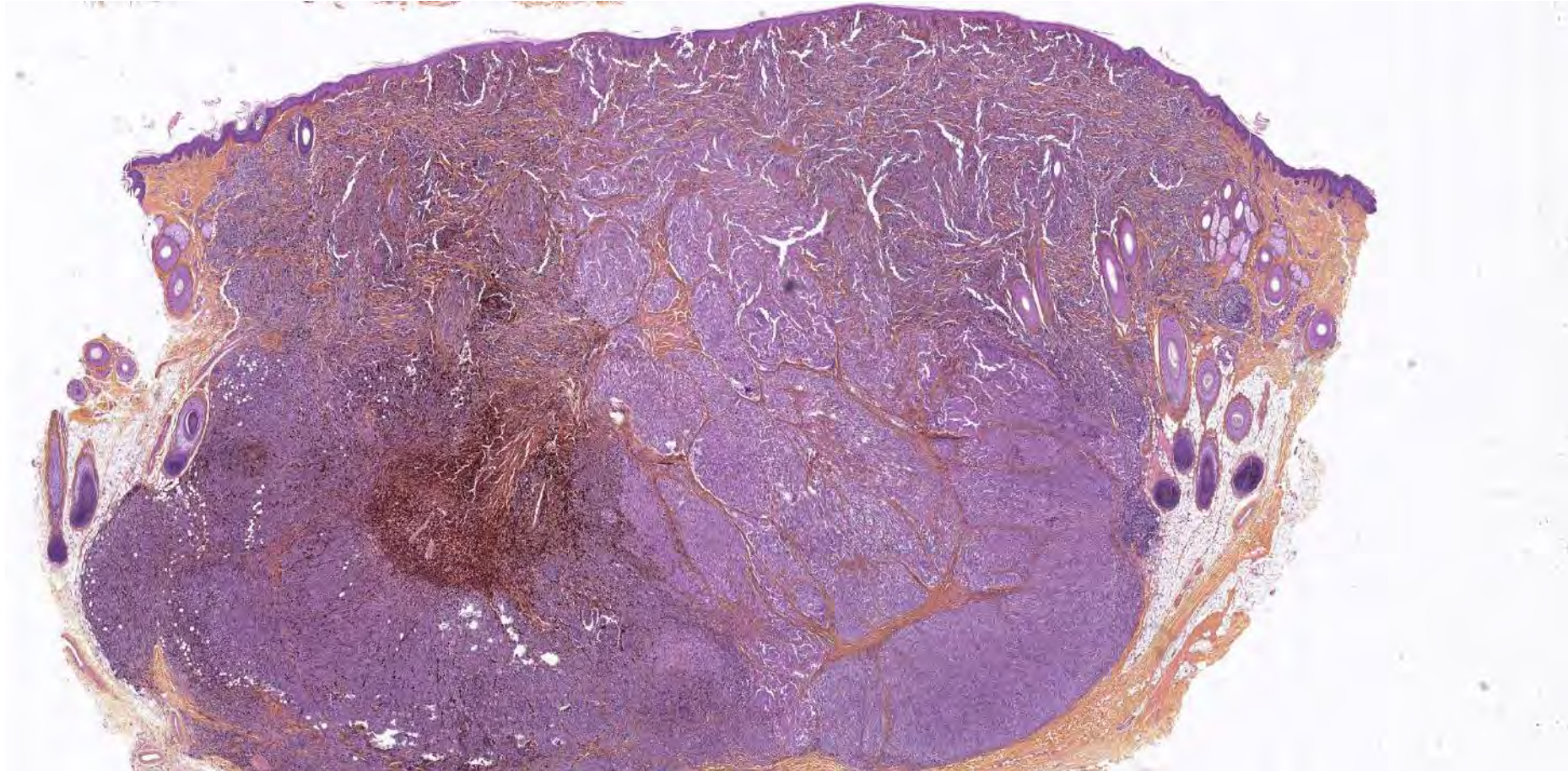
- Bulky dermal proliferation
- Pigmented clones
- Extensive tumoral necrosis



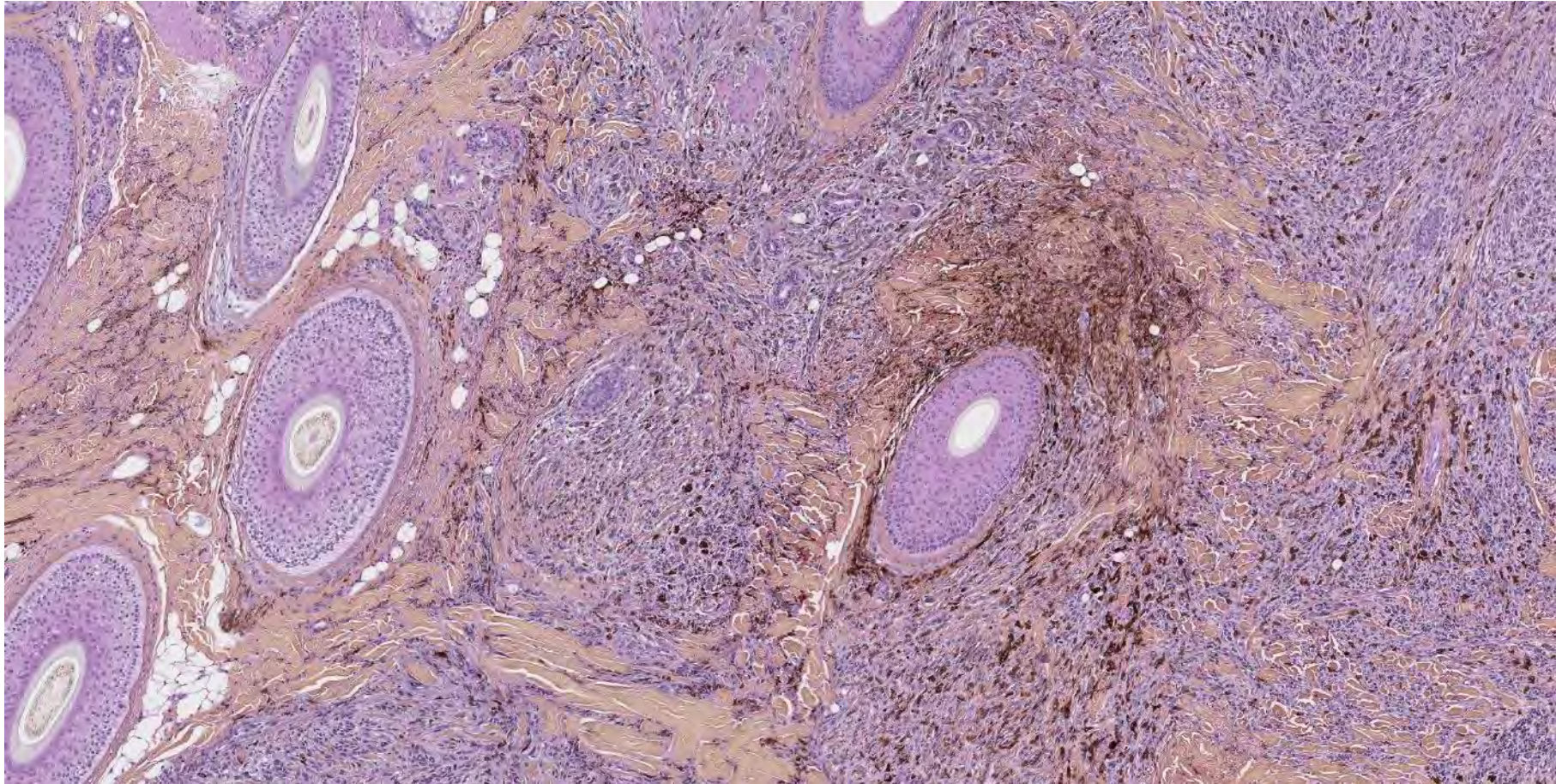
Melanoma arising from a blue nevus

- Diagnostic of malignancy is easy but classification is difficult.
- The presence of a benign or atypical blue-like lateral area is a major key for the diagnosis.

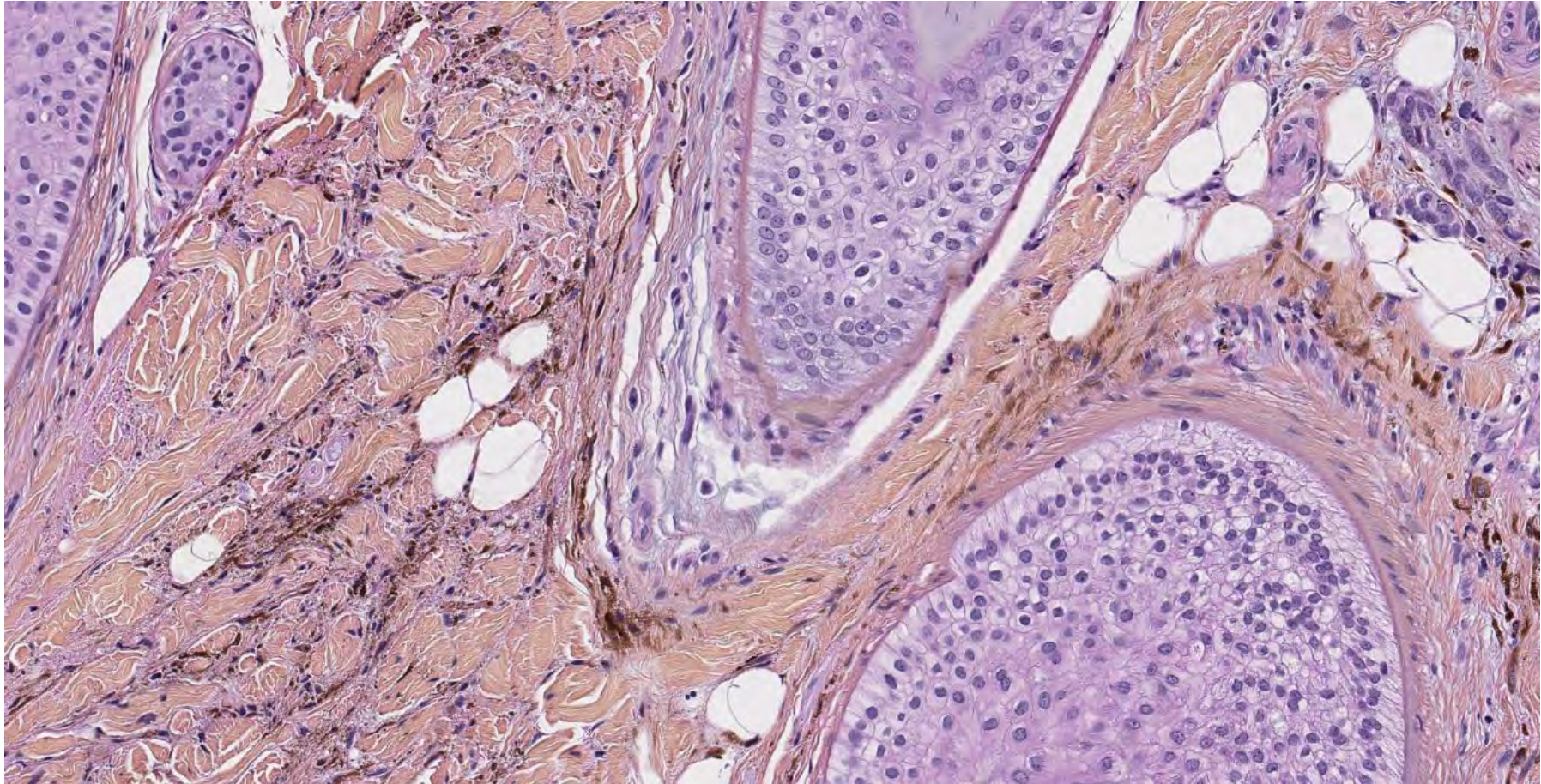
Melanoma arising from a blue nevus



Pre-existing dendritic blue nevus

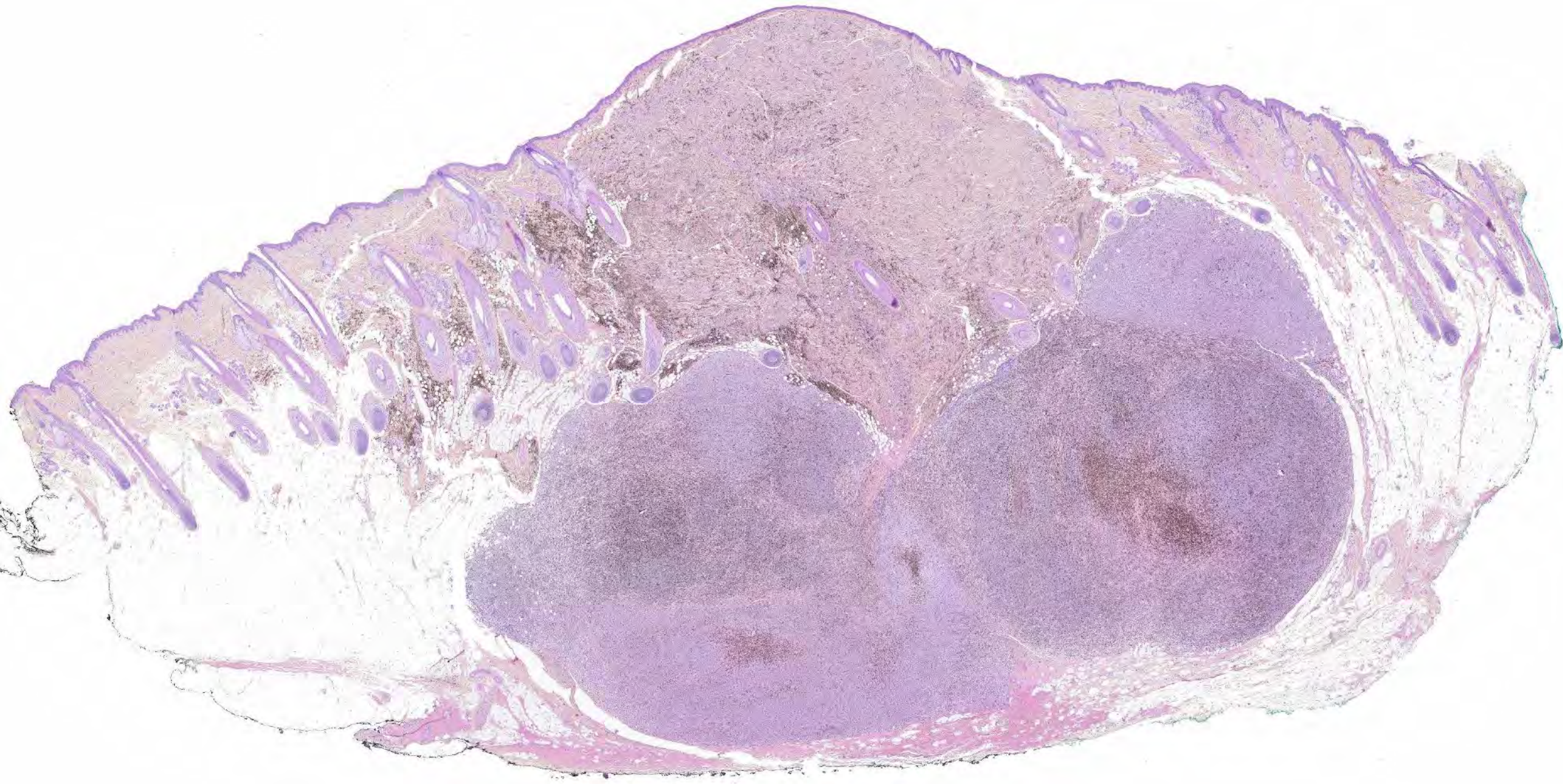


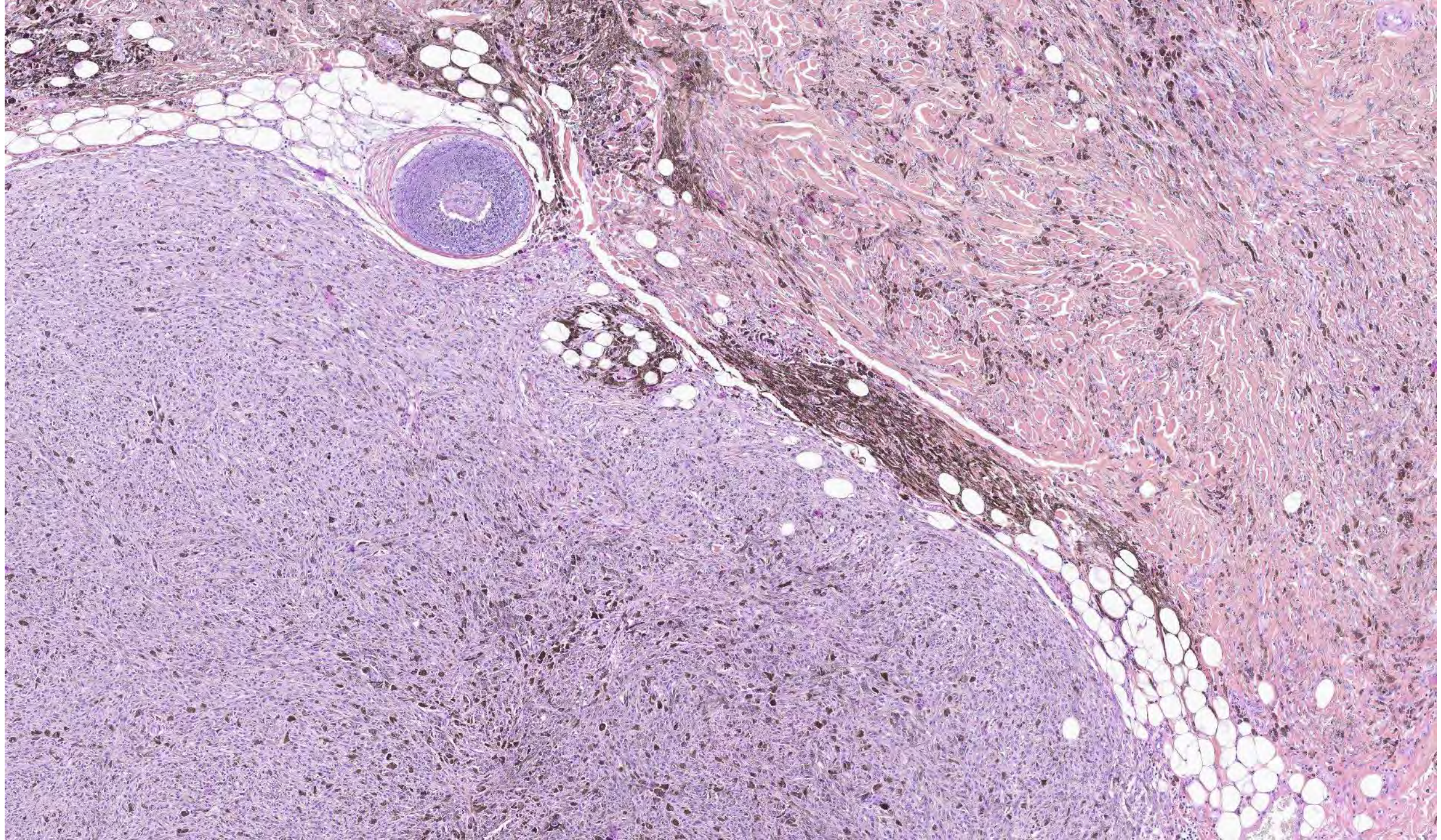
Pre-existing dendritic blue nevus



Melanoma arising from a blue nevus molecular analysis similar to Uveal Melanoma

- Protein G mutation sequencing
- Array-CGH with specific anomalies
- BAP1 IHC

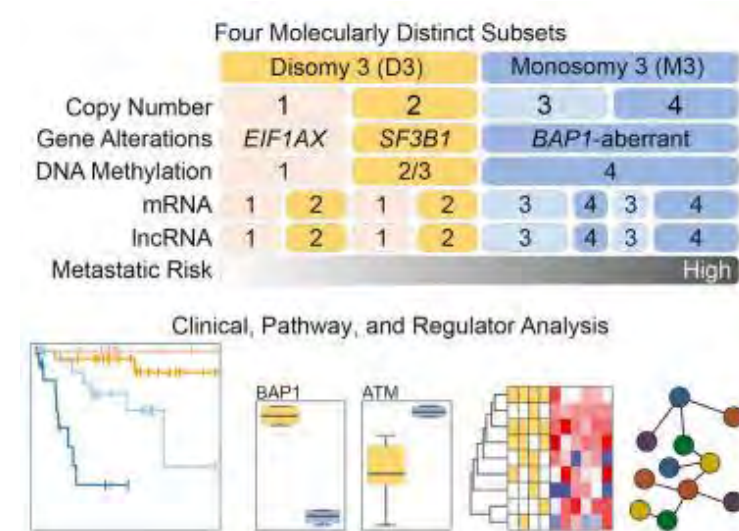




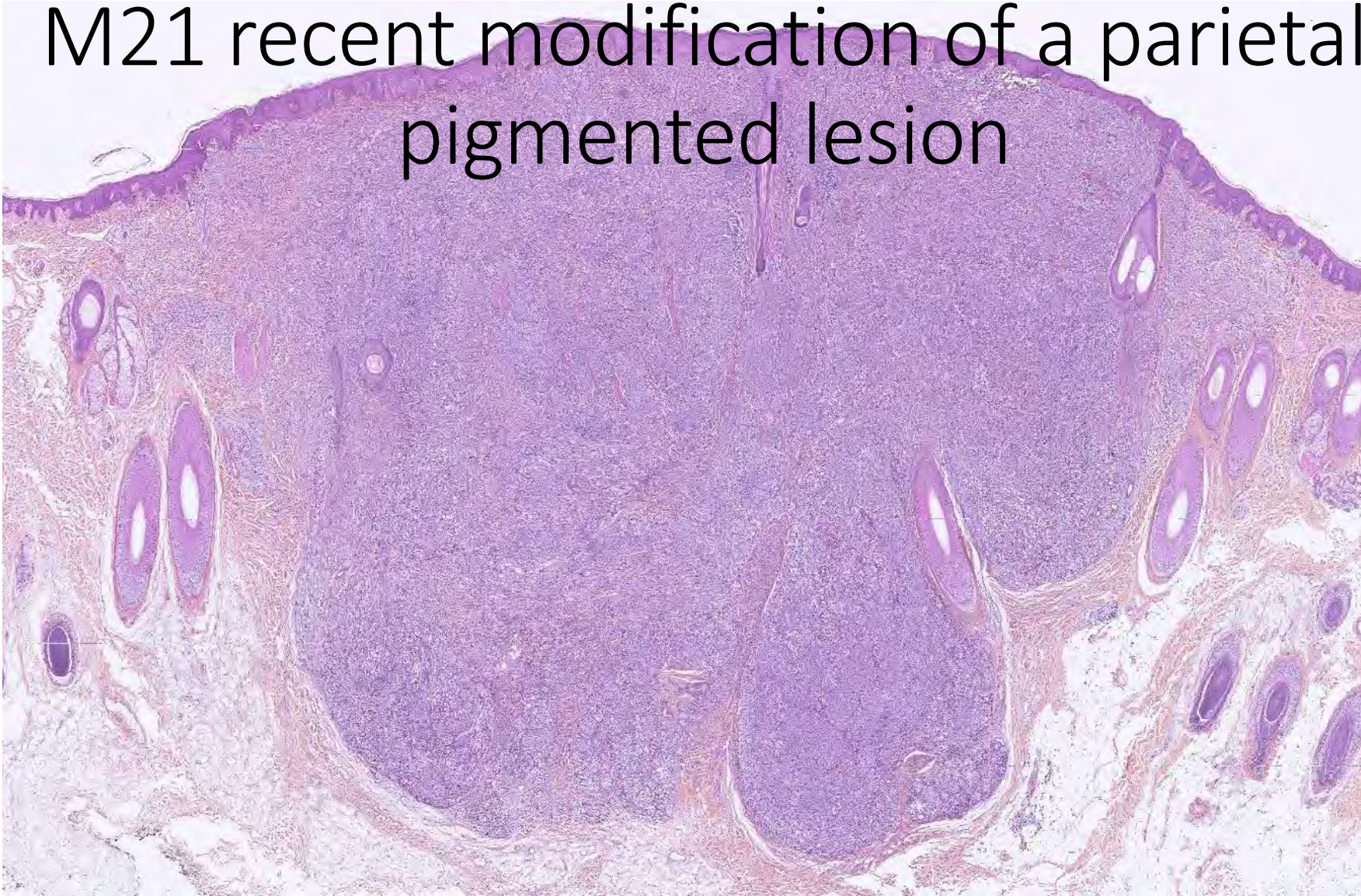
Melanoma arising from a blue nevus molecular analysis similar to Uveal Melanoma

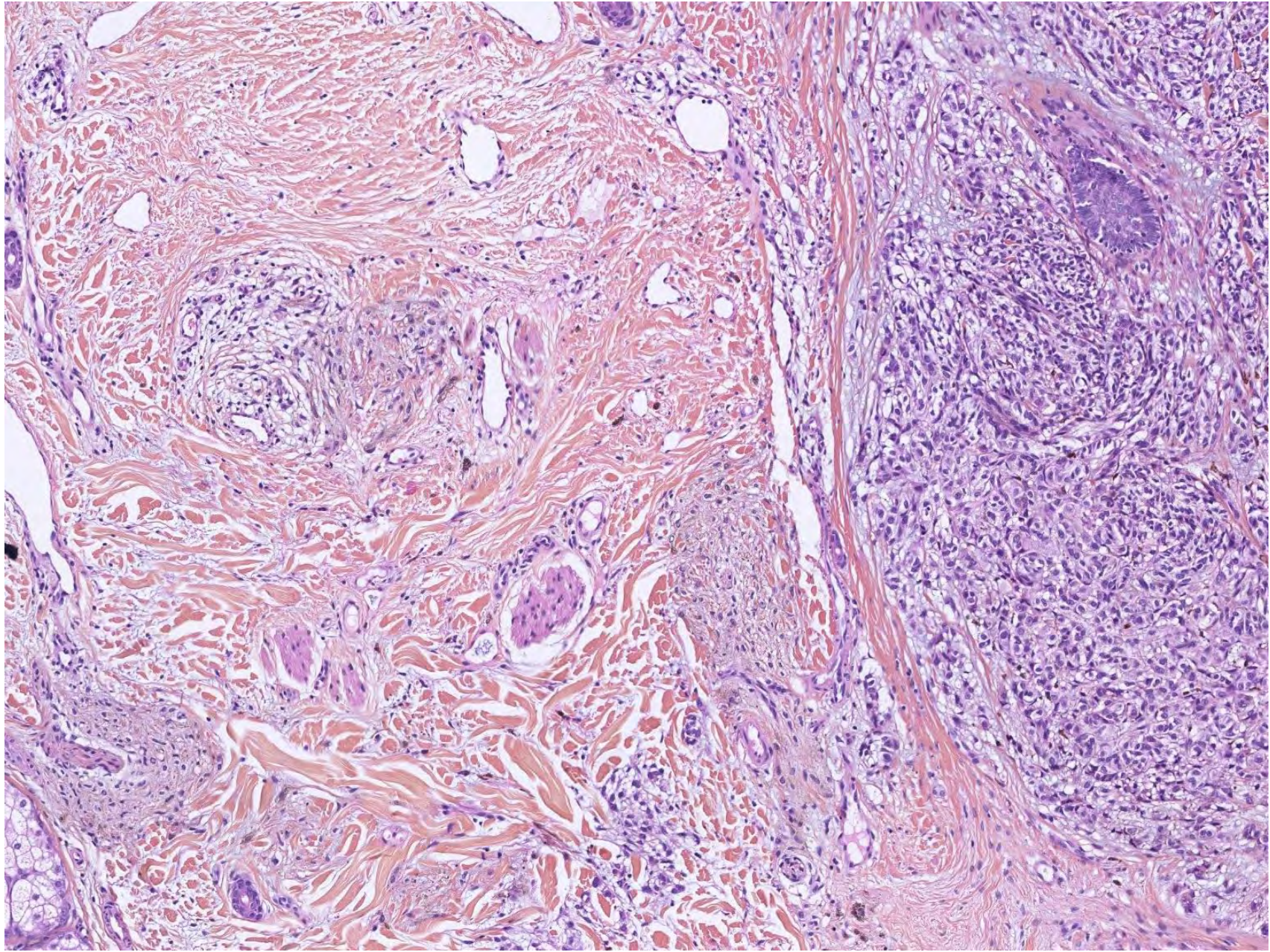
- Protein G mutation sequencing
- Array-CGH with specific anomalies
- BAP1 IHC
- **Progression** occurs through the gain of one « **BSE** » onco-event

- BAP1 : poor outcome
- SF3B1 : intermediate outcome
- EIF1AX : best outcome

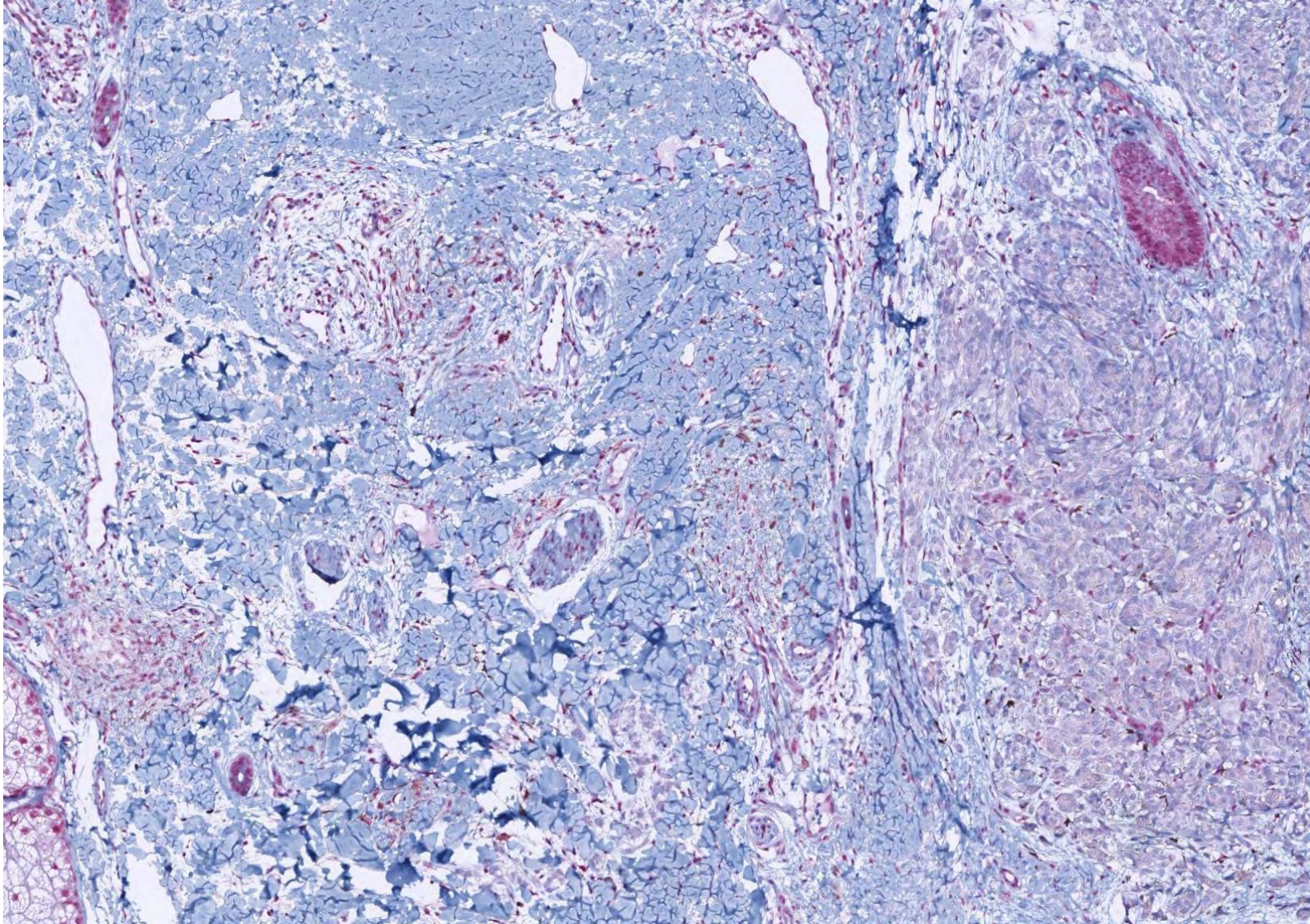


M21 recent modification of a parietal
pigmented lesion



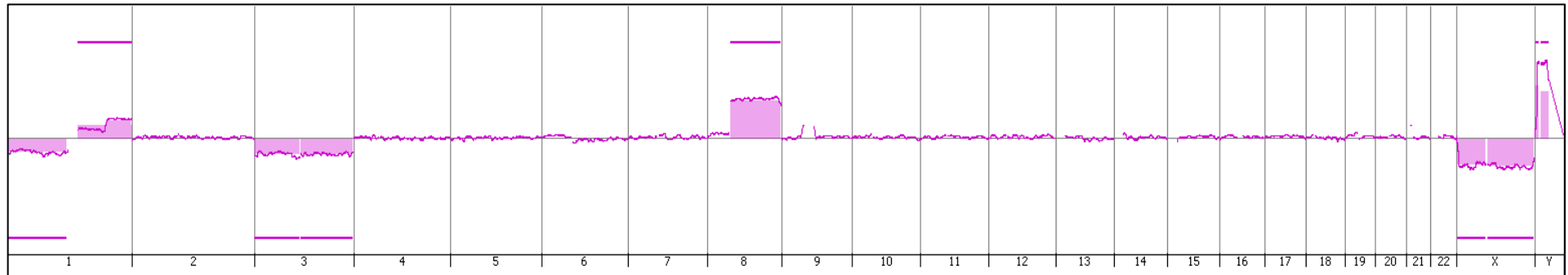


BAP1 IHC

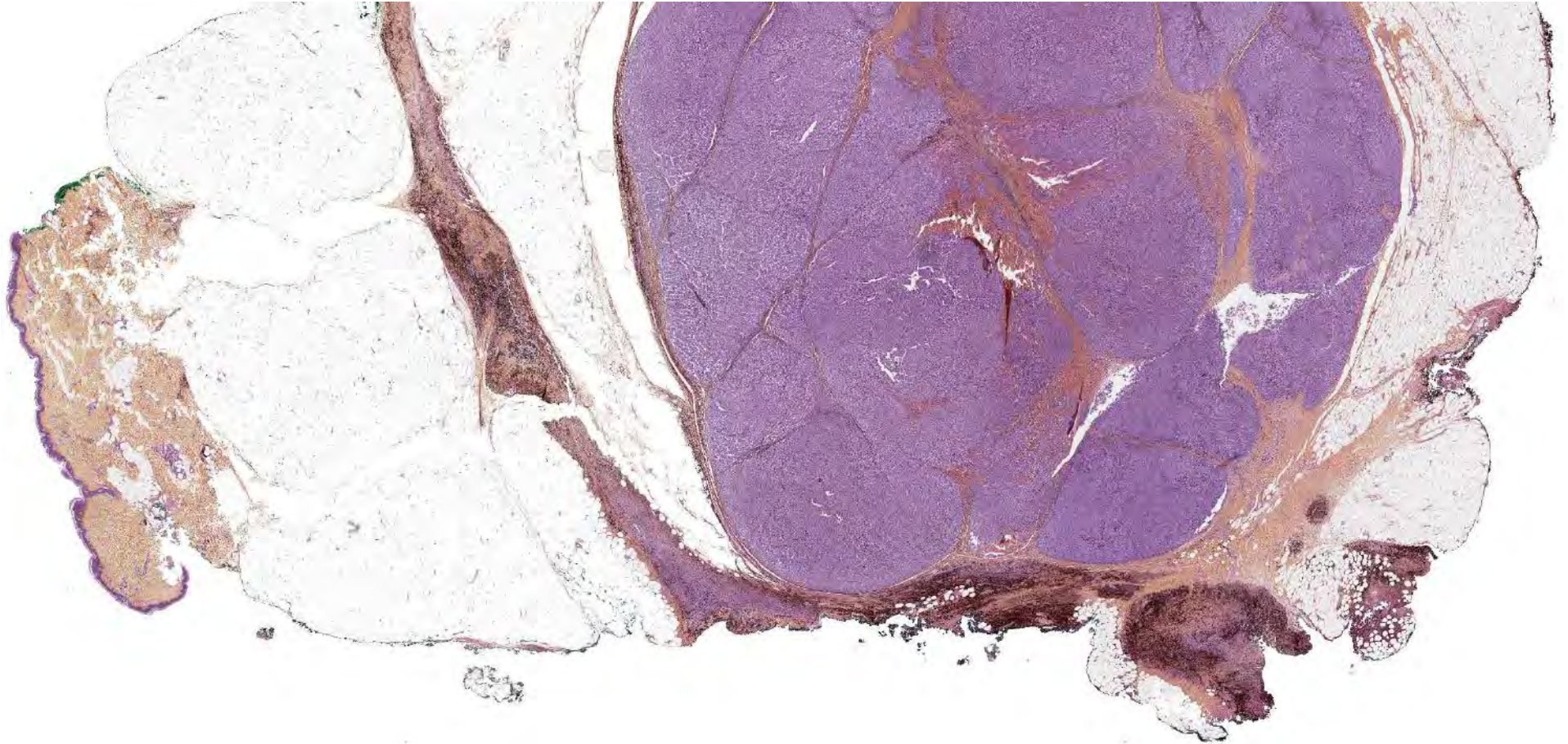


Array-CGH

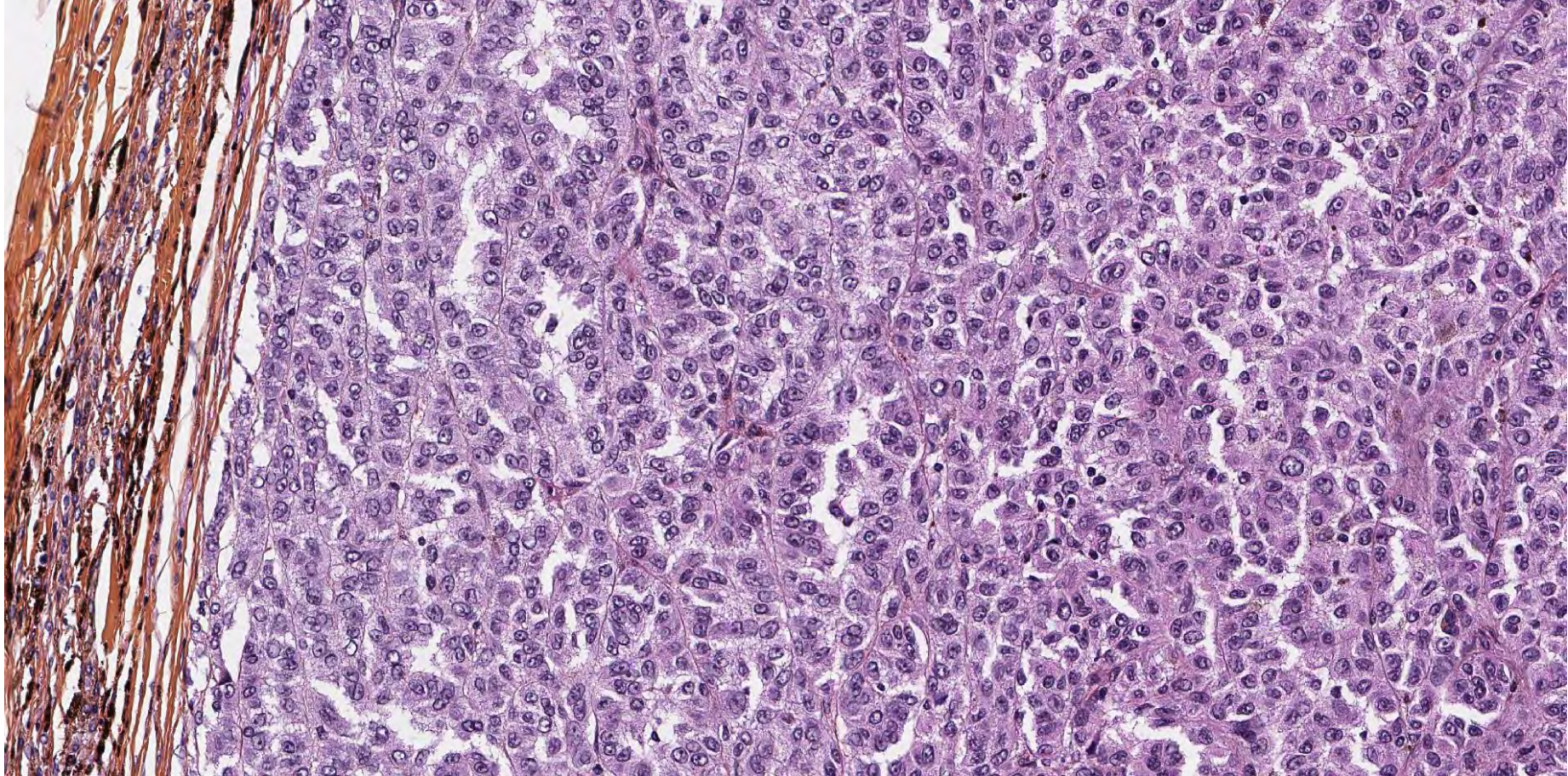
- Diagnostic/outcome profiles
- Class 1: good outcome (disomy 3) iso 6p
- Class 2: bad outcome (monosomy 3)
- Duplication of 8q (myc), loss 1p worse outcome



Melanoma *ex-plaque*-type blue nevus



Melanoma *ex-plaque*-type blue nevus

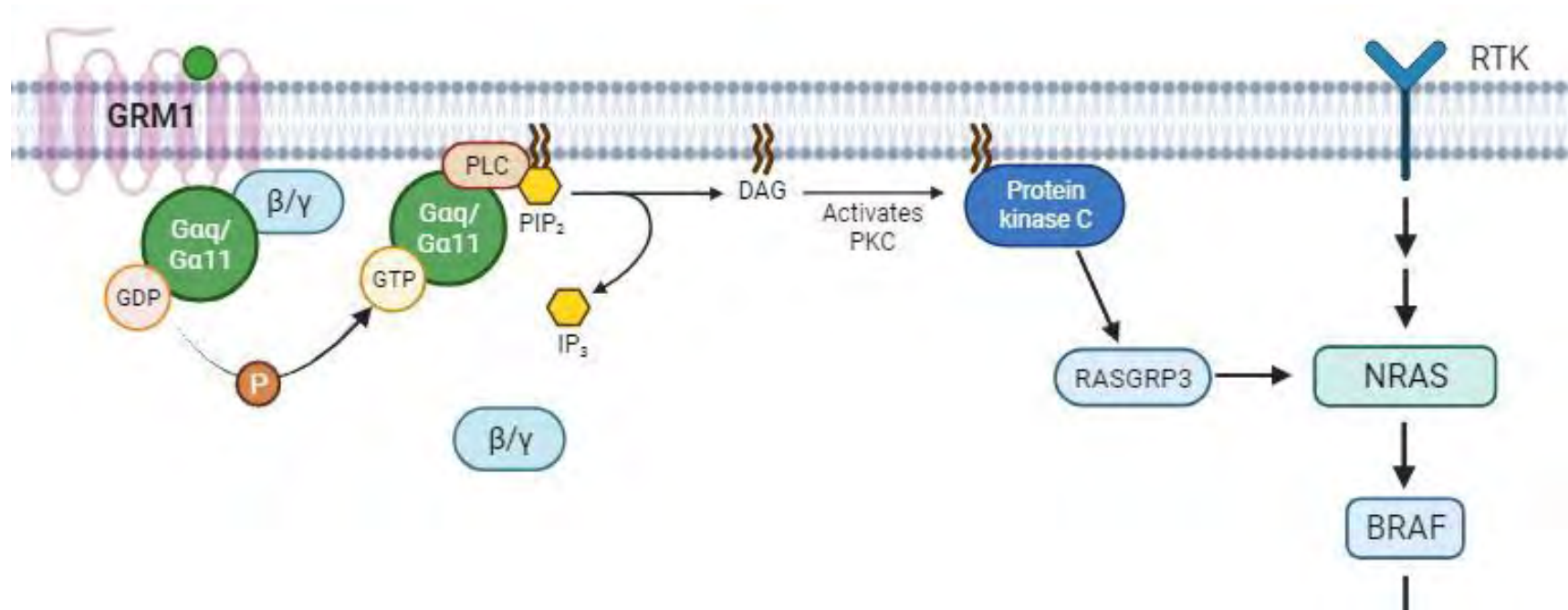


Rare/new genetic drivers/passengers in blue tumours

- *CYSLTR2* mutations
- *GRM1* fusions
- *PRKCA/B/G* fusions
- Blue nevus with *PRKAR1A*-inactivation

Blue melanocytic tumors
GRM1-fusions

GRM1 (Metabotropic Glutamate Receptor 1)



GRM1 in melanoma

- 60% of melanomas overexpress GRM1

➤ [Cancer Res.](#) 2007 Mar 1;67(5):2298-305. doi: 10.1158/0008-5472.CAN-06-3665.

Metabotropic glutamate receptor 1 and glutamate signaling in human melanoma

Jin Namkoong¹, Seung-Shick Shin, Hwa Jin Lee, Yarí E Marín, Brian A Wall, James S Goydos, Suzie Chen

Affiliations + expand

PMID: 17332361 DOI: [10.1158/0008-5472.CAN-06-3665](#)

➤ [Oncotarget.](#) 2017 Dec 23;9(5):5861-5875. doi: 10.18632/oncotarget.23637. eCollection 2018 Jan 19.

Activation of Grm1 expression by mutated BRAF (V600E) *in vitro* and *in vivo*

Ho-Chung Chen¹, Jairo Sierra^{1 2}, Lumeng Jenny Yu¹, Robert Cerchio Jr^{1 3}, Brian A Wall^{1 4}, James Goydos^{2 5}, Suzie Chen^{1 2 3 5}

Affiliations + expand

PMID: 29464040 PMCID: [PMC5814180](#) DOI: [10.18632/oncotarget.23637](#)

GRM1 in melanoma

- 60% of melanomas overexpress GRM1
- Oncogenesis shown in mouse models

➤ [Exp Dermatol](#). 2012 Oct;21(10):786-8. doi: 10.1111/j.1600-0625.2012.01560.x. Epub 2012 Aug 7.

Highly pigmented Tg(Grm1) mouse melanoma develops non-pigmented melanoma cells in distant metastases

Susanne Schiffner, Suzie Chen, Jürgen C Becker, Anja-Katrin Bosserhoff

PMID: 22882420 DOI: 10.1111/j.1600-0625.2012.01560.x

➤ [Exp Eye Res](#). 2014 Oct;127:59-68. doi: 10.1016/j.exer.2014.07.009. Epub 2014 Jul 19.

Tg(Grm1) transgenic mice: a murine model that mimics spontaneous uveal melanoma in humans?

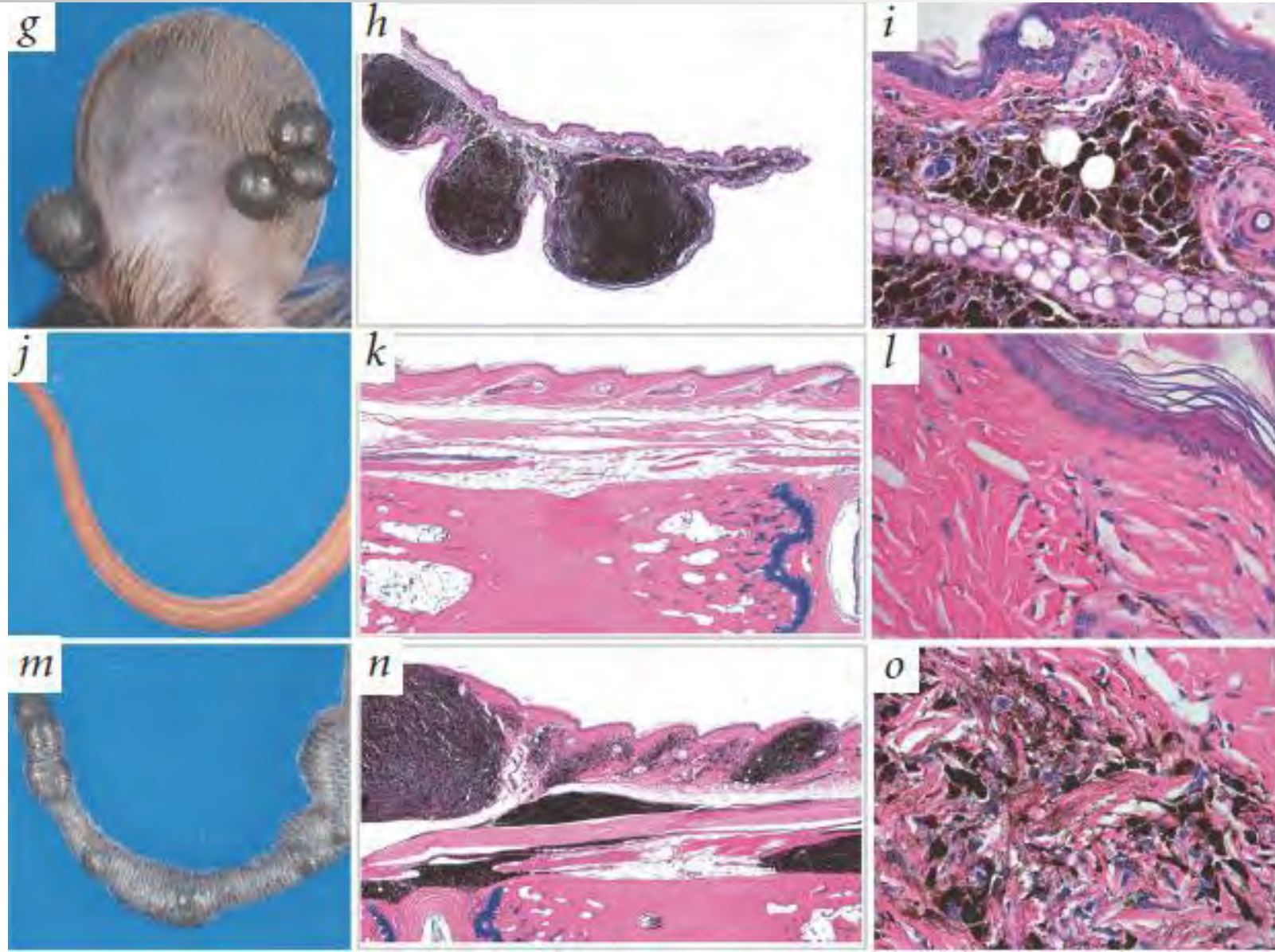
Susanne Schiffner¹, Barbara M Braunger², Miriam M de Jel¹, Sarah E Coupland³, Ernst R Tamm², Anja K Bosserhoff⁴

Affiliations + expand

PMID: 25051141 DOI: 10.1016/j.exer.2014.07.009

GRM1-ITD TG3 mouse model

Mice develop **multiple melanomas** with **blue-like** morphology



GRM1 in melanoma

- 60% of melanomas overexpress GRM1
- Oncogenesis shown in humans

➤ [Cancer Res.](#) 2014 May 1;74(9):2499-509. doi: 10.1158/0008-5472.CAN-13-1531. Epub 2014 Feb 3.

Activation of the glutamate receptor GRM1 enhances angiogenic signaling to drive melanoma progression

Yu Wen ¹, Jiadong Li, Jasmine Koo, Seung-Shick Shin, Yong Lin, Byeong-Seon Jeong, Janice M Mehnert, Suzie Chen, Karine A Cohen-Sola, James S Goydos

Affiliations + expand

PMID: 24491800 PMCID: [PMC4008638](#) DOI: [10.1158/0008-5472.CAN-13-1531](#)

GRM1 overexpression in melanoma

- 60% of melanomas overexpress GRM1
- GRM1 targeting strategies have been developed

➤ [Pigment Cell Melanoma Res.](#) 2015 Jan;28(1):105-9. doi: 10.1111/pcmr.12327. Epub 2014 Nov 28.

Riluzole is a radio-sensitizing agent in an in vivo model of brain metastasis derived from GRM1 expressing human melanoma cells

Brian A Wall ¹, Lumeng J Yu, Atif Khan, Bruce Haffty, James S Goydos, Suzie Chen

Affiliations + expand

PMID: 25363352 PMCID: [PMC5661976](#) DOI: [10.1111/pcmr.12327](#)

➤ [Cancer Res.](#) 2019 Apr 15;79(8):1799-1809. doi: 10.1158/0008-5472.CAN-18-1500. Epub 2019 Apr 15.

Concurrent Targeting of Glutaminolysis and Metabotropic Glutamate Receptor 1 (GRM1) Reduces Glutamate Bioavailability in GRM1⁺ Melanoma

Raj Shah ^{# 1 2}, Simar J Singh ^{# 3}, Kevin Eddy ¹, Fabian V Filipp ^{# 4 5}, Suzie Chen ^{# 6 2 7}

Affiliations + expand

PMID: 30987979 PMCID: [PMC6469683](#) DOI: [10.1158/0008-5472.CAN-18-1500](#)

[Clinical Trial](#) ➤ [Pigment Cell Melanoma Res.](#) 2018 Jul;31(4):534-540. doi: 10.1111/pcmr.12694.

Epub 2018 Apr 10.

A phase II trial of riluzole, an antagonist of metabotropic glutamate receptor 1 (GRM1) signaling, in patients with advanced melanoma

Janice M Mehnert ¹, Ann W Silk ¹, J H Lee ¹, Liesel Dudek ¹, Byeong-Seon Jeong ¹, Jiadong Li ¹, Jason M Schenkel ², Evita Sadimin ¹, Michael Kane ¹, Hongxia Lin ¹, Weichung J Shih ¹, Andrew Zloza ¹, Suzie Chen ³, James S Goydos ¹

Affiliations + expand

PMID: 29453787 PMCID: [PMC6013351](#) DOI: [10.1111/pcmr.12694](#)

➤ [J Invest Dermatol.](#) 2010 Sep;130(9):2240-9. doi: 10.1038/jid.2010.126. Epub 2010 May 27.

The glutamate release inhibitor Riluzole decreases migration, invasion, and proliferation of melanoma cells

Maithao N Le ¹, Joseph L-K Chan, Stephen A Rosenberg, Adam S Nabatian, Kim T Merrigan, Karine A Cohen-Solal, James S Goydos

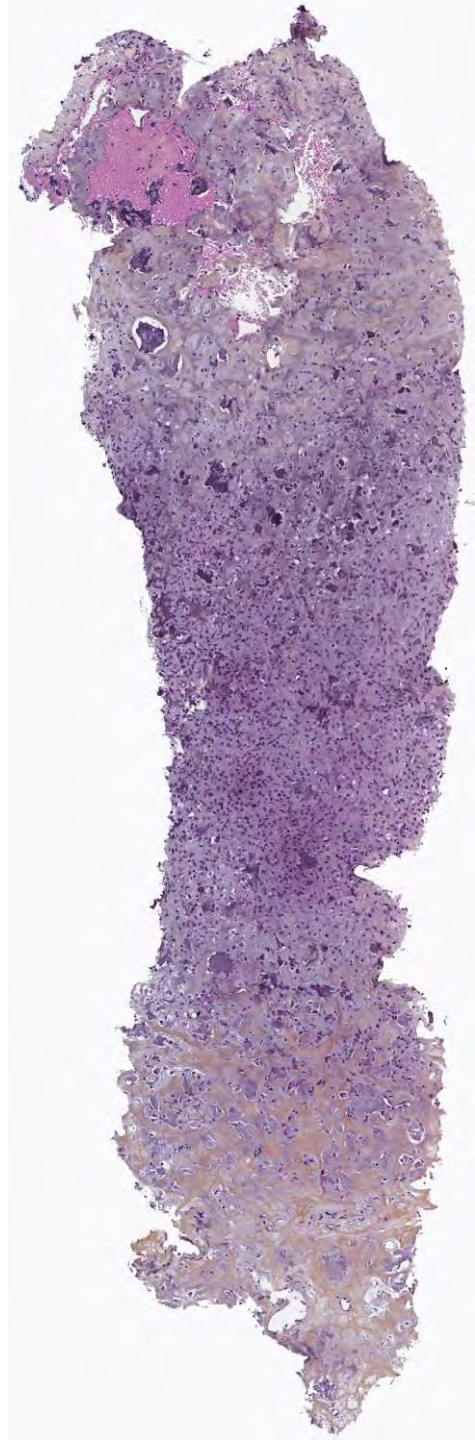
Affiliations + expand

PMID: 20505744 PMCID: [PMC4004181](#) DOI: [10.1038/jid.2010.126](#)

GRM1-fusions

Chondromyxoid Fibroma

- **Rare**, locally aggressive, **bone tumor** located at acral sites
- Fusion involving the 5' end of the gene => **normal protein**



GRM1-fused Blue tumors

➤ [Mod Pathol. 2023 Jun 28;36\(10\):100264. doi: 10.1016/j.modpat.2023.100264. Online ahead of print.](#)

GRM1 Gene Fusions as an Alternative Molecular Driver in Blue Nevus and Related Melanomas

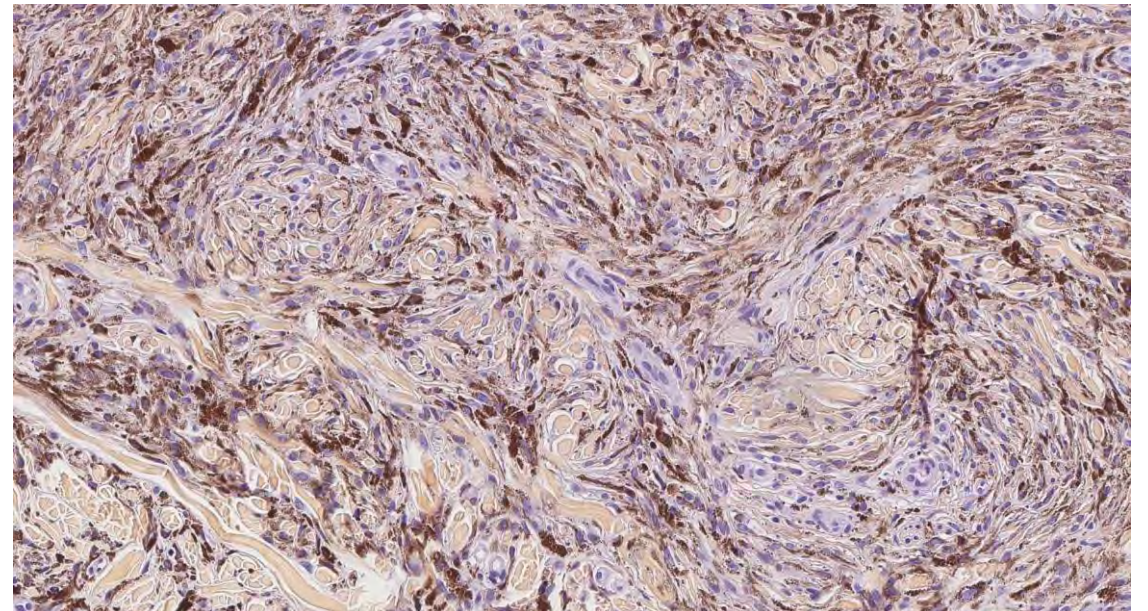
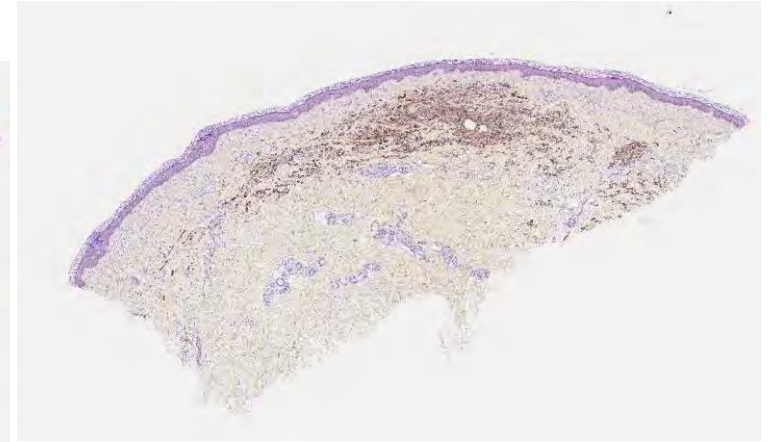
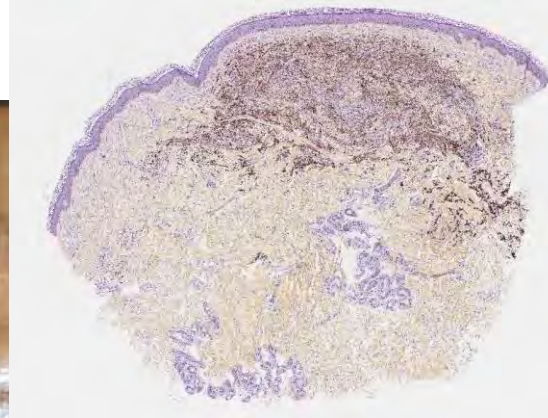
Thibault Kervarrec ¹, Giuseppe Lo Bello ², Daniel Pissaloux ³, Franck Tirode ⁴, Nicolas Poulalhon ⁵,
Mahtab Samimi ⁶, Aurélie Houlier ⁷, Arnaud de la Fouchardière ⁸

Affiliations + expand

PMID: 37391170 DOI: [10.1016/j.modpat.2023.100264](#)

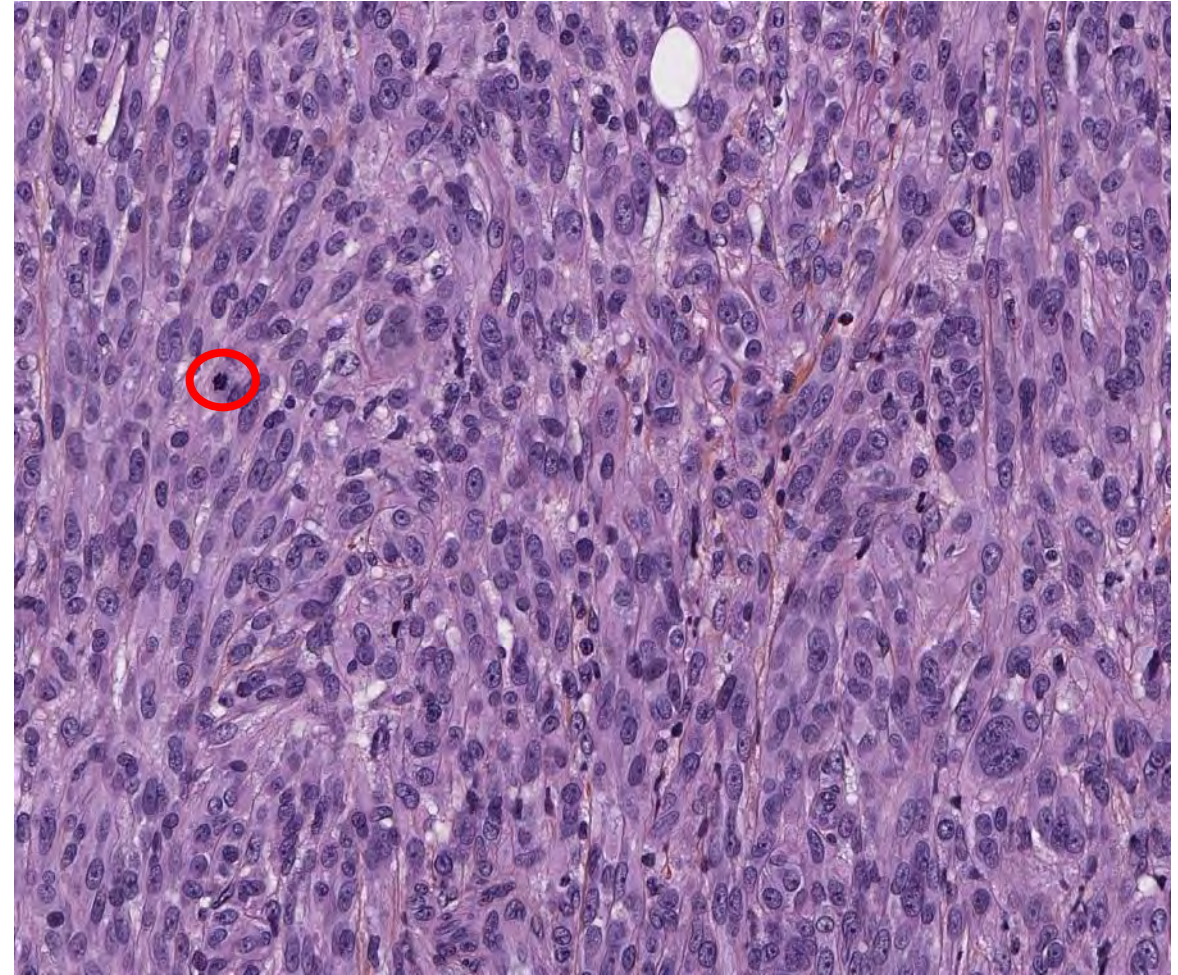
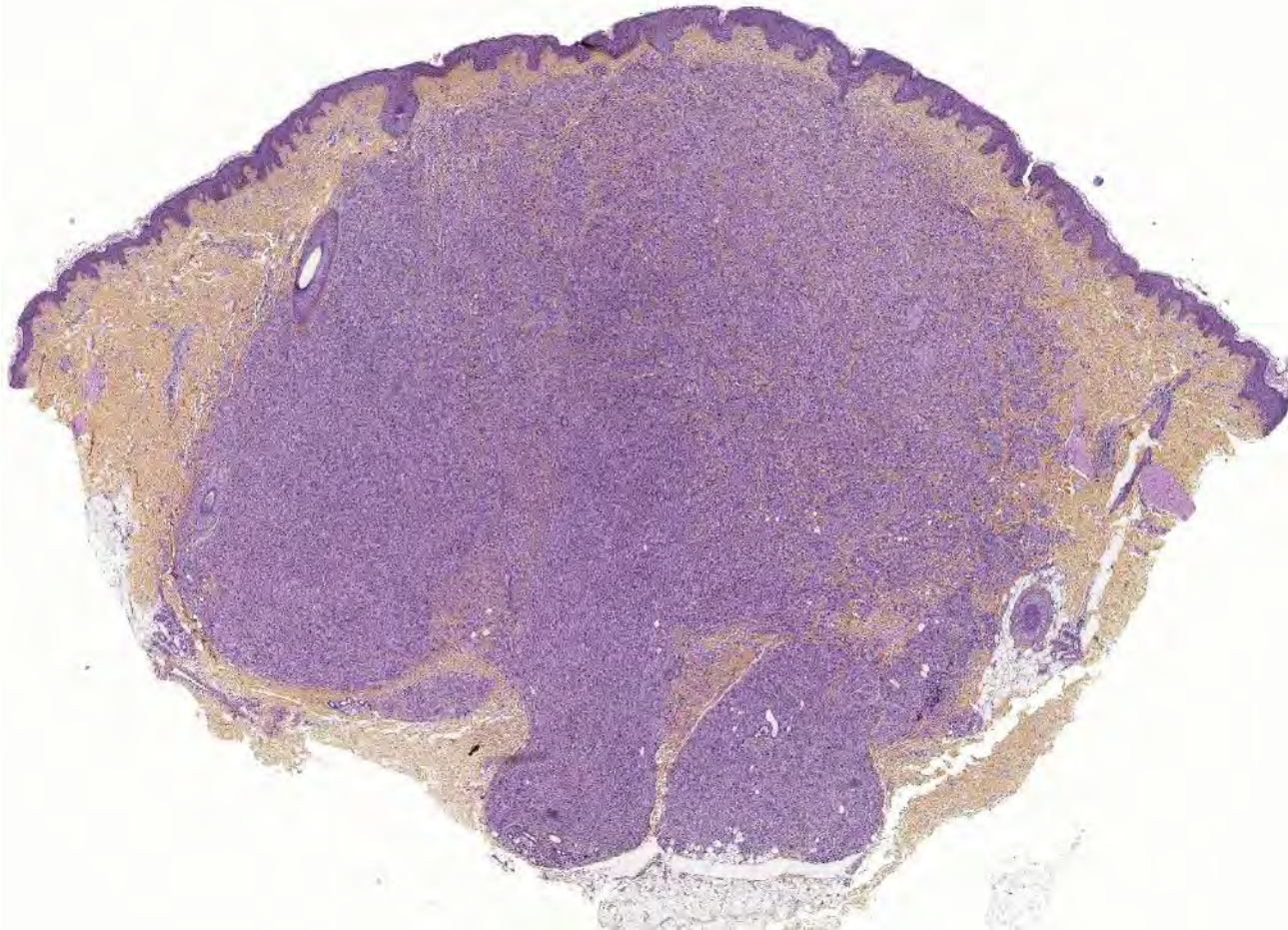
GRM1-fused Blue tumors

- **Plaque-type** blue nevi including Ota nevus



GRM1-fused Blue tumors

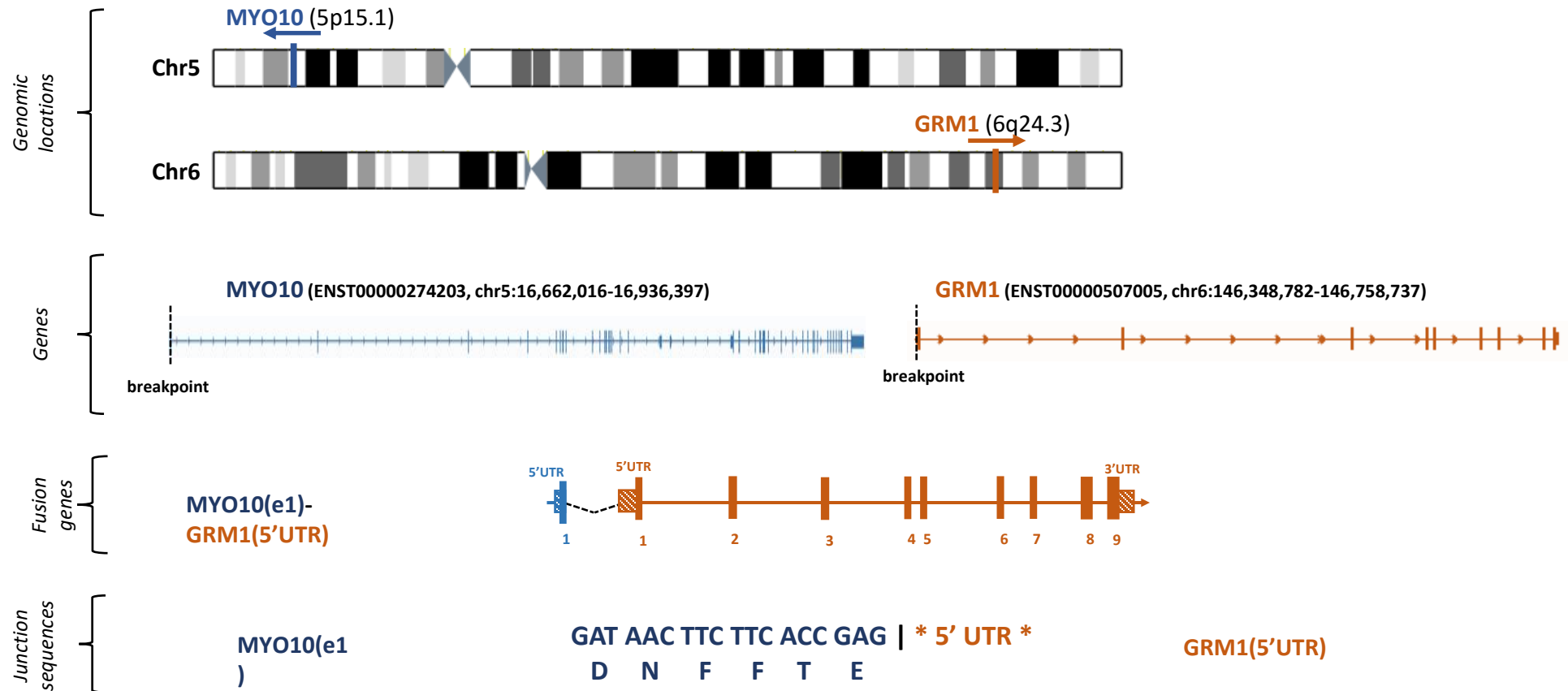
- **Atypical** cellular blue nevus



GRM1-fused Blue tumors

- **Malignant** Blue melanoma *MYO10::GRM1* fusion + *SF3B1* mutation

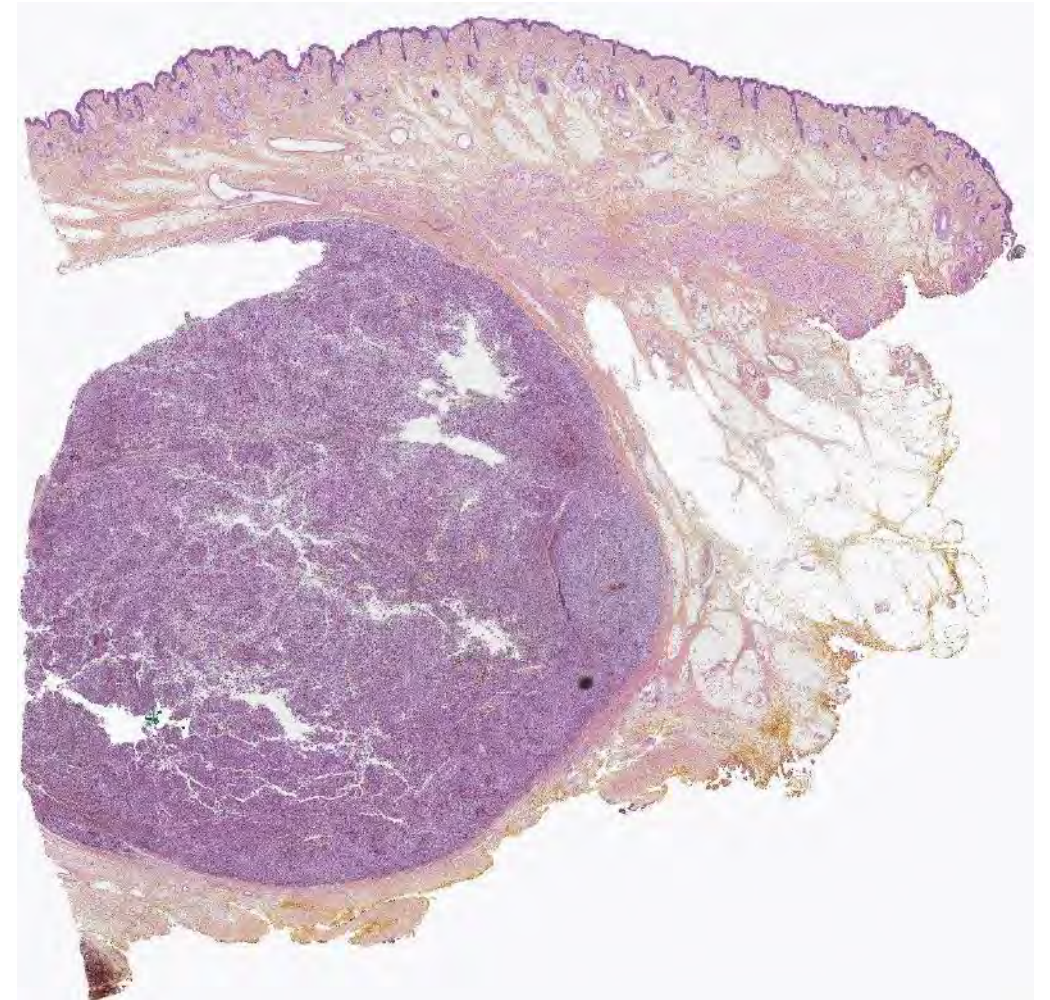
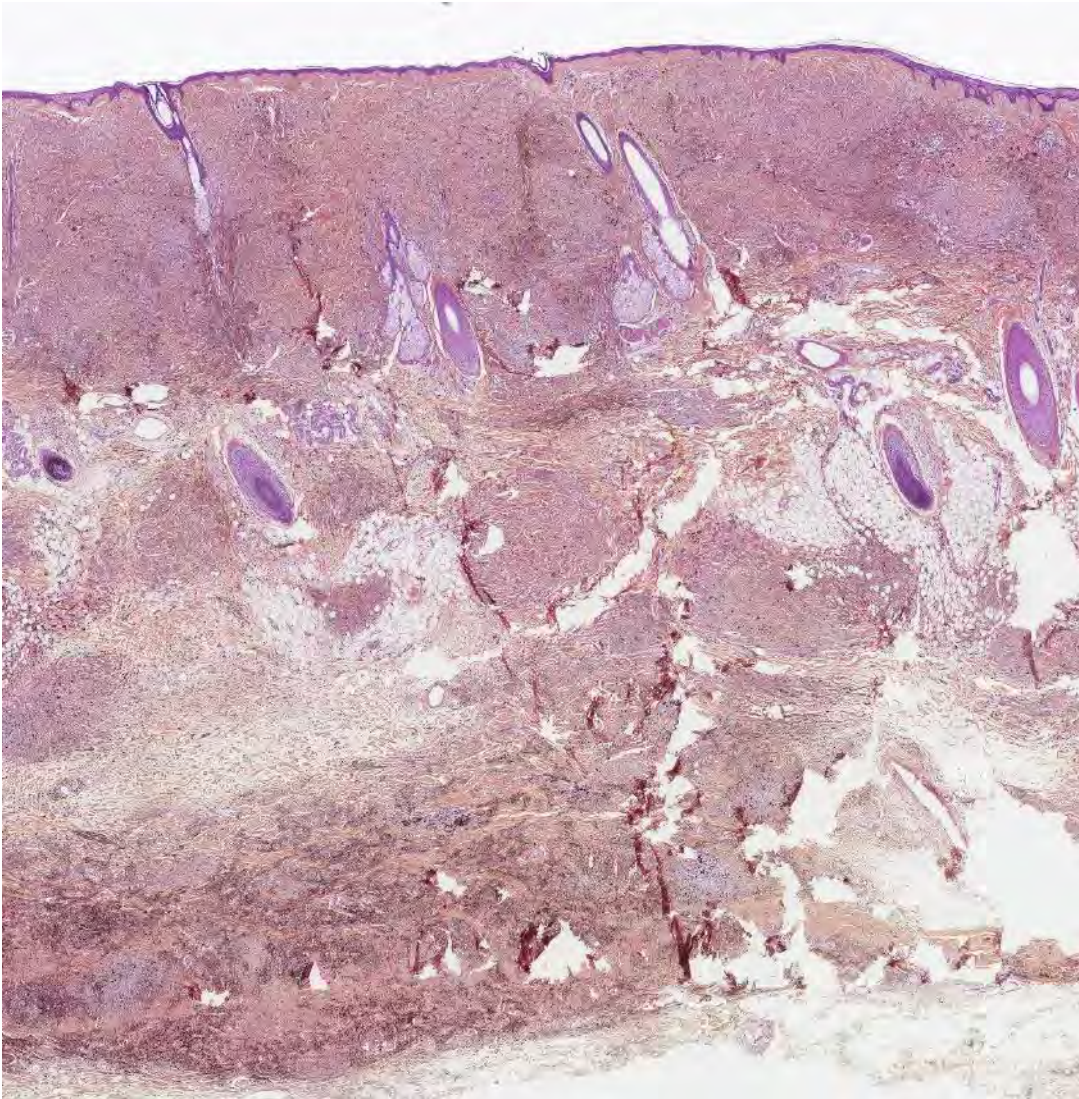
Schematic representation of *MYO10::GRM1* fusion transcripts

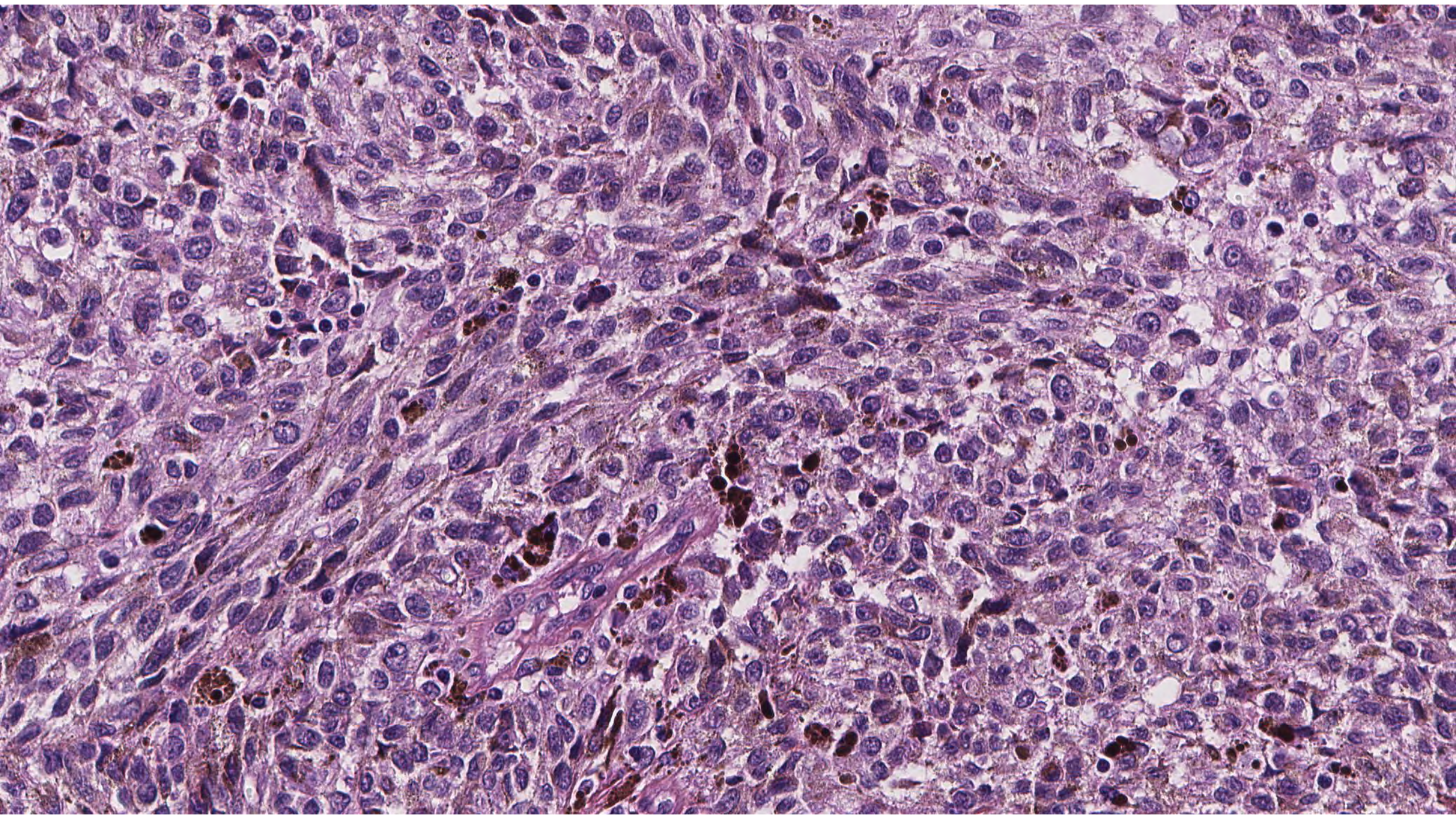


GRM1-fused Blue tumors

Melanoma *ex*-Ota nevus

M36

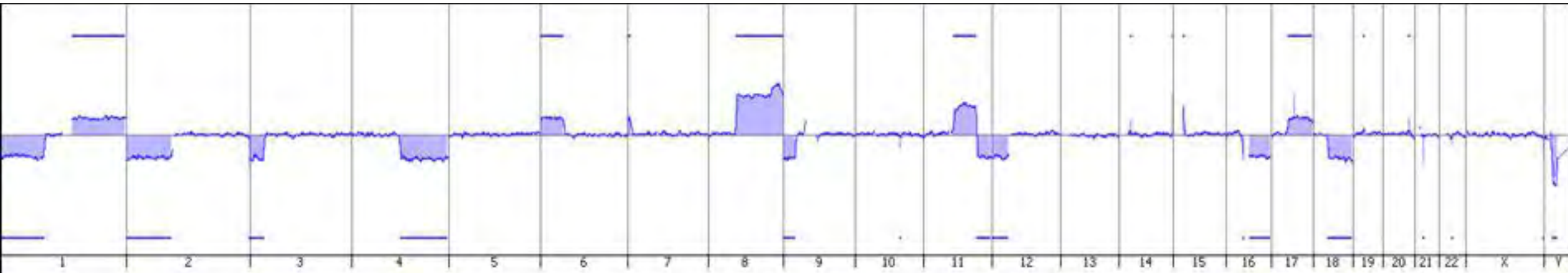
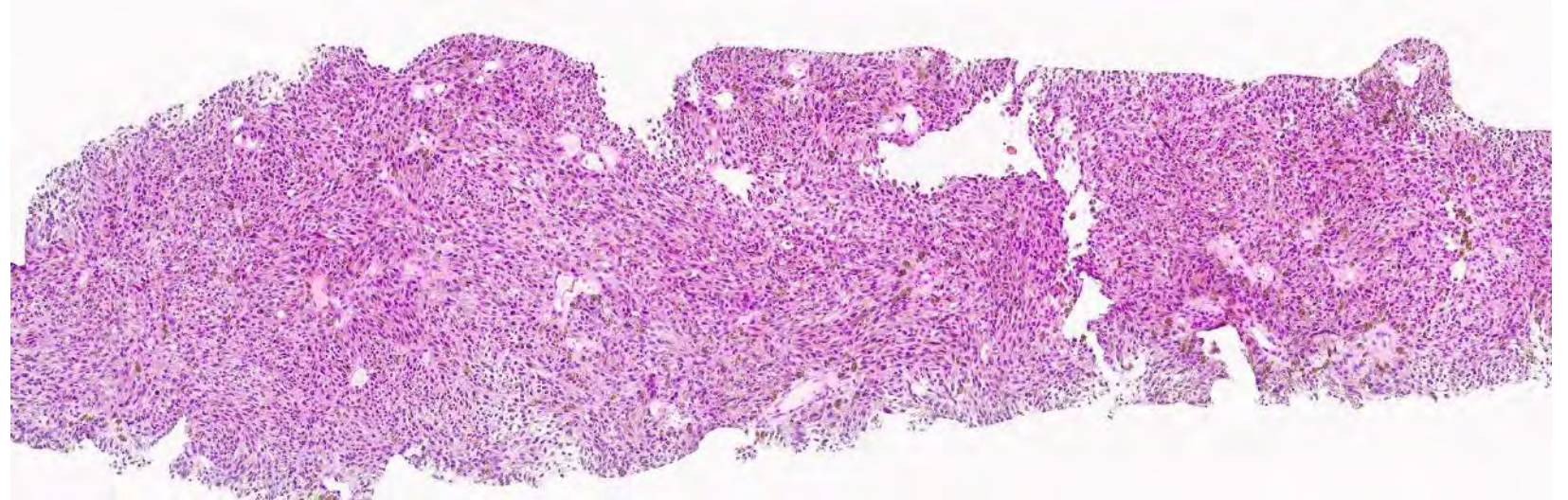
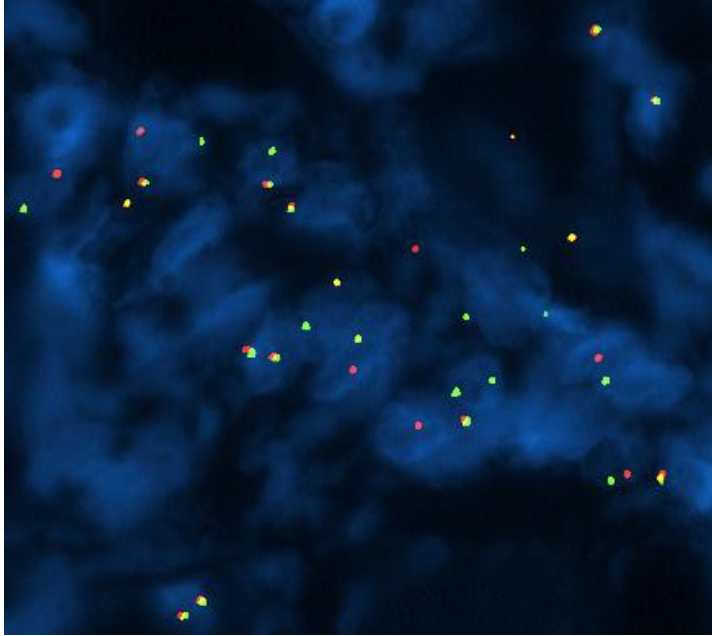




MYO10::GRM1

Melanoma *ex-Ota* nevus

M36



GRM1-fused Blue tumors

Take home messages

- *GRM1* overexpression previously known in melanoma oncogenesis models
- Plaque-type lesions predominate, including Ota nevus
- Full spectrum of lesions (benign, intermediate, malignant)
- Targeted therapeutic potential

Blue melanocytic tumors
PRKCA/B/G-fusions

PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

- Most are hypertrophic/exophytic tumors
- 1/3 are pigmented

Case Report/Case Series

Pigment-Synthesizing Melanocytic Neoplasm With Protein Kinase C Alpha (*PRKCA*) Fusion

Armita Bahrami, MD; Seungjae Lee, PhD; Gang Wu, PhD; Justin Korbett, MD; Maral Rahvar, MD; Xinmin Li, PhD; John Ezelon, PhD; Jinghui Zhang, PhD; Raymond L. Barnhill, MD

Figure 1. Clinical and Pathological Findings

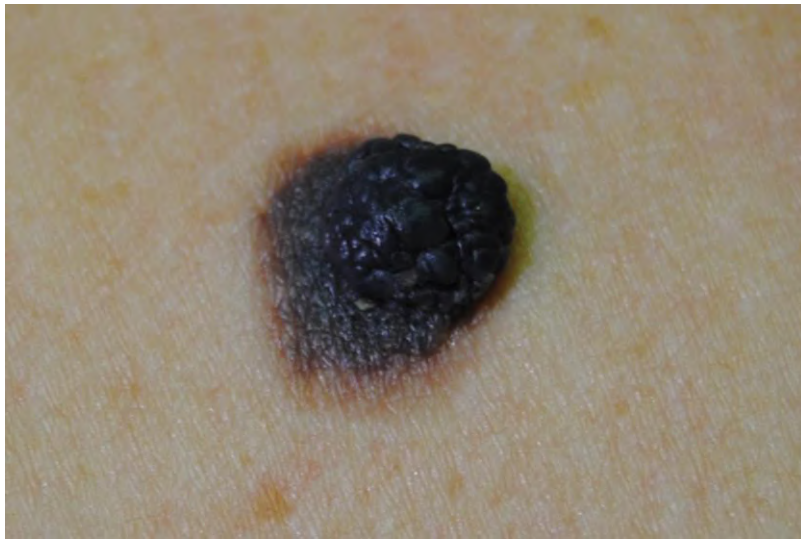


A. Protuberant mass on the scalp of a 5-month-old girl. B. Hyperdense, heterogeneous mass in the scalp invading the underlying calvarium. C. Skin overlying the mass is partially ulcerated and covered with crust over a 2.0 × 2.0-cm² area. D. Uniform dark brown cut surface of the mass.

PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

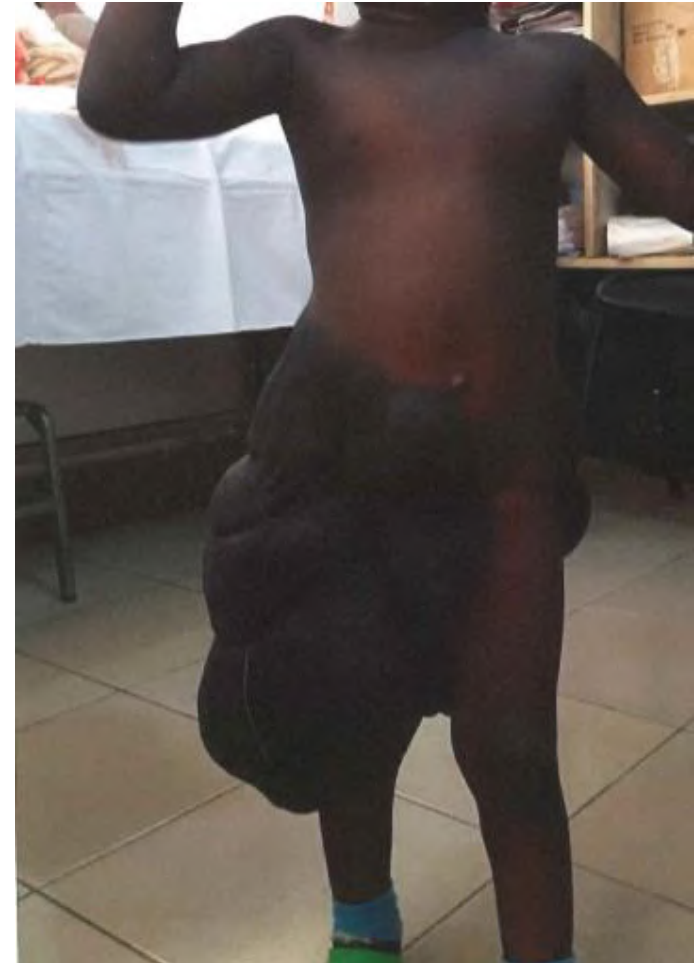
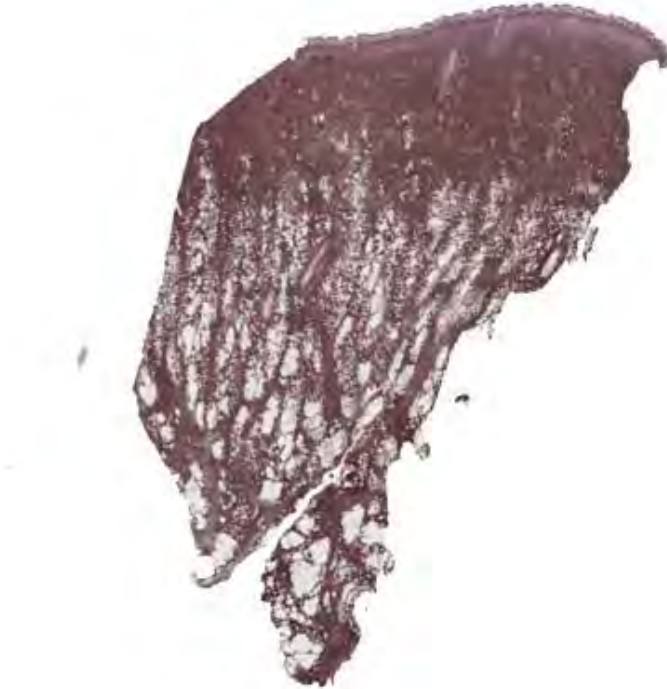
- Most are hypertrophic/exophytic tumors
- 1/3 are hyperpigmented



PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

- Most are hypertrophic/exophytic tumors
- 1/3 are hyperpigmented
- Giant congenital variants are possible



PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

- Most are hypertrophic/exophytic tumors
- 1/3 are hyperpigmented
- Giant congenital variants are possible
- Malignant progression can occur during childhood



PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

- Most are hypertrophic/exophytic tumors
- 1/3 are hyperpigmented
- Giant congenital variants are possible
- Malignant progression can occur during childhood



PRKCA/B-fused «Blue» melanocytic tumors

Clinical features

- Giant congenital variants are possible
- Malignant progression can occur during childhood



Annales de Dermatologie et de Vénéréologie
Volume 147, Issue 11, November 2020, Pages 746-754

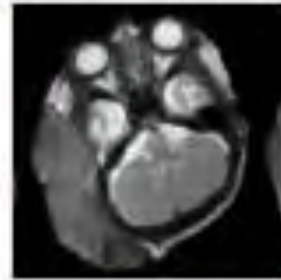


Cas clinique

Apport des nouveaux tests moléculaires dans le diagnostic d'un mélanome sur nævus congénital chez un nourrisson

The role of new molecular tests in the diagnosis of melanoma in a setting of congenital nævus in an infant

M. Masson Regnault^{a, b, 1}, S. Fraitag^{d, 1}, L. Lamant^e, A. Maza^a, A. De la Fouchardière^f, E. Tournier^f, F. Lauwers^g, L. Carfagna^h, N. Meyer^h, A. De Berail^g, K.J. Busamⁱ, R. Lazova^{b, c}, J. Mazereeuw-Hautier^{a, 1}



- Retrospective genetic diagnosis on CGH
- *PRKCA* Fusion
- Child died at age 6

PKC gene fused melanocytic tumors

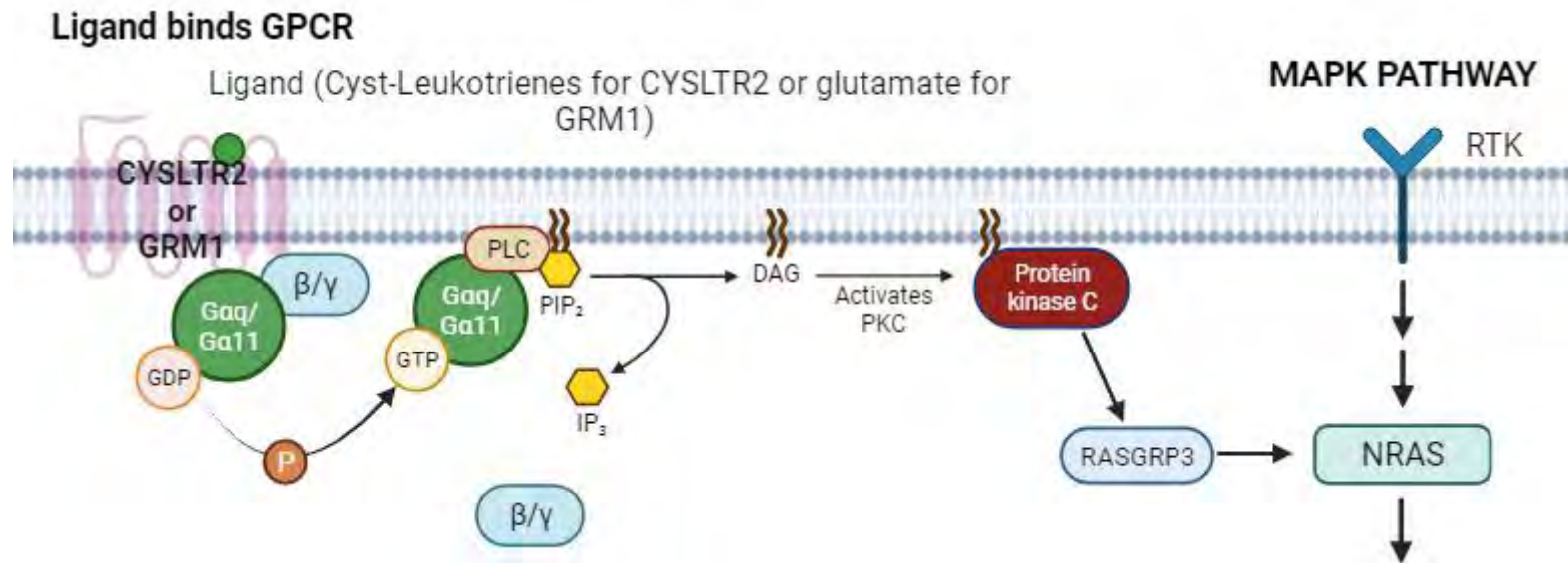
Genetics

- 2/3 **PRKCA** fusions
- 1/3 PRKCB fusions
- PRKCG fusions extremely rare

PKC gene fused melanocytic tumors

Genetics

- 2/3 **PRKCA** fusions
- 1/3 PRKCB fusions
- PRKCG fusions extremely rare



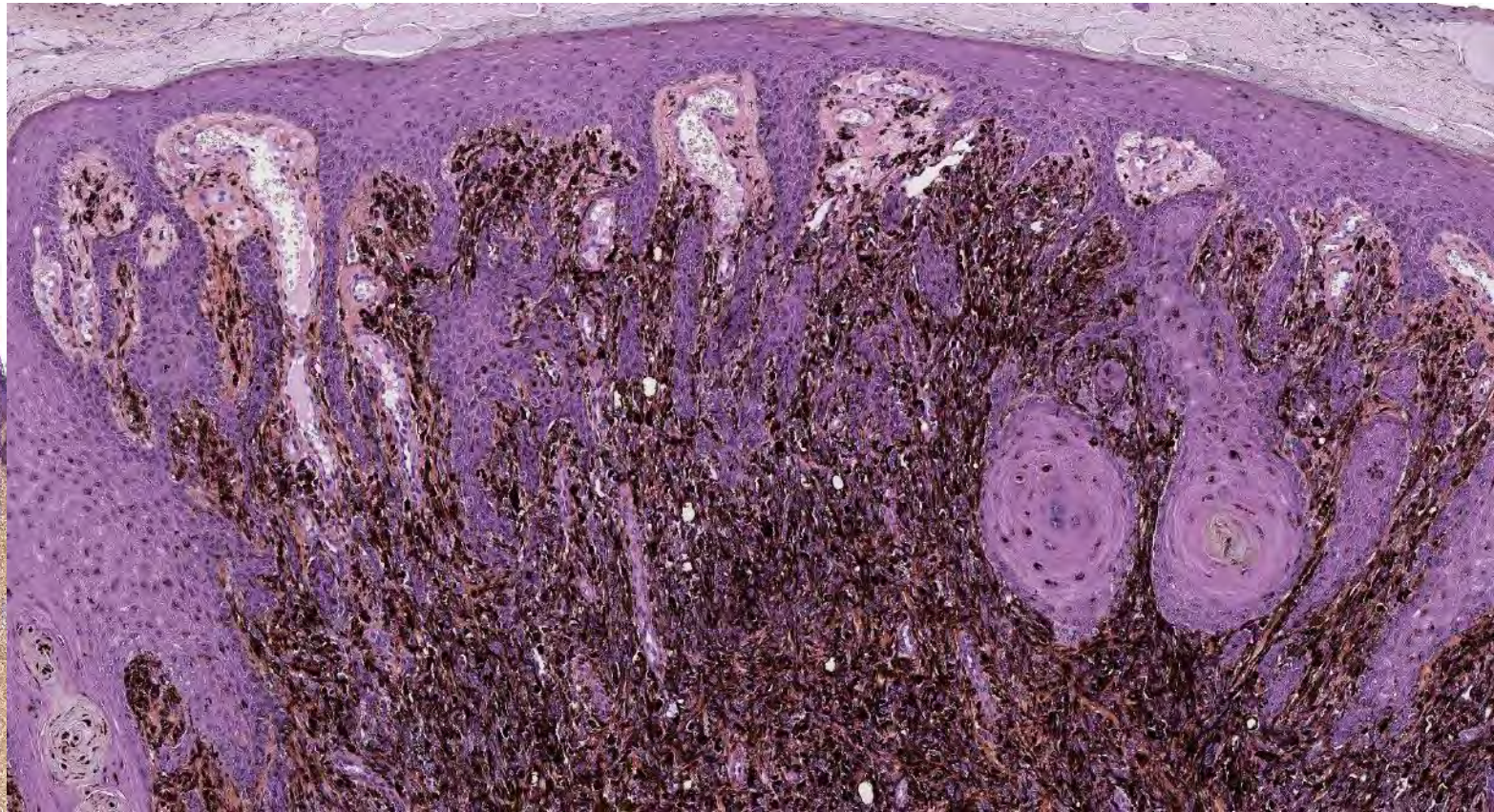
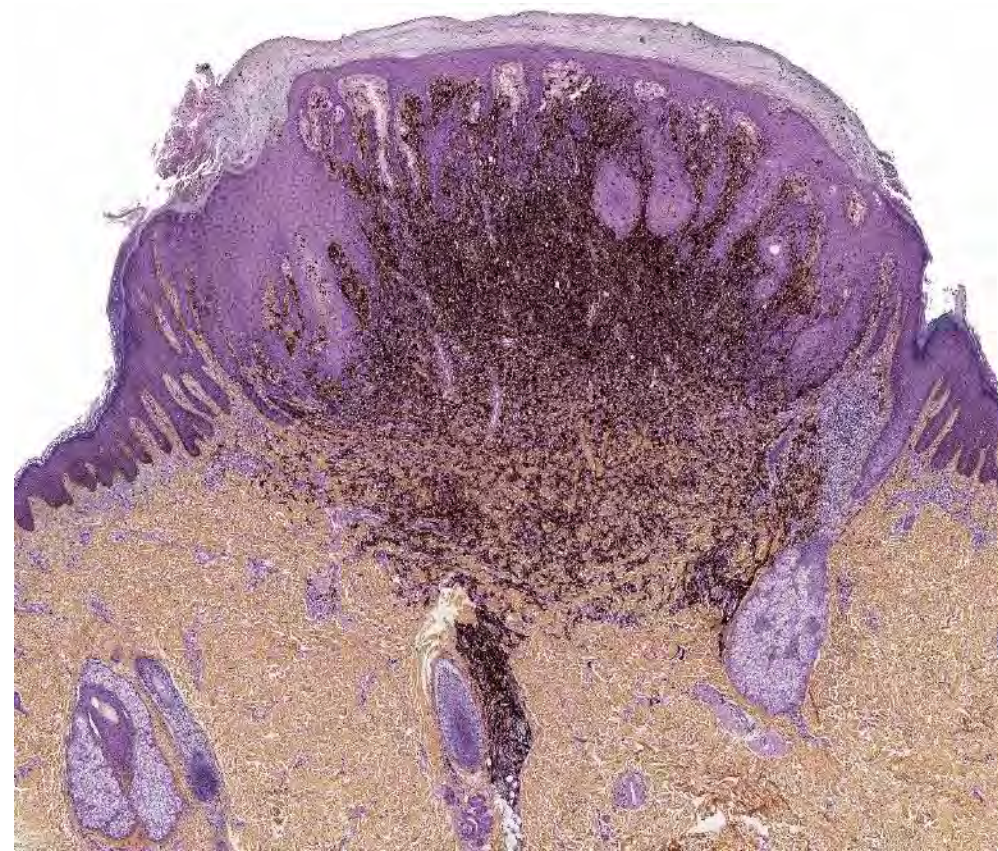
PKC gene fused melanocytic tumors

highly variable morphology

- Junctional PEM-like features
 - Upper dermis horizontal band
 - Dermal combined blue nevus features
 - Smooth muscle hyperplasia
 - Variable pigment load
 - Variable but constant fibrosis
-
- « PEM + Common + Blue » mixture suggests PKC gene fused tumour
 - Can have partial features and/or extreme ends of the spectrums

PKC gene fused melanocytic tumors

Junctional PEM-like features



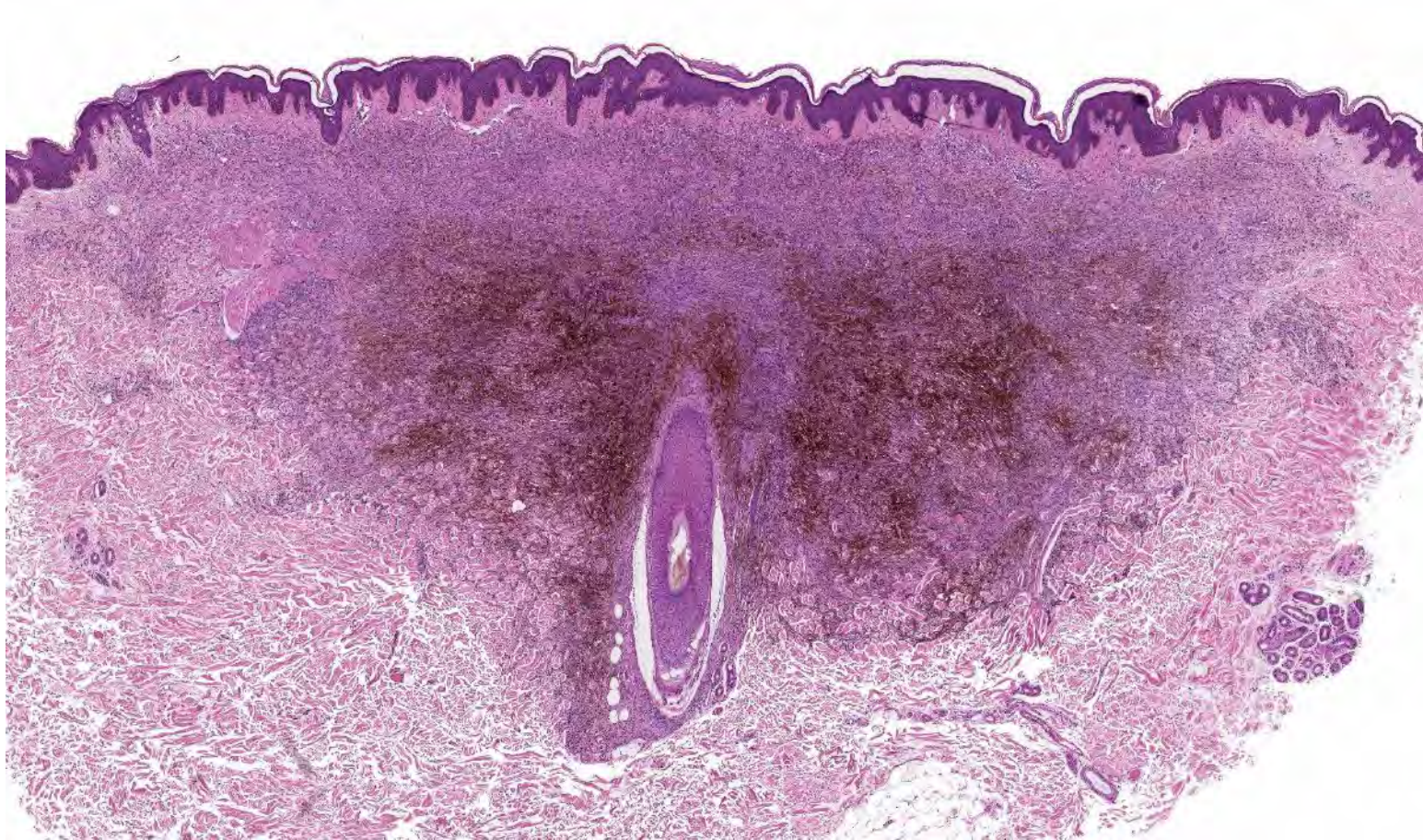
PKC gene fused melanocytic tumors

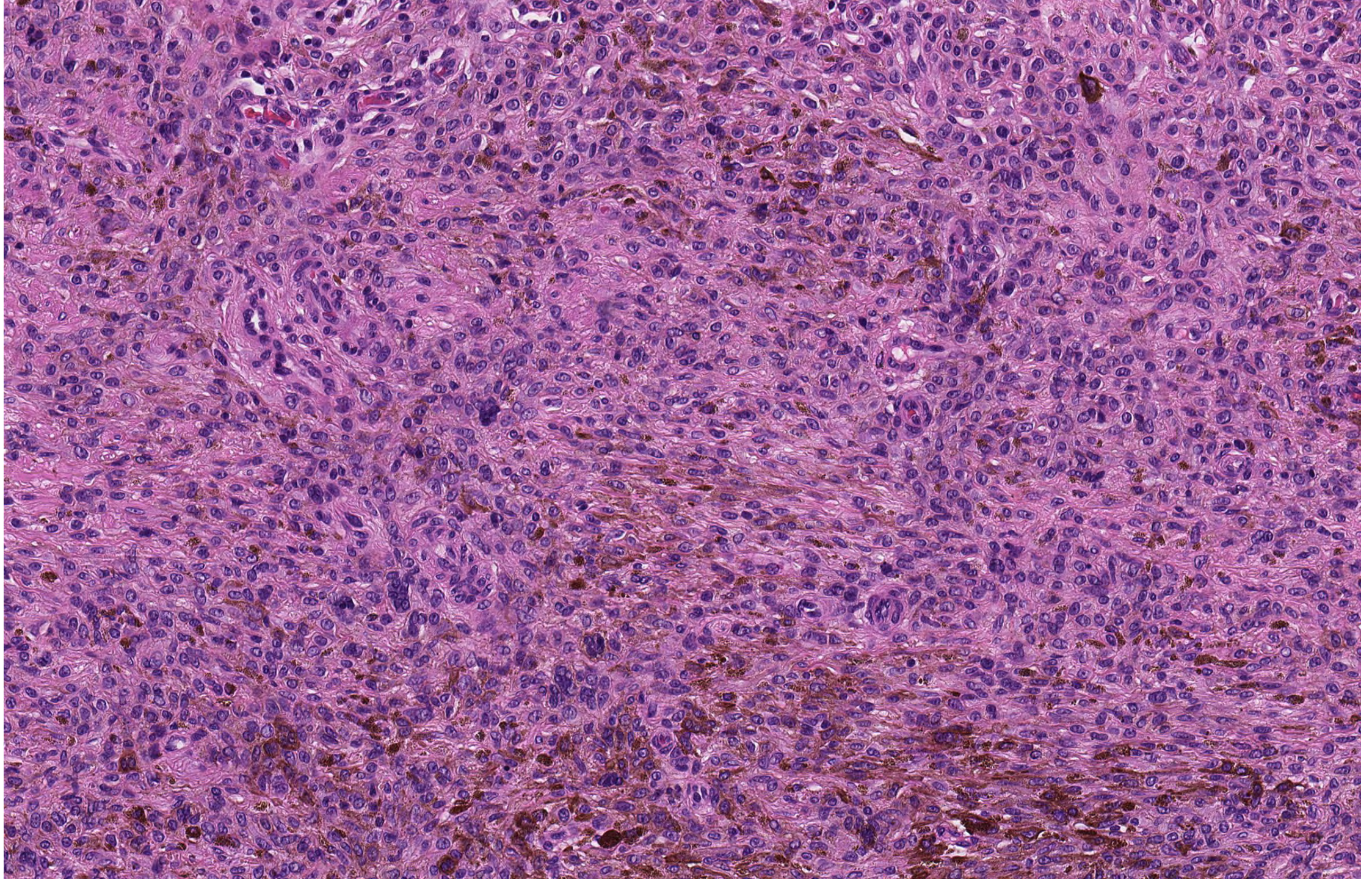
Upper dermis horizontal band

- Horizontal band of nevocytoid melanocytes
- Separated from the epidermis by a grenz zone
- Less pigmented than the rest of the tumor
- Interweaved at the bottom with pigmented dendritic melanocytes

PKC gene fused melanocytic tumors

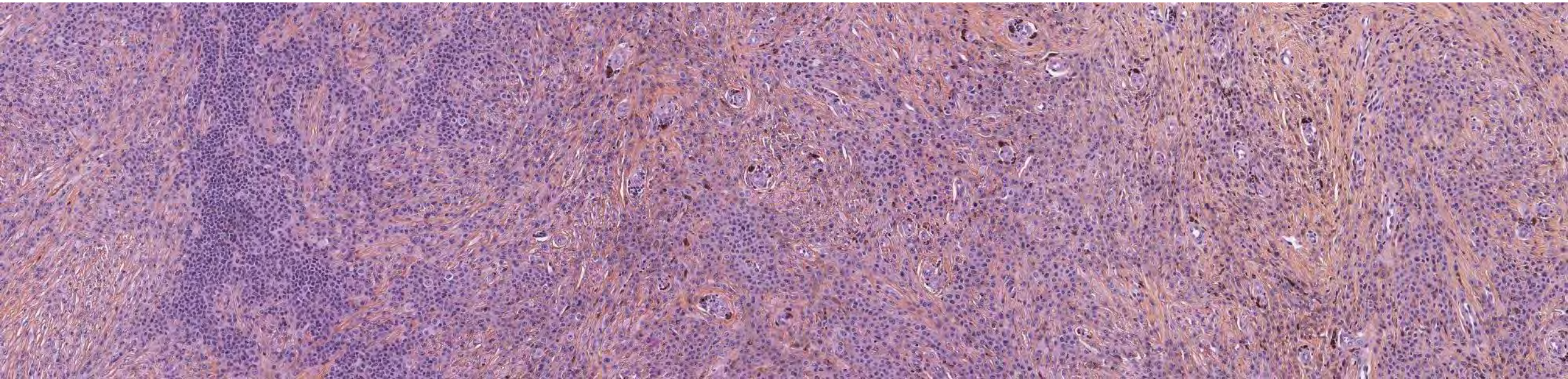
Upper dermis horizontal band

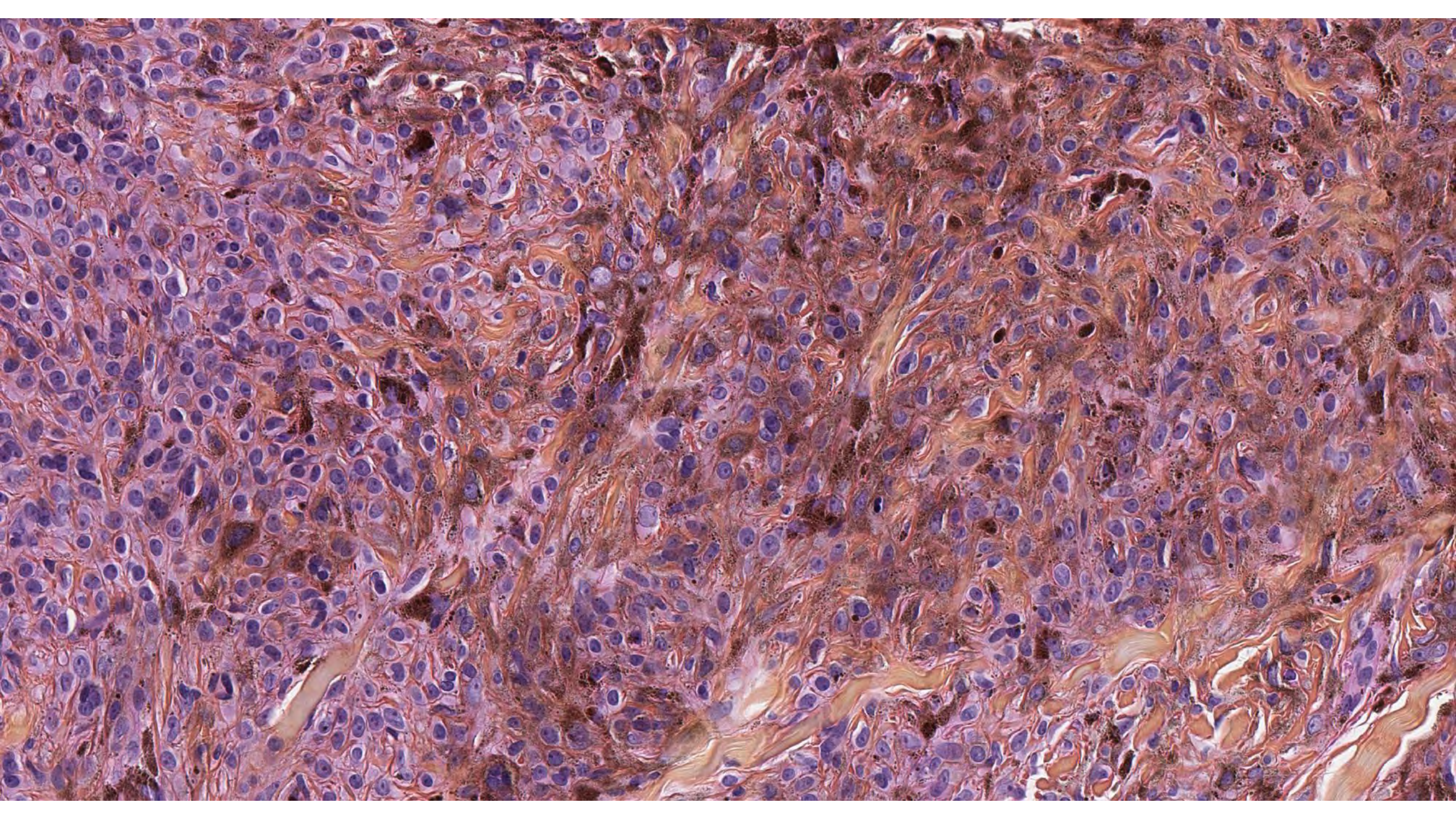


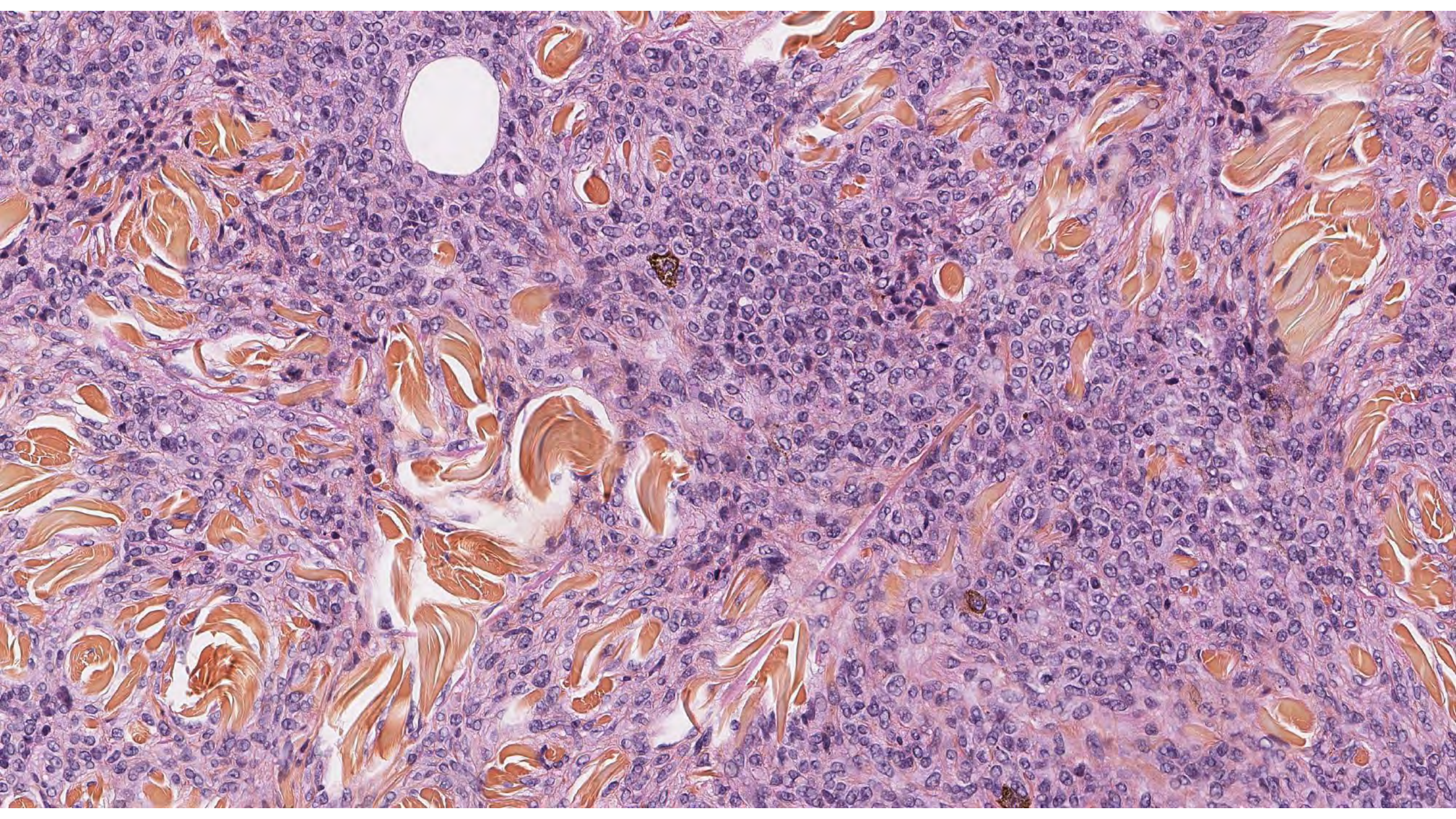


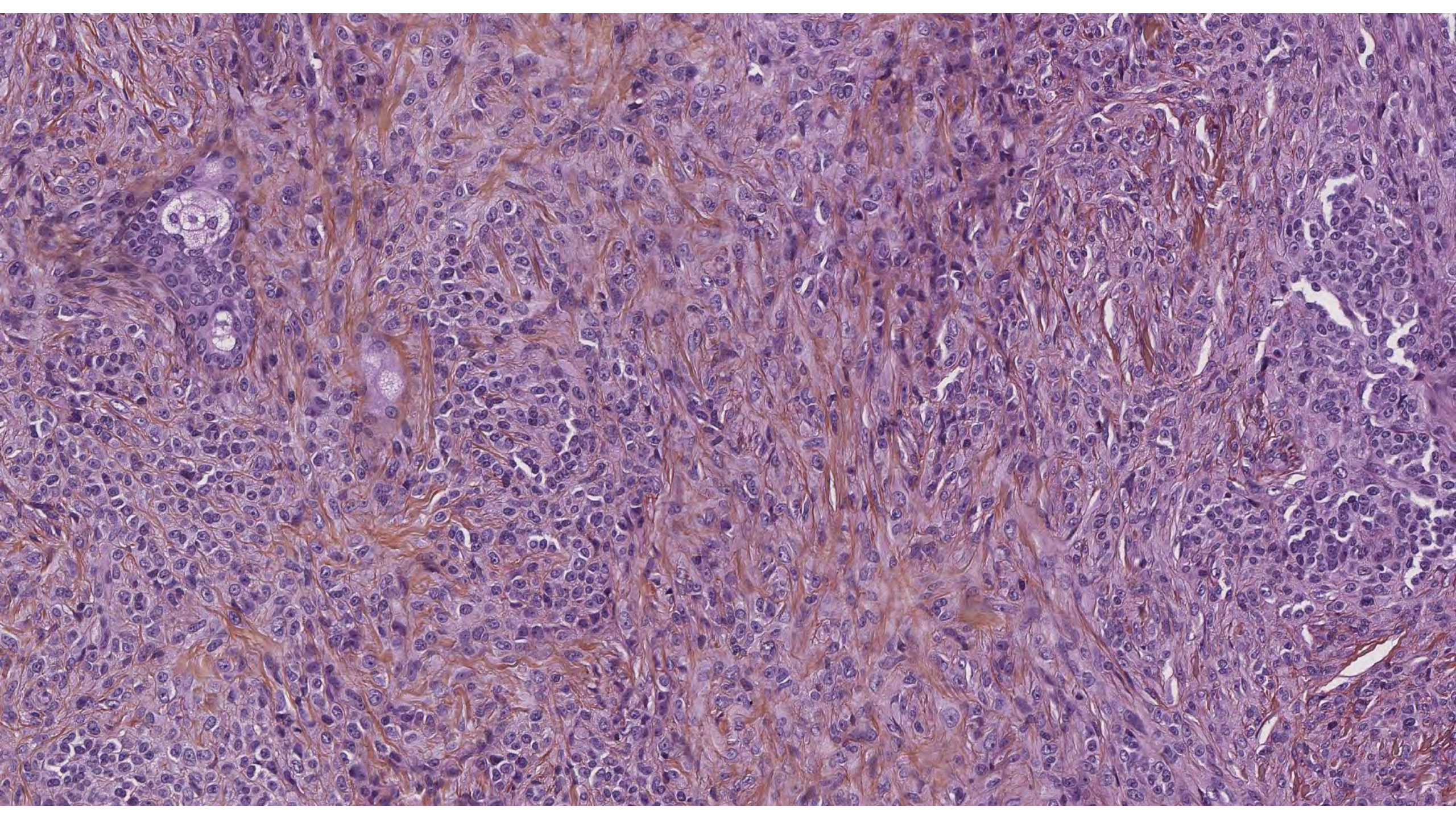
PKC gene fused blue nevus
highly variable morphology
Biphasic architecture (dermis)

«Combined common nevus + blue» morphology

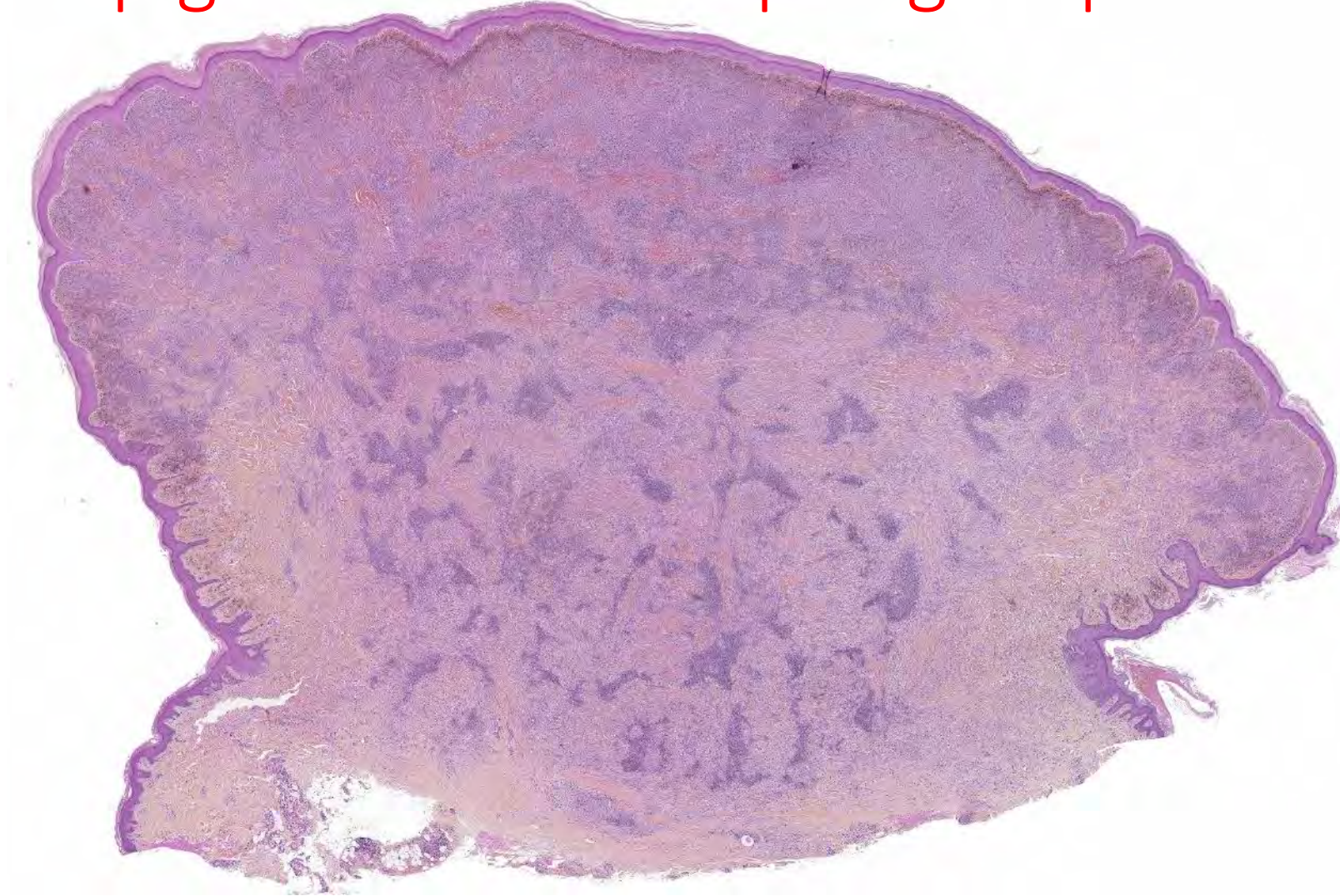


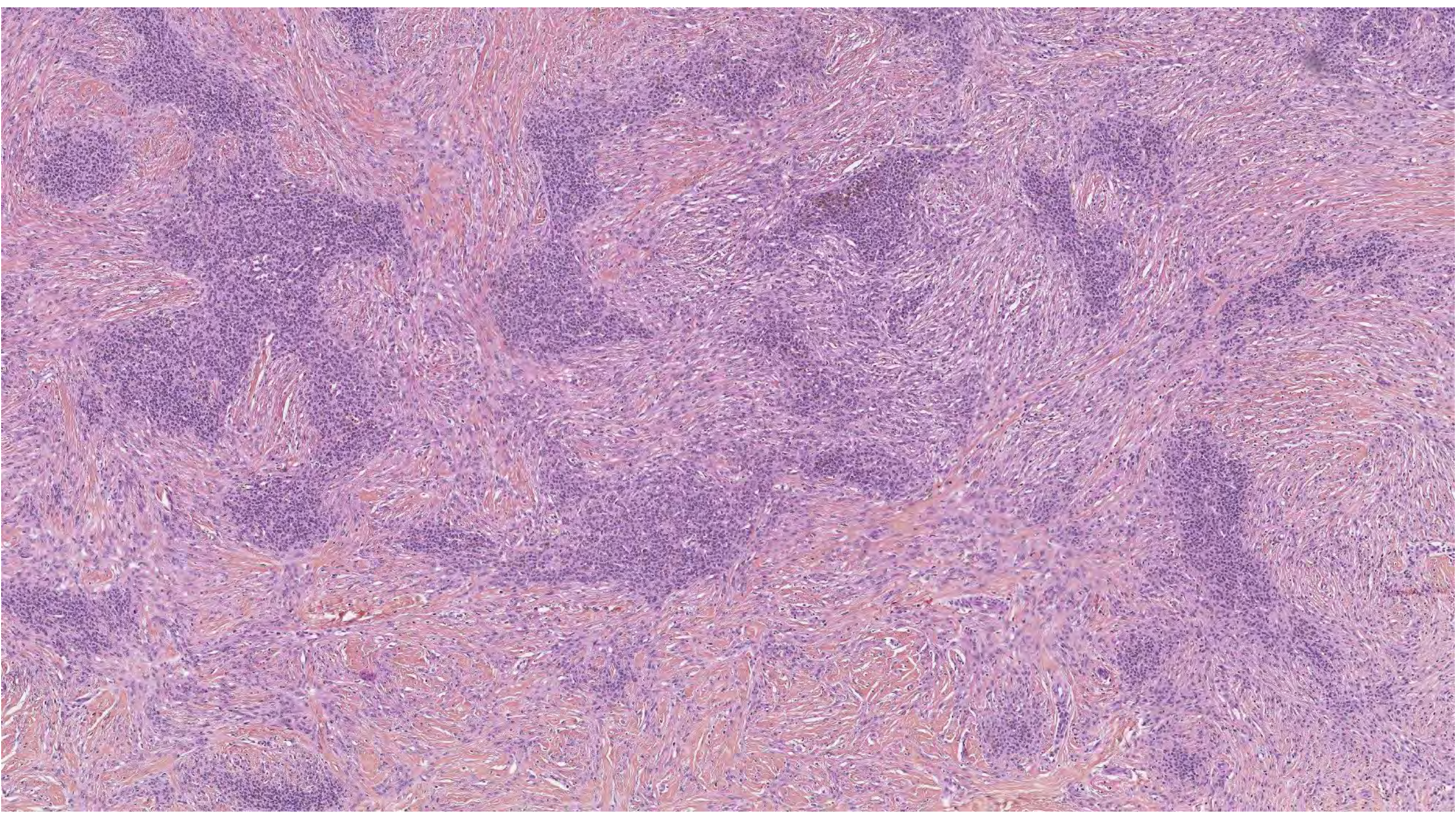


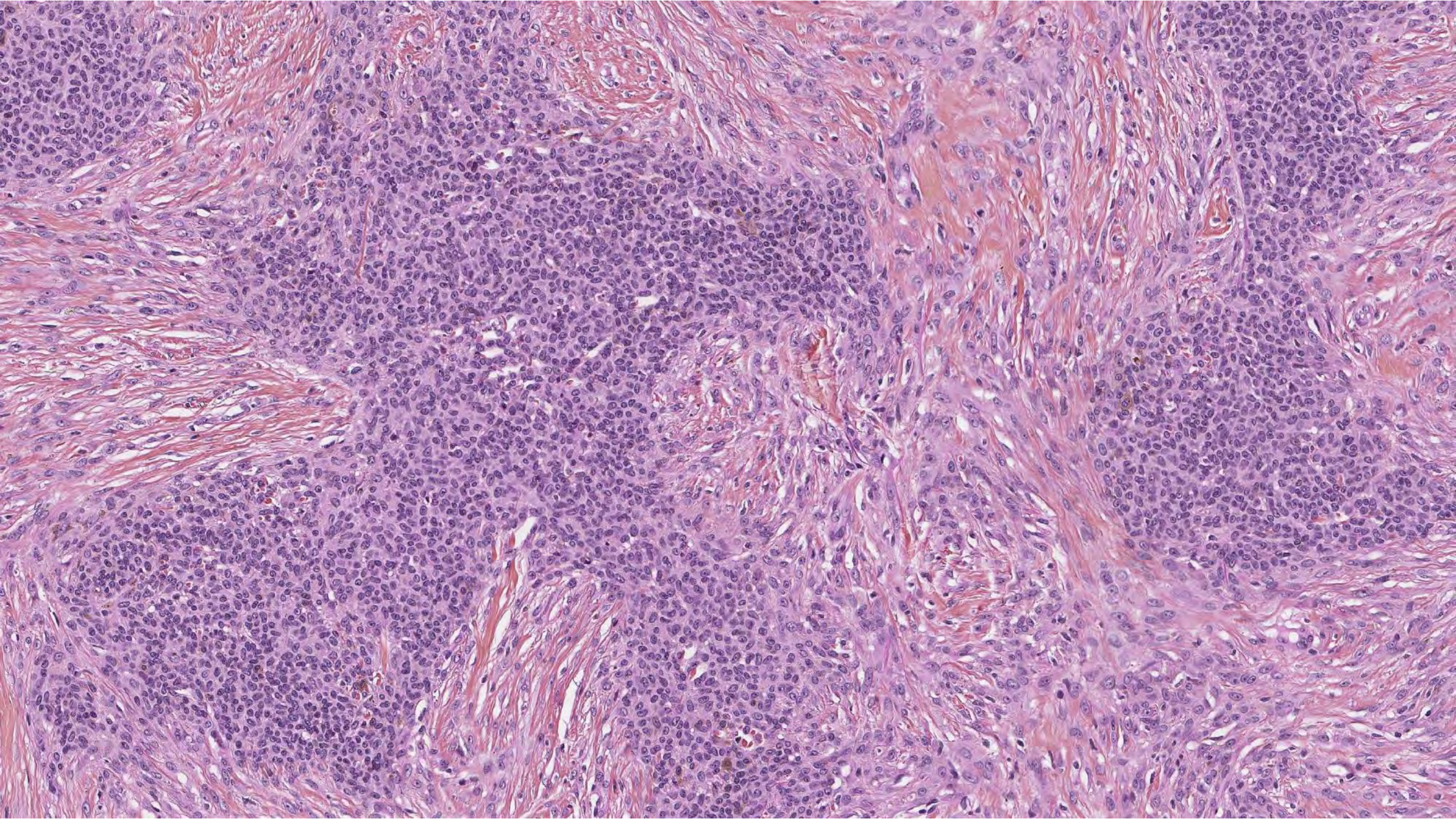




PKC gene fused melanocytic tumors
Band + Biphasic architecture (dermis)
Unpigmented « archipelago » pattern

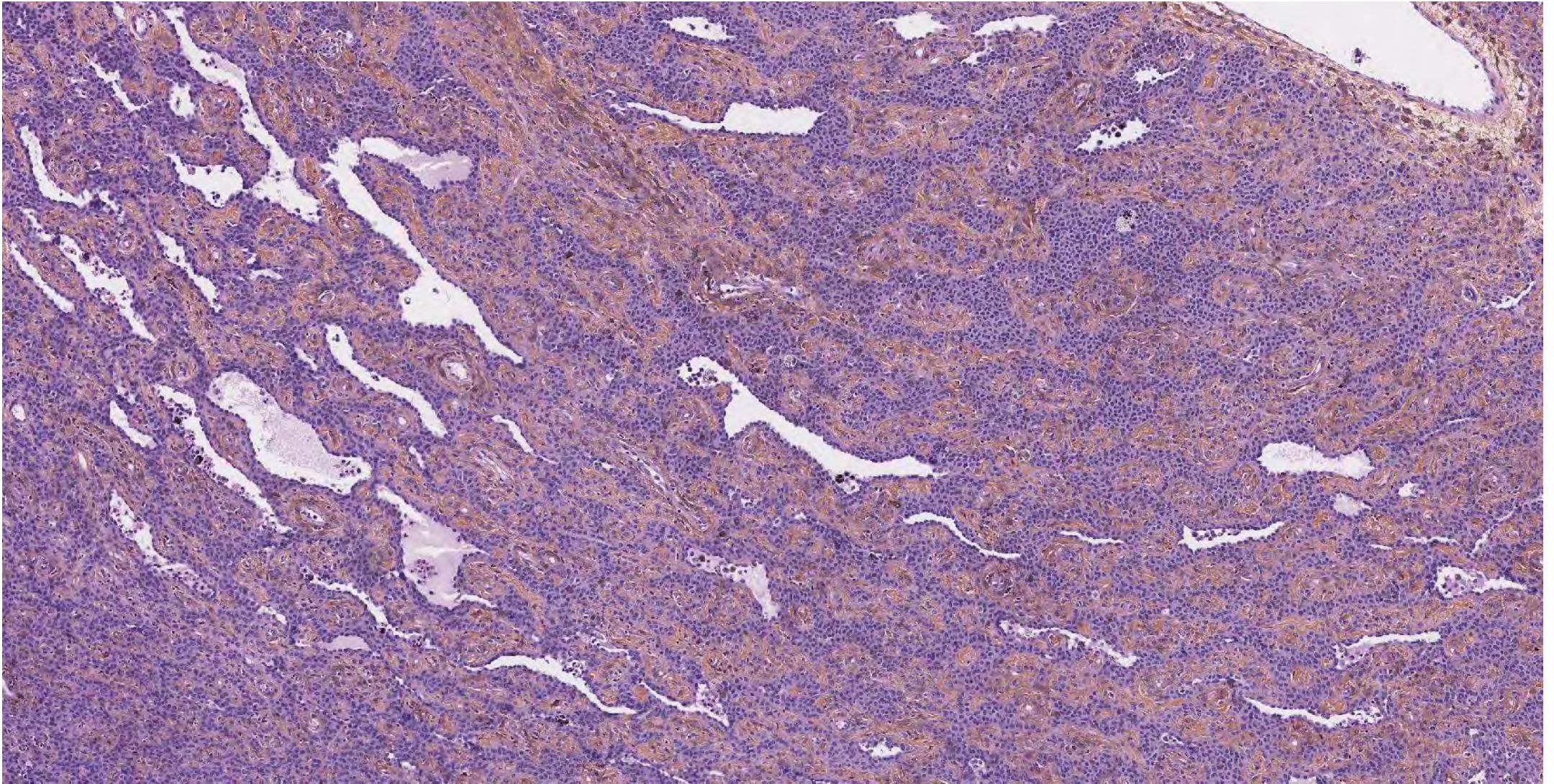






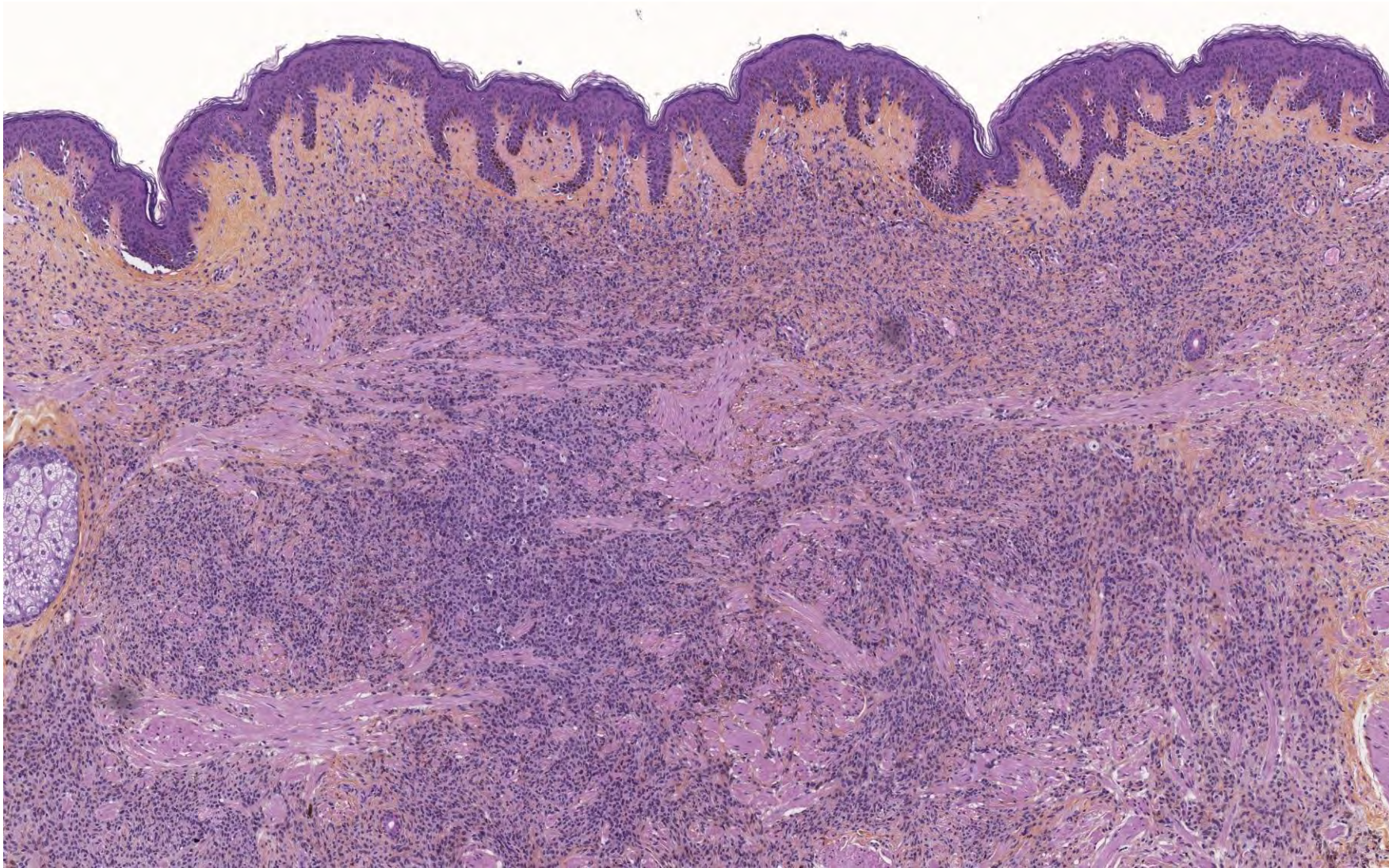
PKC gene fused melanocytic tumors

Pseudo-vascular clefting in cellular areas



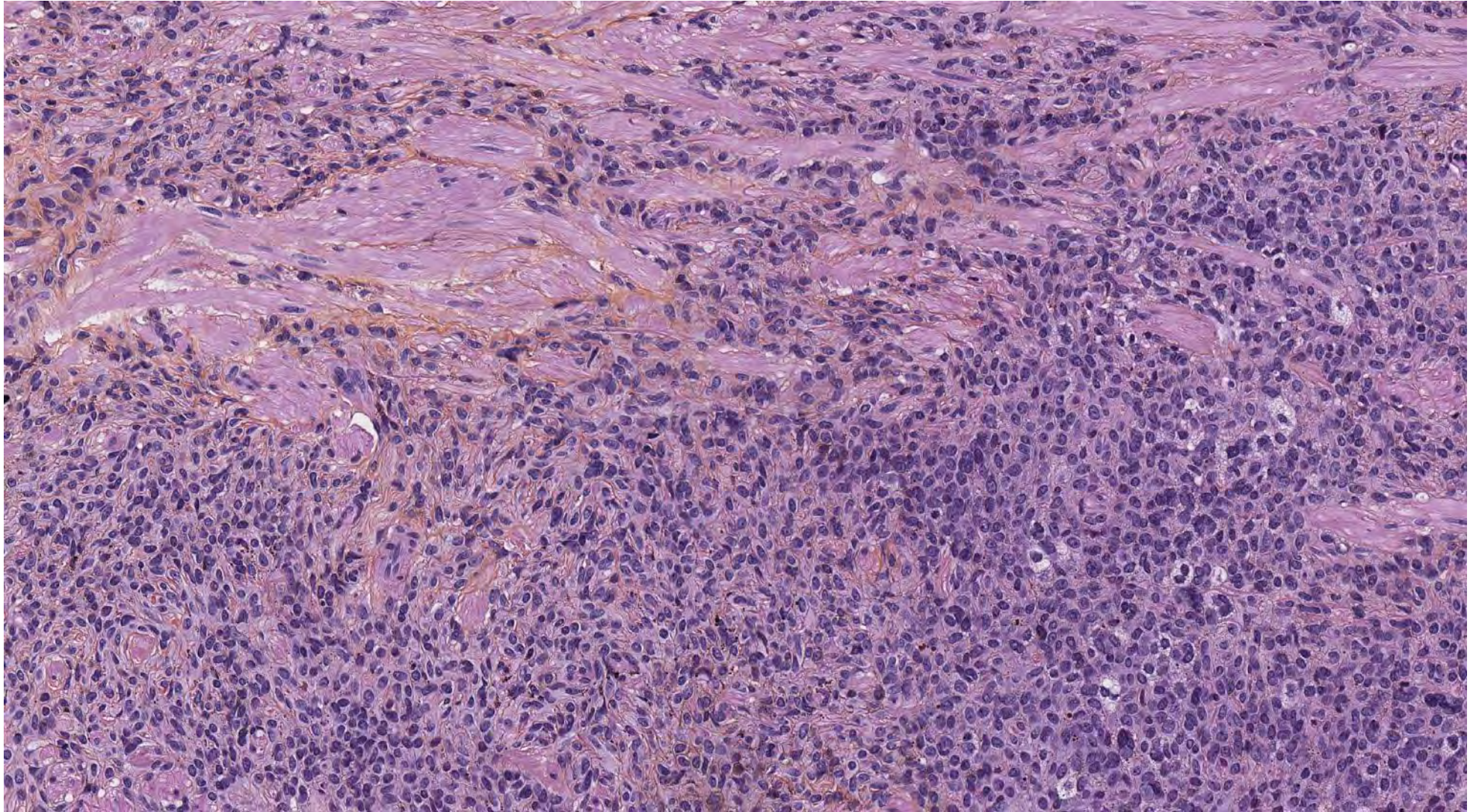
PKC gene fused melanocytic tumors

Smooth muscle hyperplasia



PKC gene fused melanocytic tumors

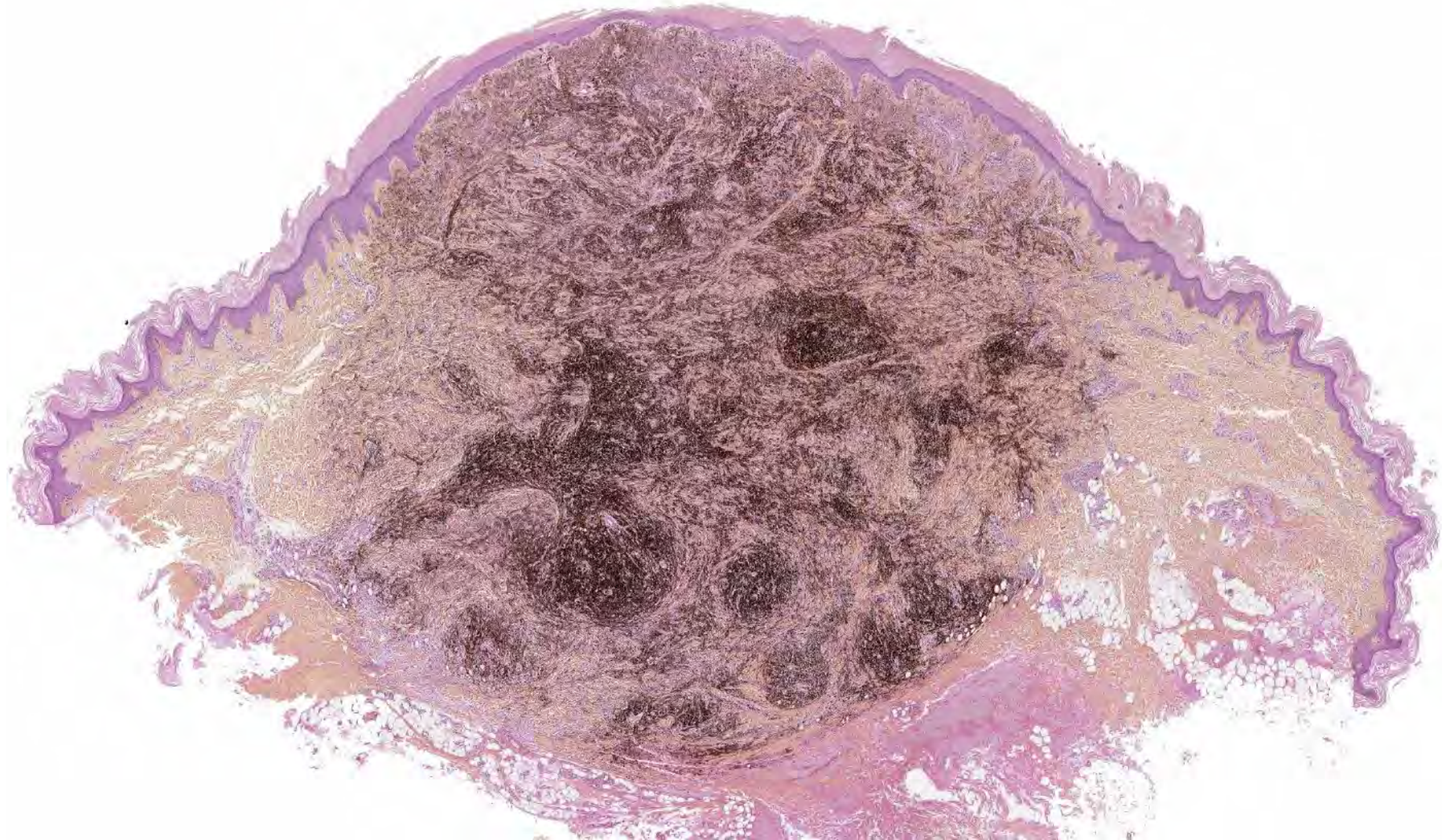
Smooth muscle hyperplasia



PKC gene fused melanocytic tumors

Medium power clues :

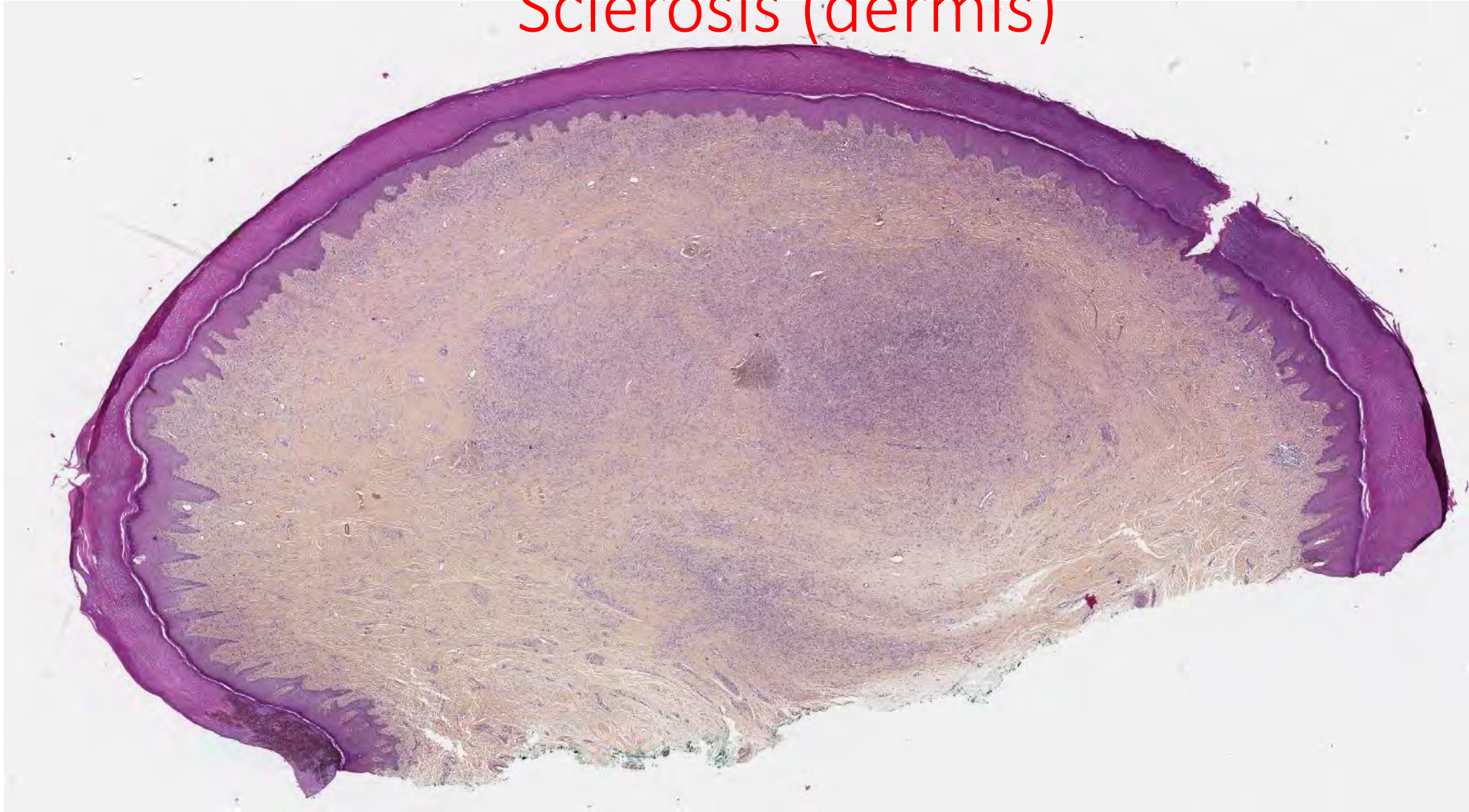
Fibrosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

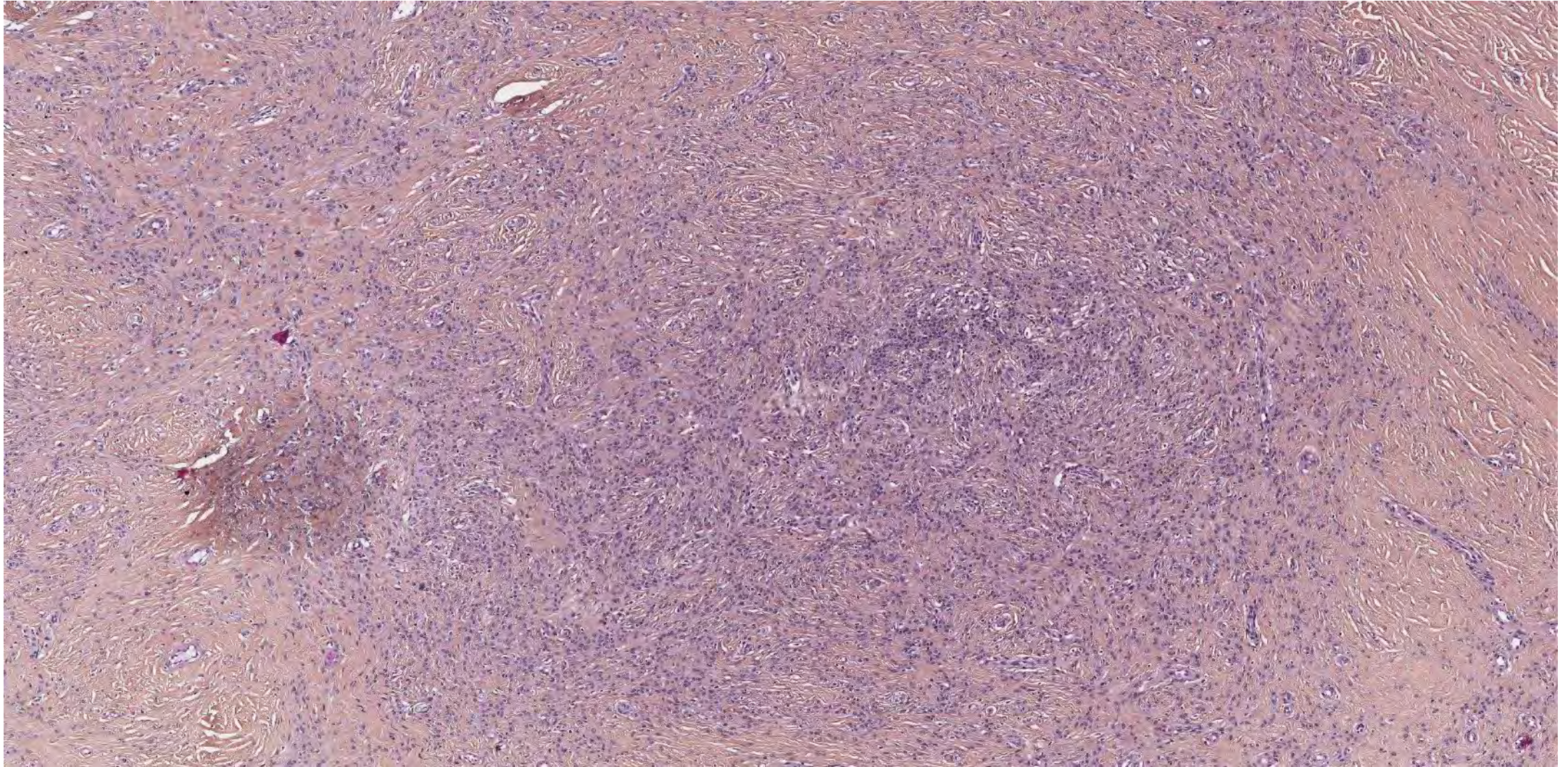
Sclerosis (dermis)



PKC gene fused melanocytic tumors

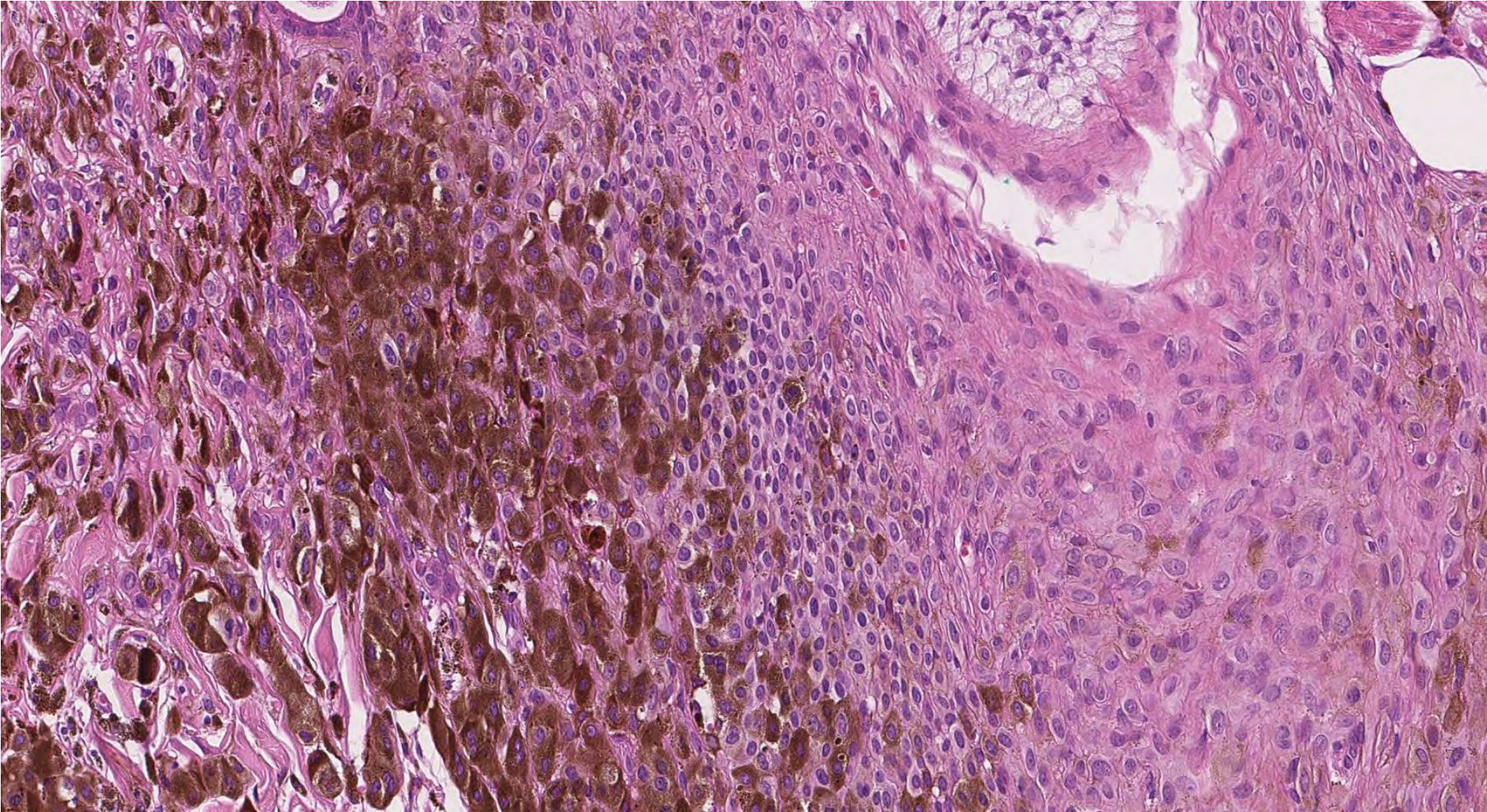
Medium power clues :

Sclerosis (dermis)



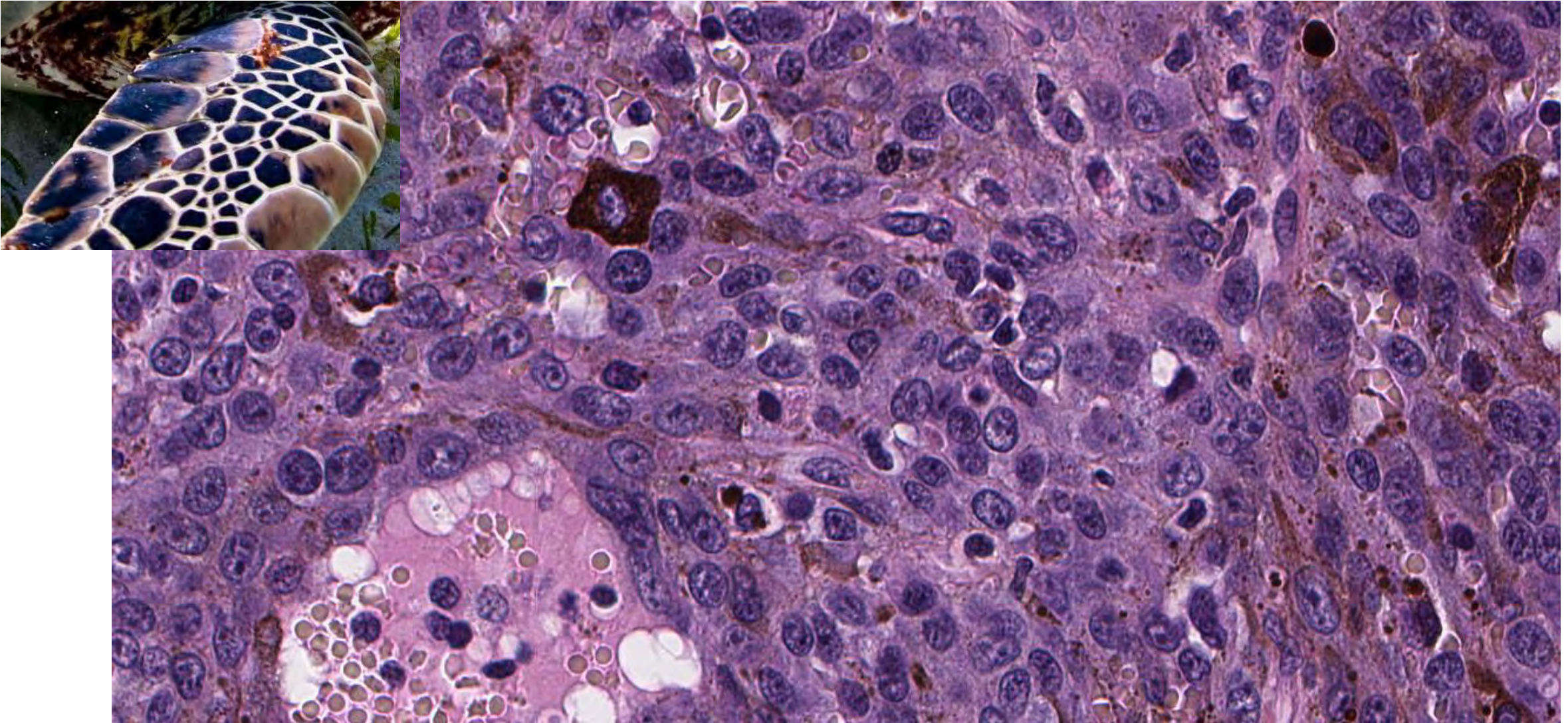
PKC gene fused melanocytic tumors

Cobblestone +/- pigmented (dermis)



PKC gene fused melanocytic tumors

Green sea Turtle/Dragonscale cells



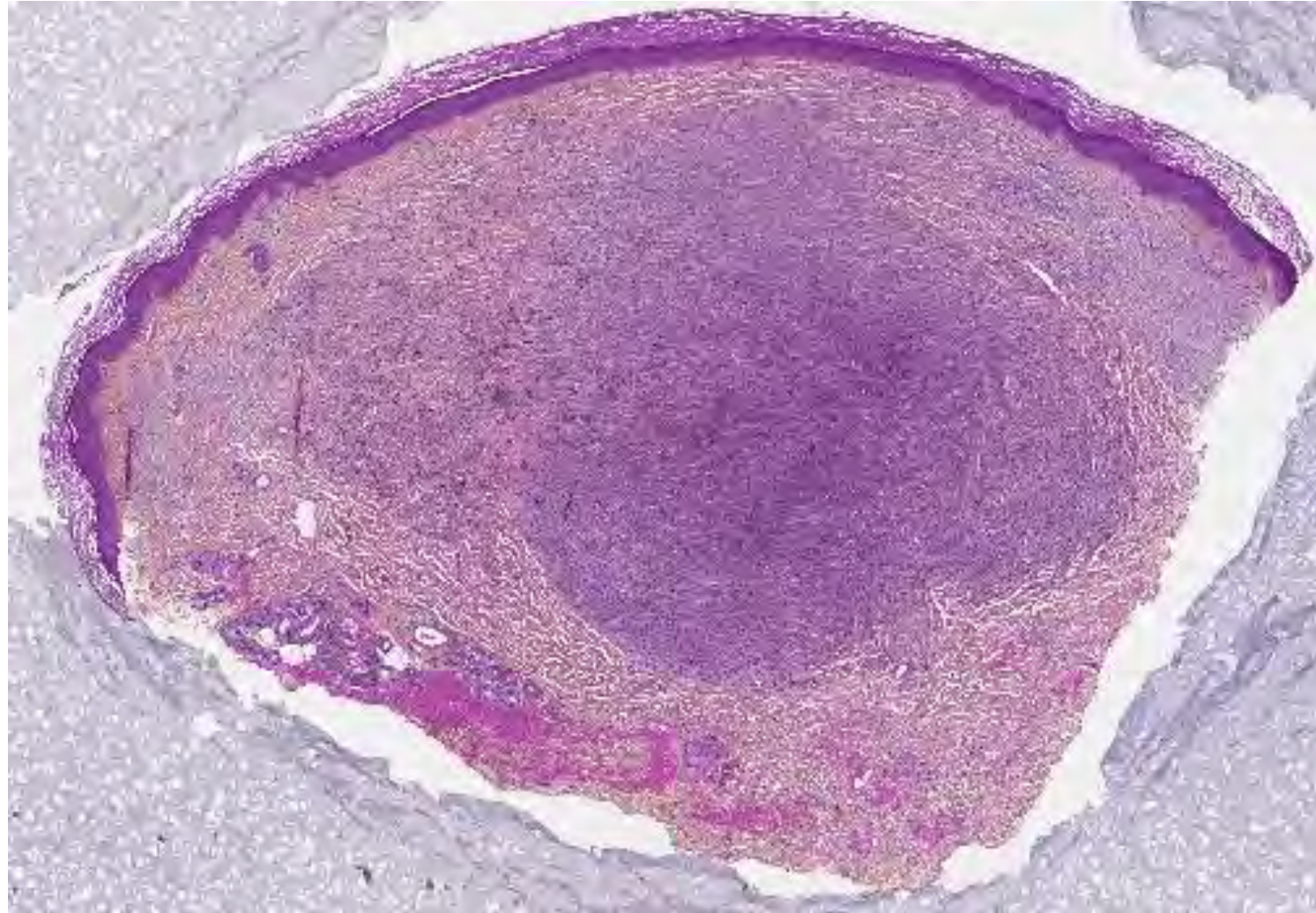
PKC gene fused melanocytic tumors

highly variable morphology

- Junctional PEM-like features
 - Upper dermis horizontal band
 - Dermal combined blue nevus features
 - Smooth muscle hyperplasia
 - Variable pigment load
 - Variable but constant fibrosis
-
- « PEM + Common + Blue » mixture suggests PKC gene fused tumour
 - Can have partial features and/or extreme ends of the spectrums

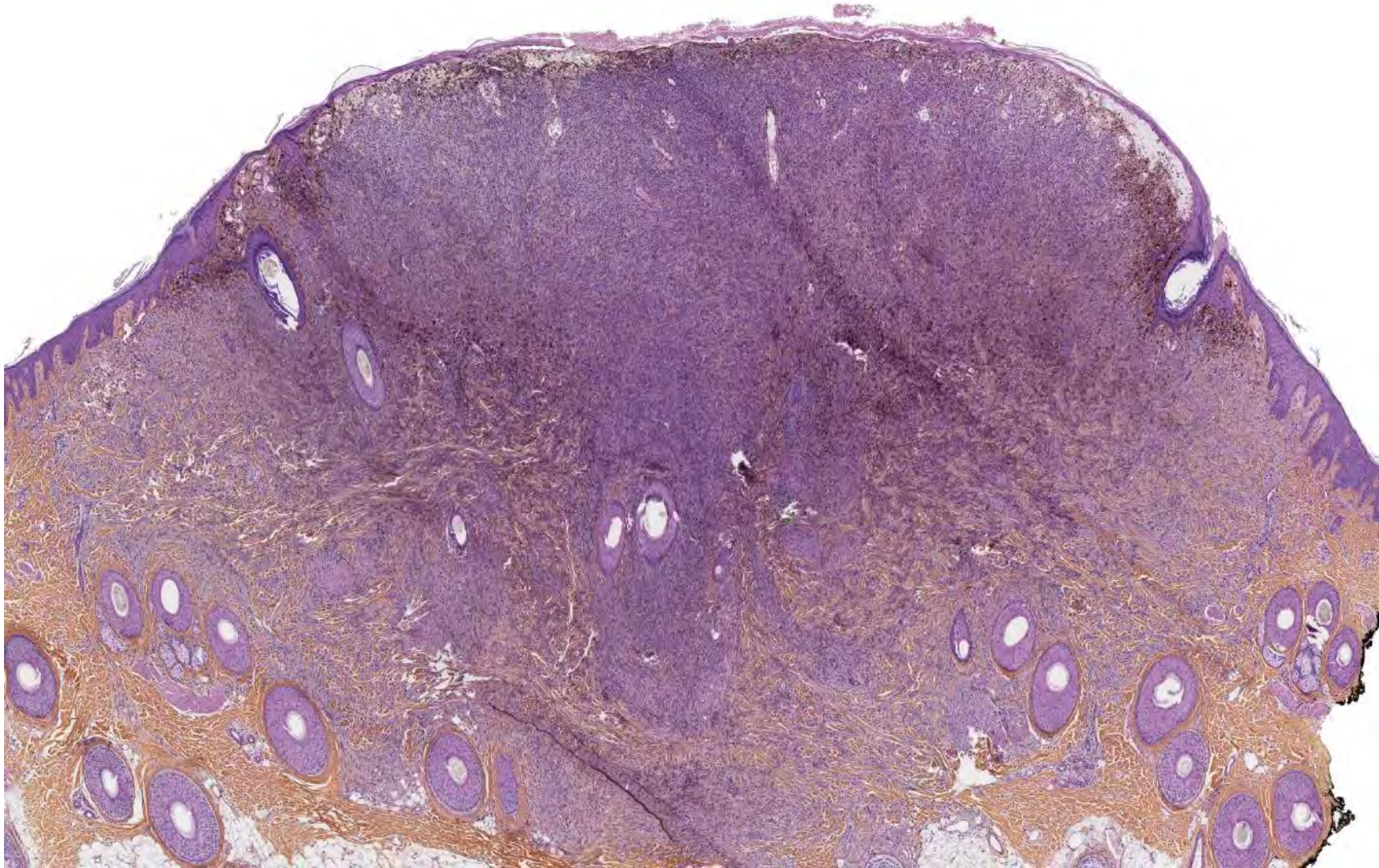
PKC gene fused melanocytic tumors

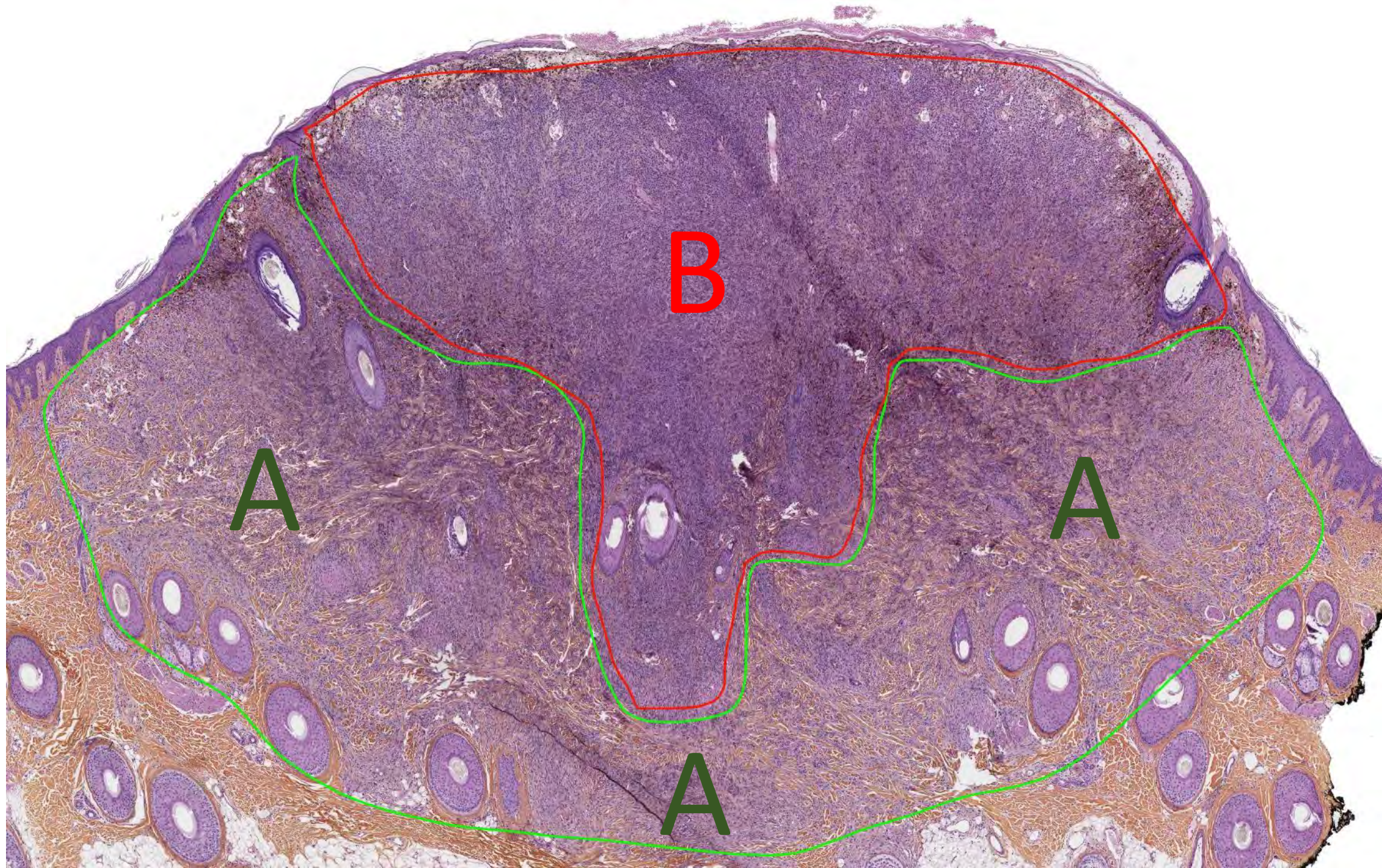
Melanocytoma ex nevus



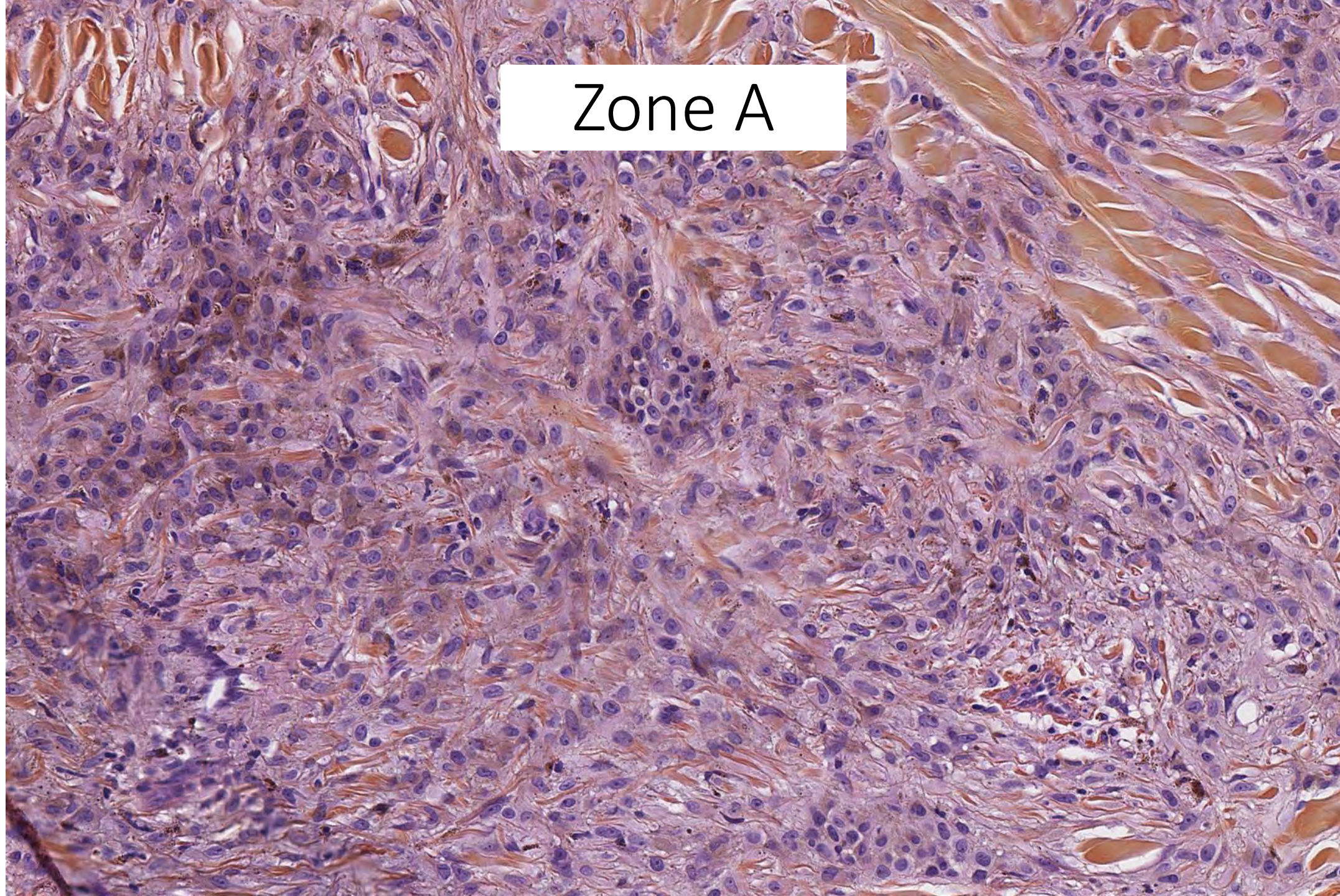
PKC gene fused melanocytic tumors

Melanoma ex-nevus

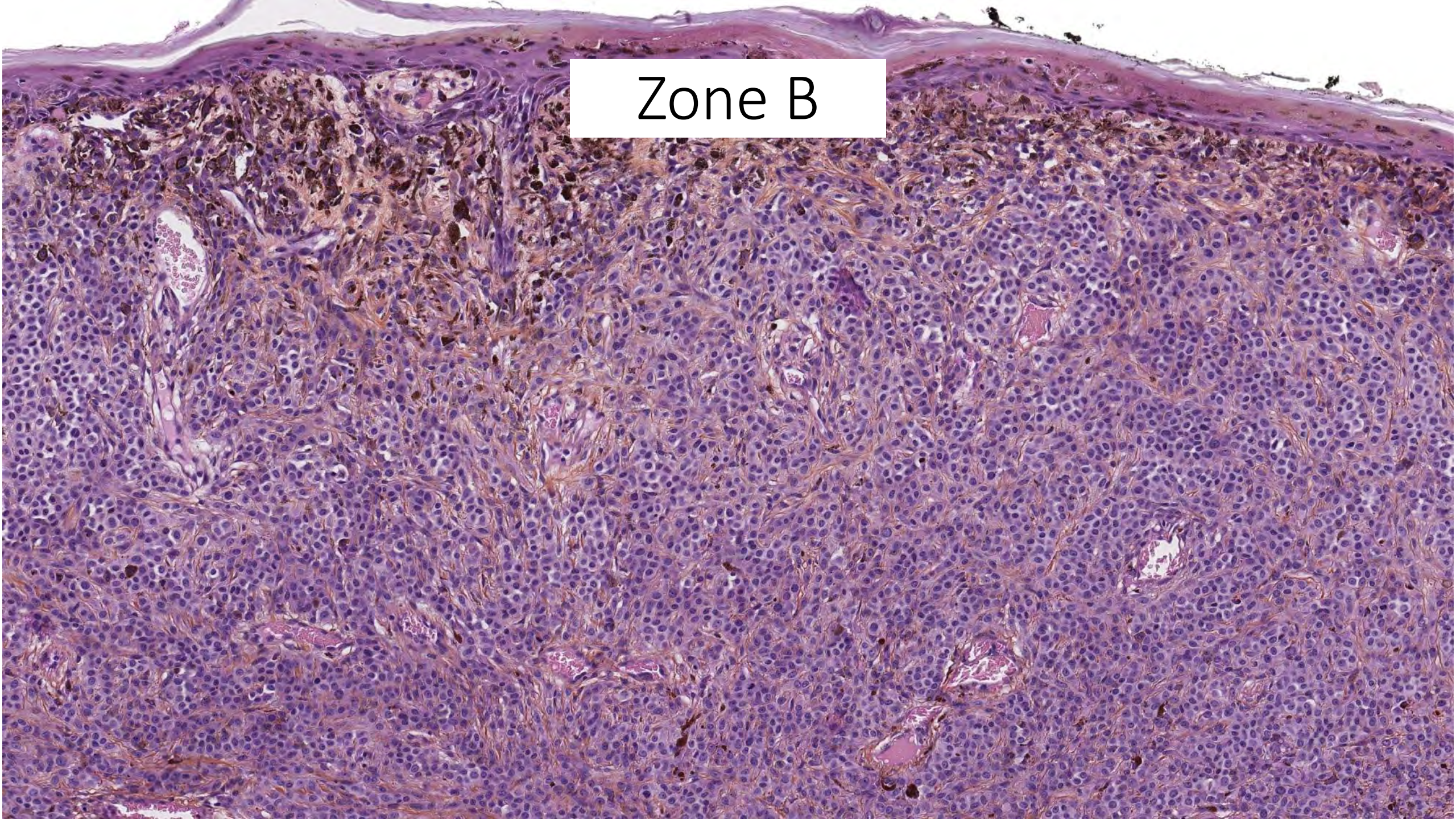




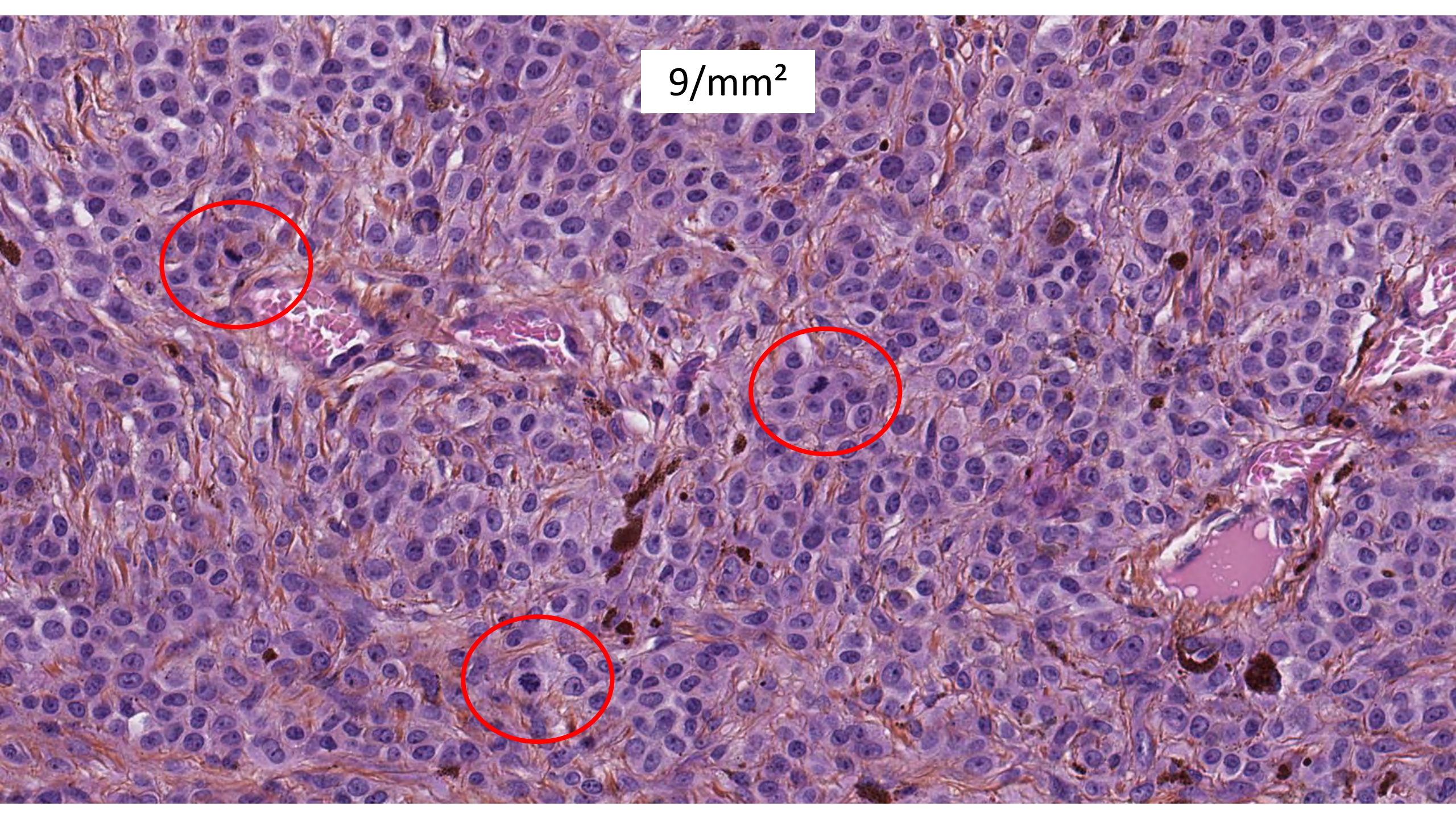
Zone A



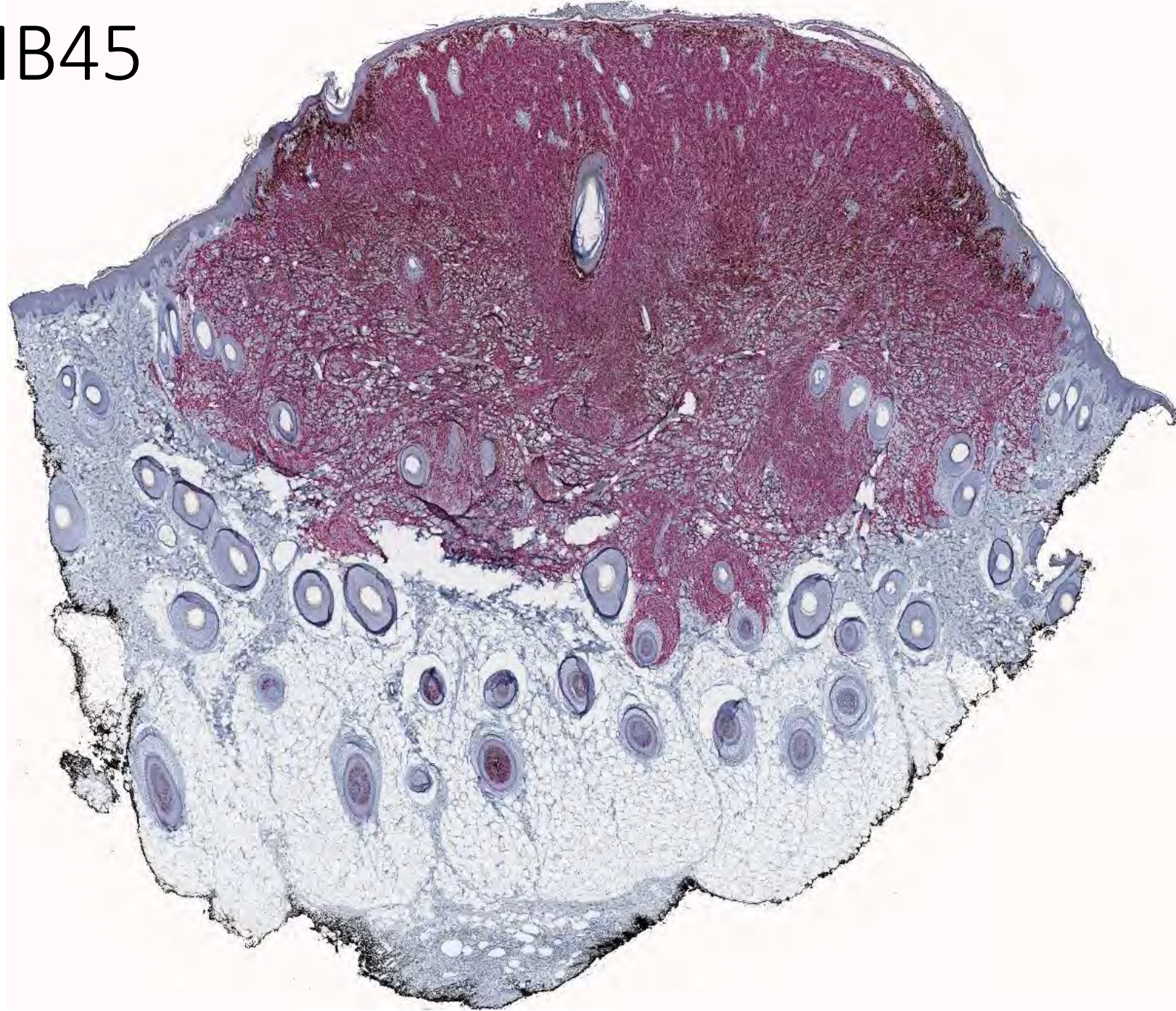
Zone B



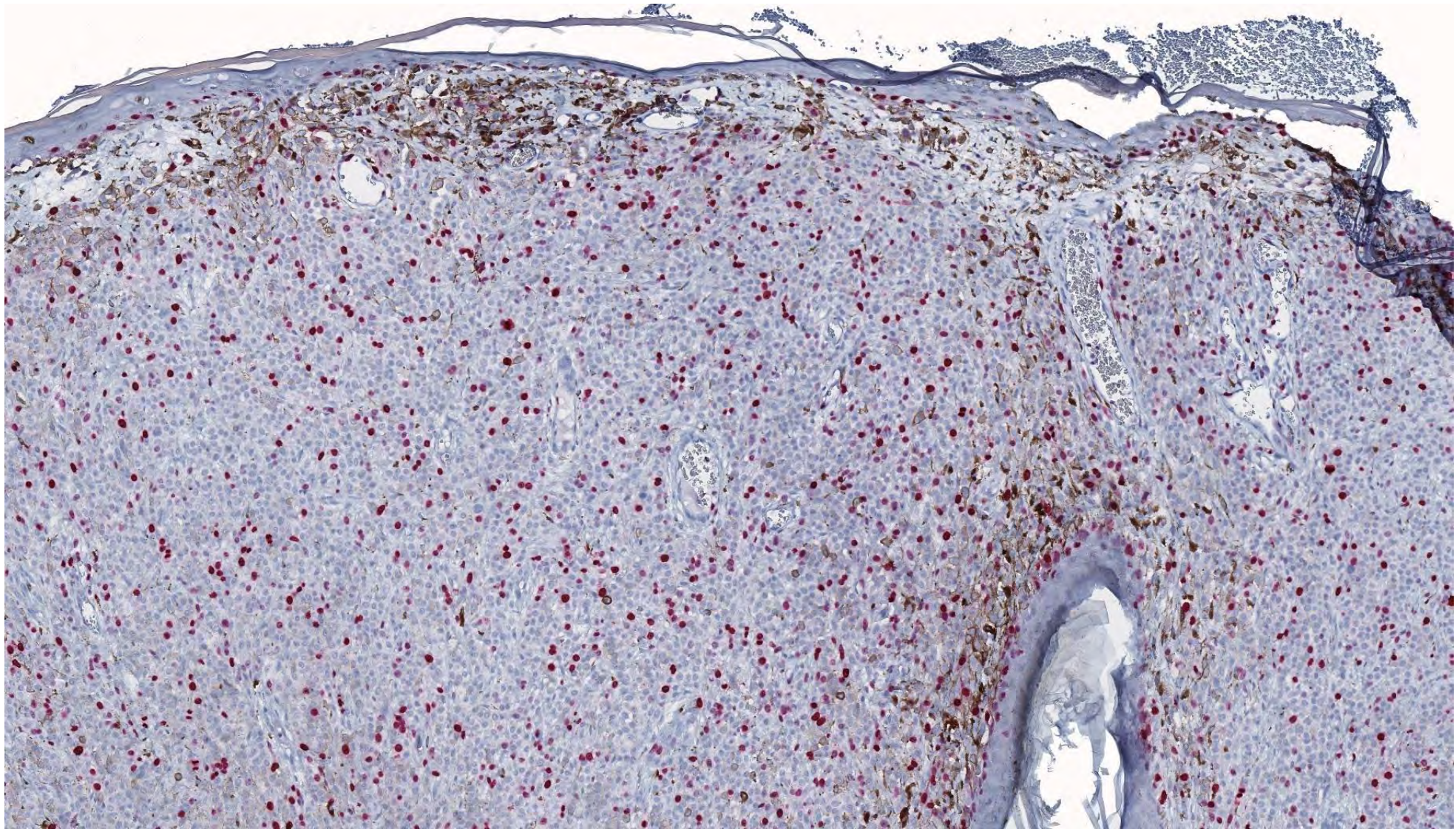
9/mm²



HMB45

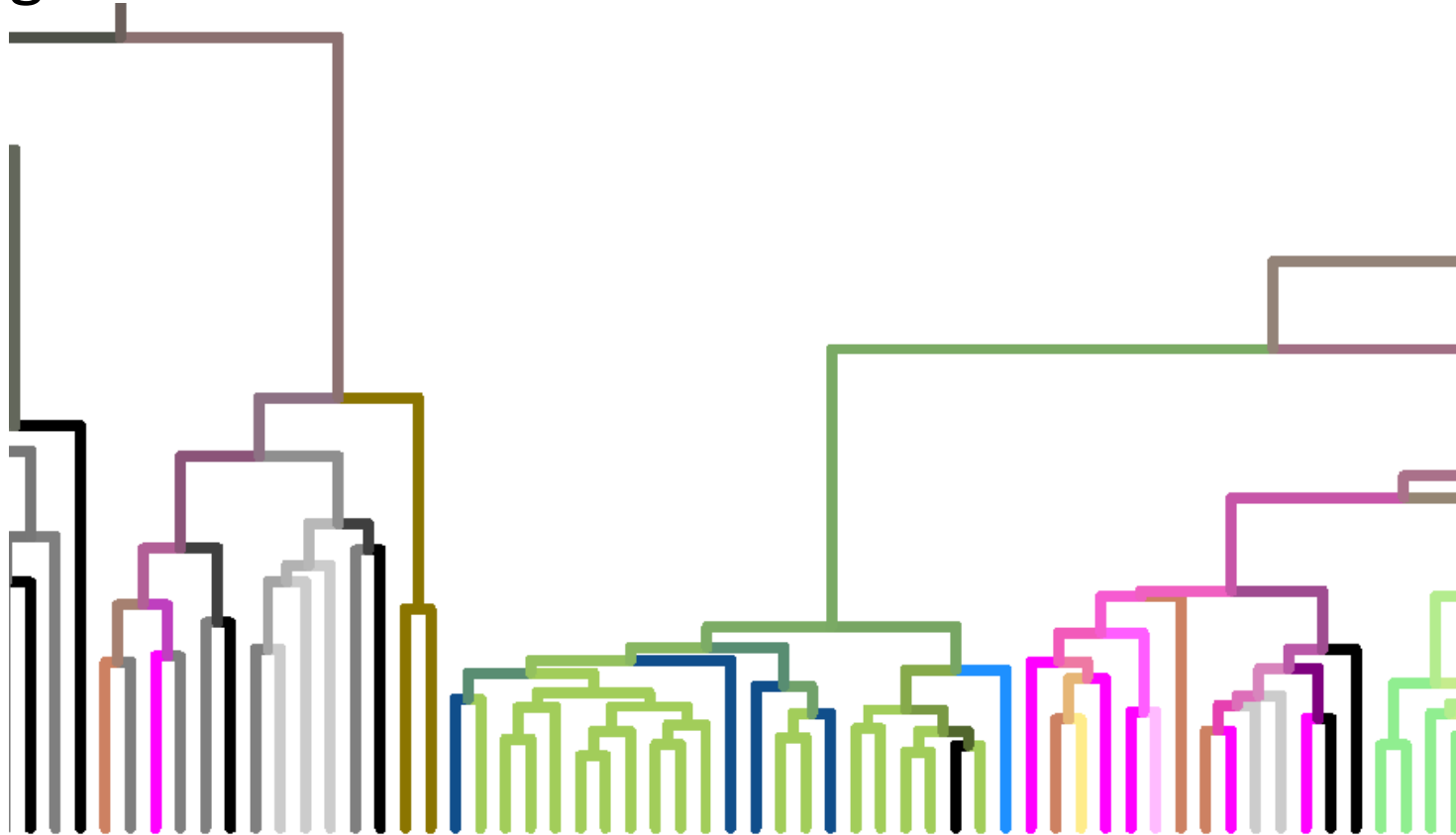


IHC ki67>20%

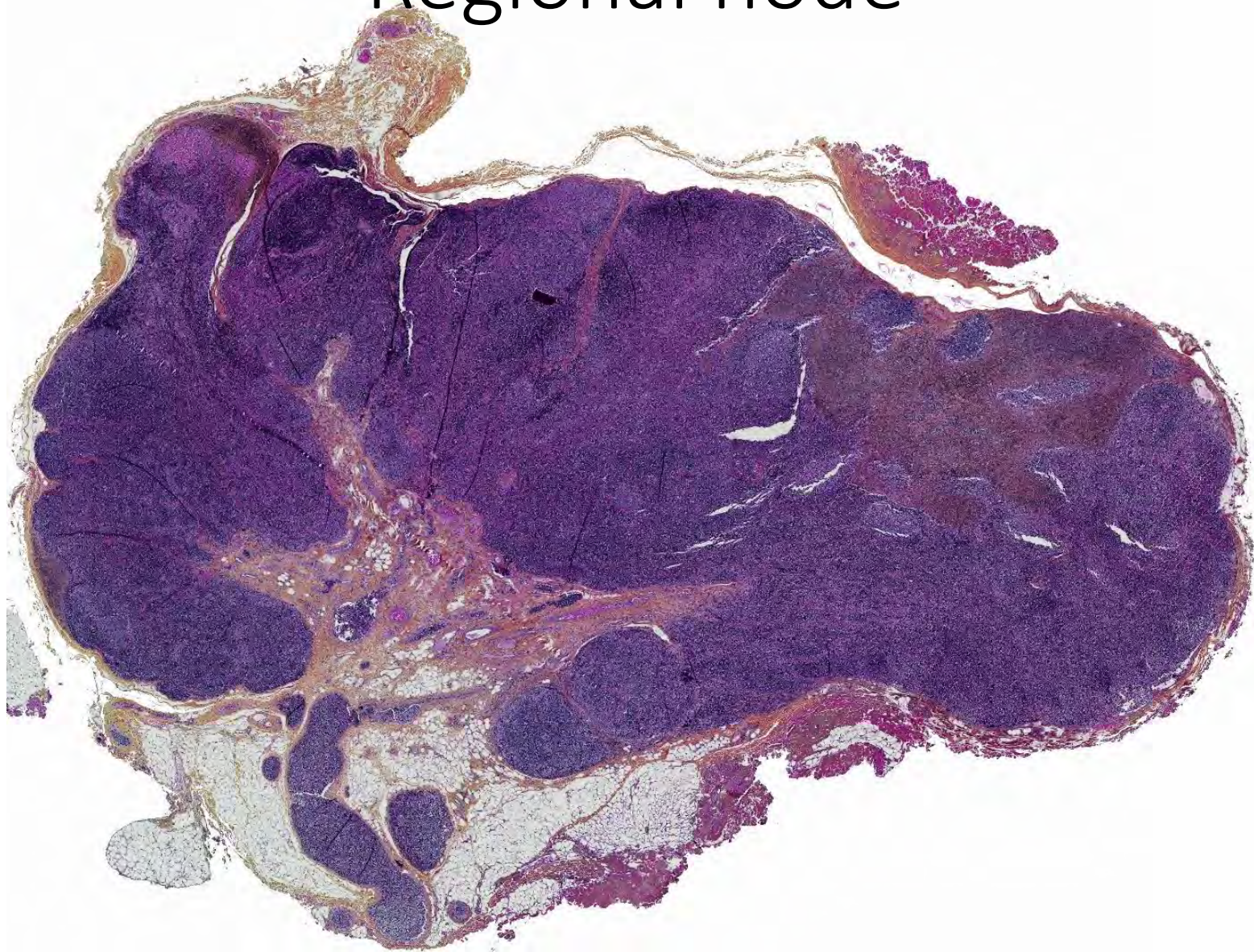


RNAseq

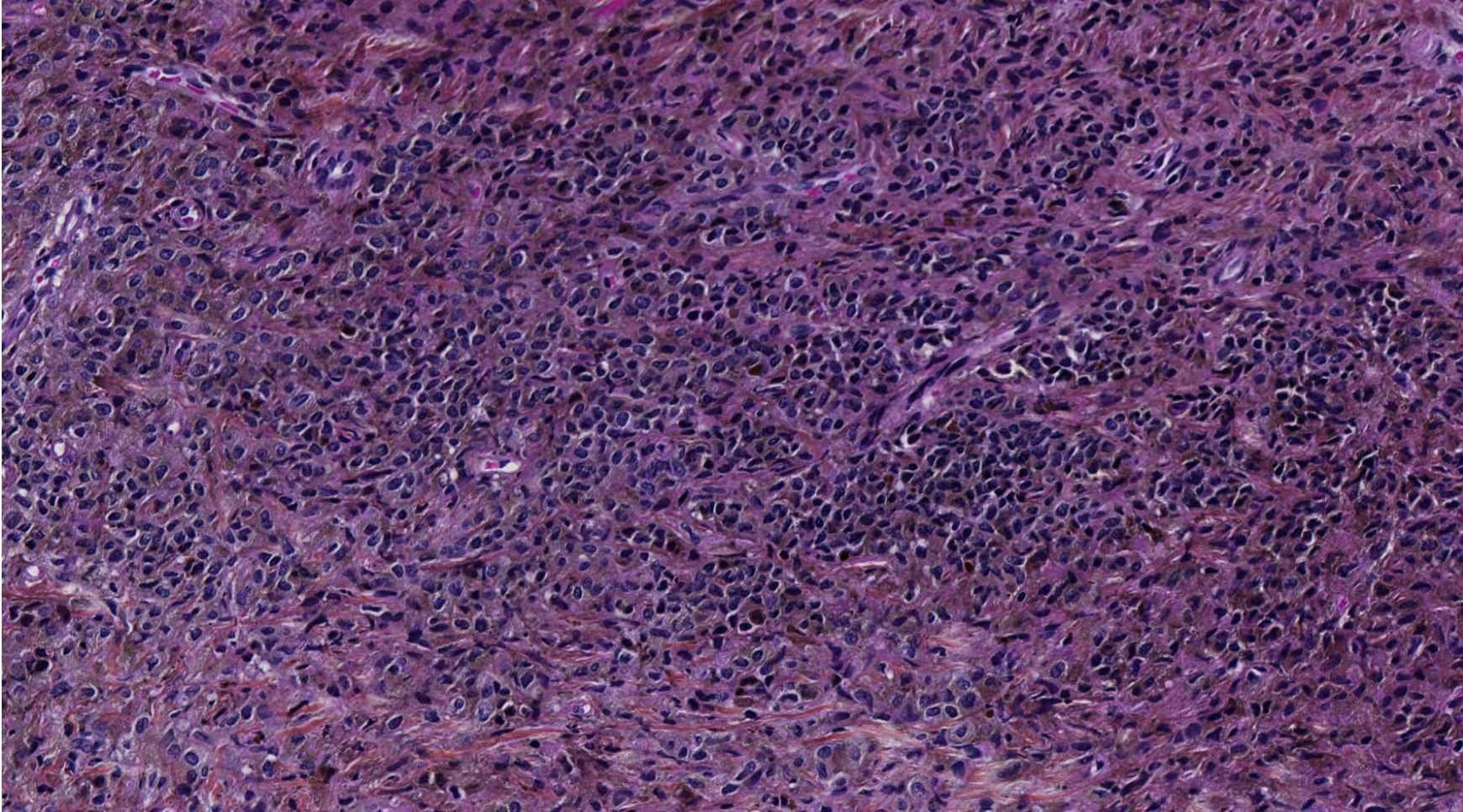
- *SCARB1::PRKCA*
- Clustering with other *PRKCA* fused



Regional node



Regional lymph node



• Kudos @N_Macagno

PRKCA/B-fused «Blue» melanocytic tumors

Take home messages

- Frequent tumour with **complex morphologic features**
Fibrosis +/- biphasic blue-common +/- dermal band +/- PEM-like
- Most cases are **benign**
- Clonal evolution can lead to rare malignant/potentially fatal cases even in children +/- BAP1-inactivation


Reconceptualisation of Pigmented Epithelioid Melanocytoma (PEM)

- PEM is defined by **PRKAR1A inactivation**
- *PRKAR1A* inactivation can potentially occur in all known genetic backgrounds that give rise to a nevus , including Spitz and **blue**

Attempting to Solve the Pigmented Epithelioid Melanocytoma (PEM) Conundrum

**PRKAR1A Inactivation Can Occur in Different Genetic Backgrounds
(Common, Blue, and Spitz Subgroups) With Variation in Their
Clinicopathologic Characteristics**

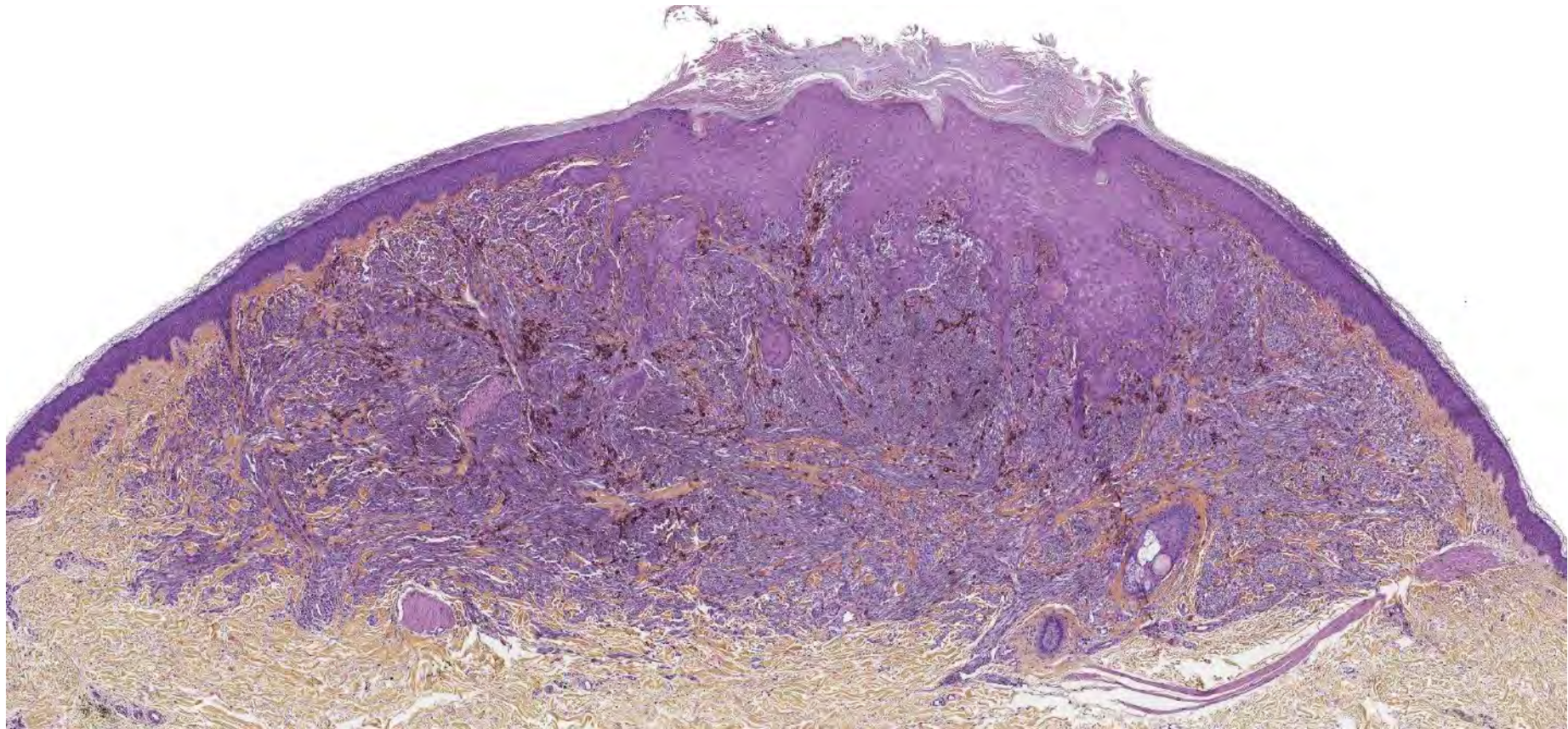
de la Fouchardiere, Arnaud MD, PhD^{*,†}; Tirode, Franck PhD^{*,†}; Castillo, Christine MD[‡]; Buisson, Adrien PharmD[†]; Boivin, Felix MSc^{*}; Macagno, Nicolas MD, PhD^{†,§}; Pissaloux, Daniel PhD^{*,†}

Author Information 

The American Journal of Surgical Pathology: March 22, 2022 - Volume - Issue -
doi: 10.1097/PAS.0000000000001888

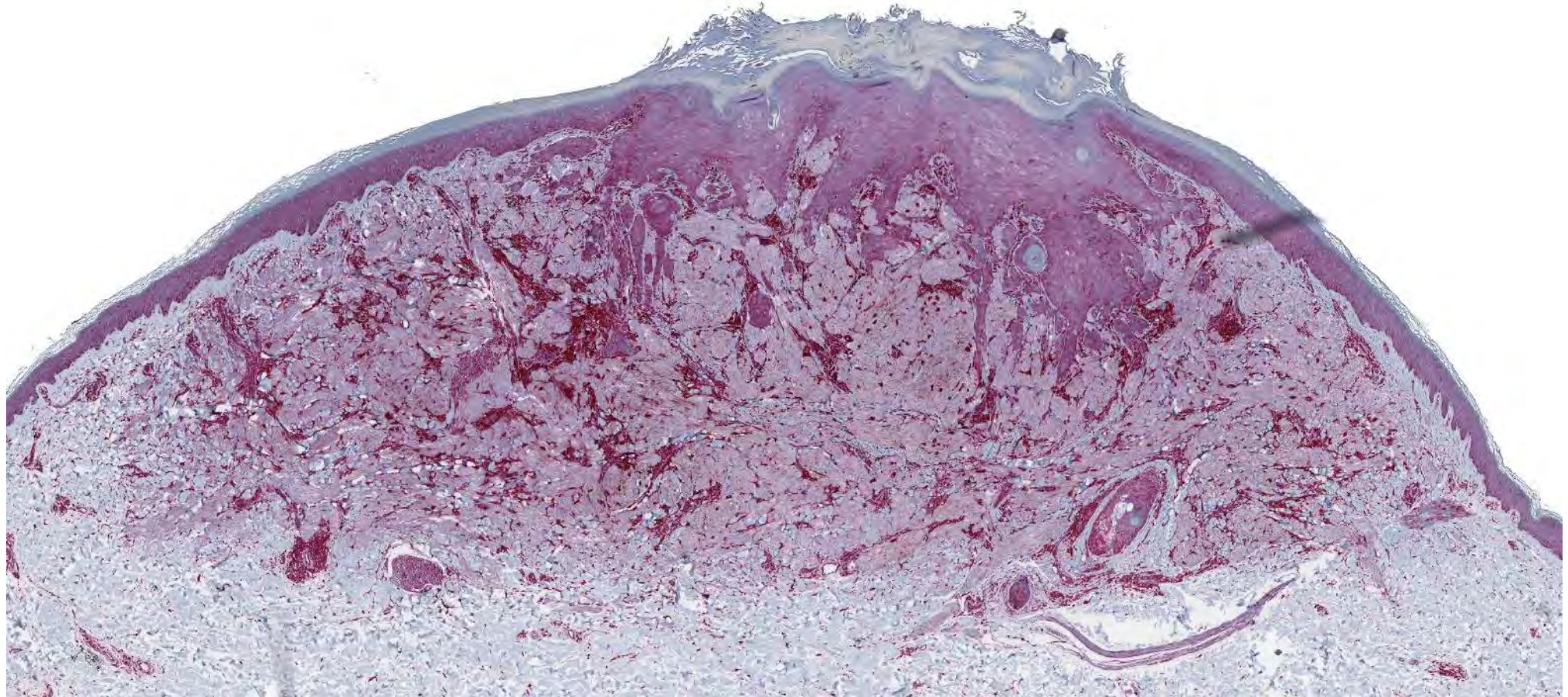
PRKAR1A-inactivated melanocytic tumor with a blue-genetic background

- Adults
- Exophytic with epidermal hyperplasia



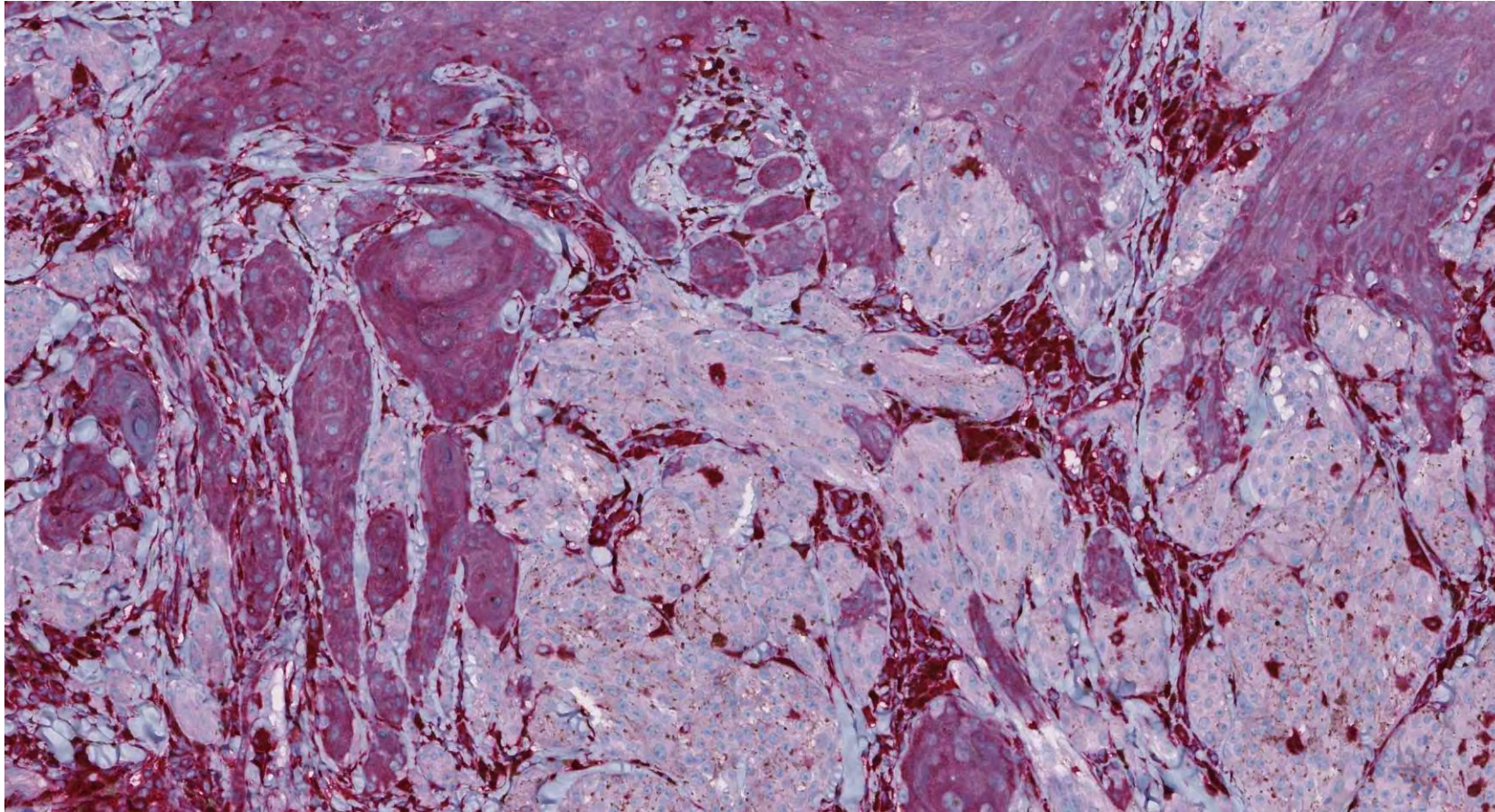
PRKAR1A immunohistochemistry

Cytoplasmic loss of expression



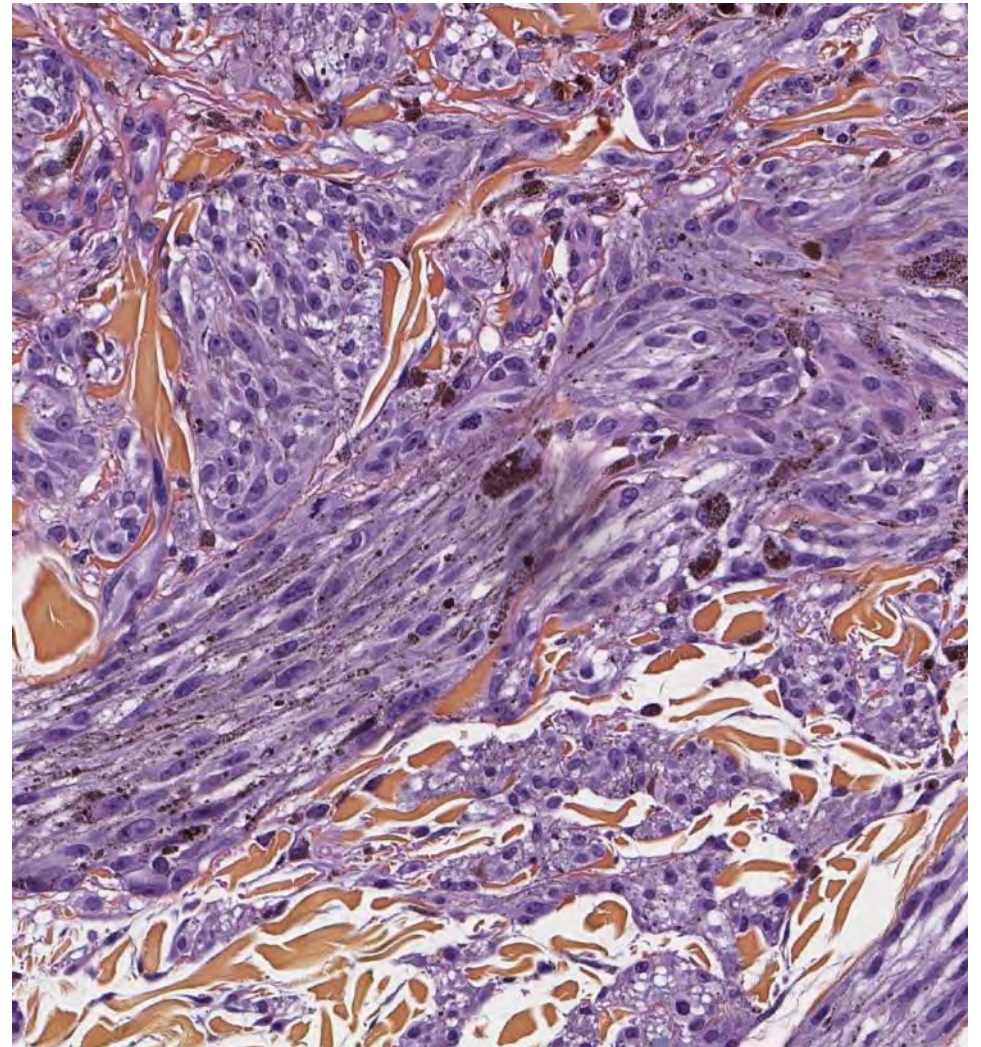
PRKAR1A immunohistochemistry

Cytoplasmic loss of expression



PRKAR1A-inactivated melanocytic tumor with a blue-genetic background

- Adults
- Exophytic with epidermal hyperplasia
- Broad spindled, dermal fascicules
- Melanocytes >> Melanophages

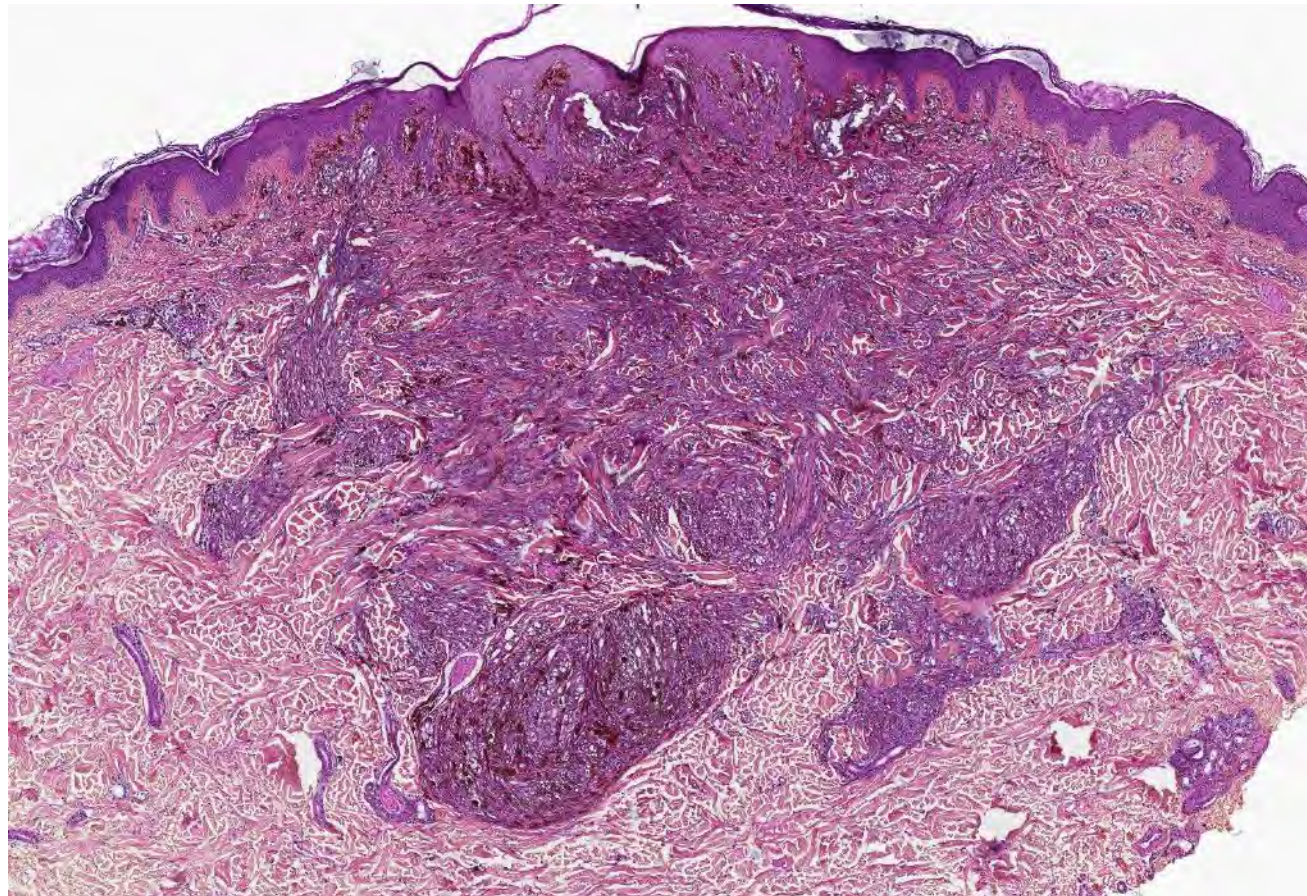


PRKAR1A-inactivated melanocytic tumor with a blue–genetic background

- Adults
- Exophytic with epidermal hyperplasia
- Broad spindled, dermal fascicles
- Melanocytes >> Melanophages
- Occasional vertical dumbbell expansions

PRKAR1A-inactivated melanocytic tumor with a blue–genetic background

- Occasional vertical dumbbell expansions



PRKAR1A-inactivated melanocytic tumor with a blue–genetic background : new concept

- Usual clinical features
- Unusual histological features:
 - Compound disposition with epidermal hyperplasia
 - Absence of biphasic architecture
 - Epithelioid cytology
- Potential to progress toward malignancy
- Terminology: to be determined
- «Epithelioid blue nevus» rehabilitation?

Blue melanocytic tumors

Take home messages

- Distinctive clinical and morphological variants of blue tumors
- The genetic background of blue tumors is expanding
- Growing complexity in the classification of tumors (modularity)
- Molecular pathology is becoming the standard
- Stay open minded



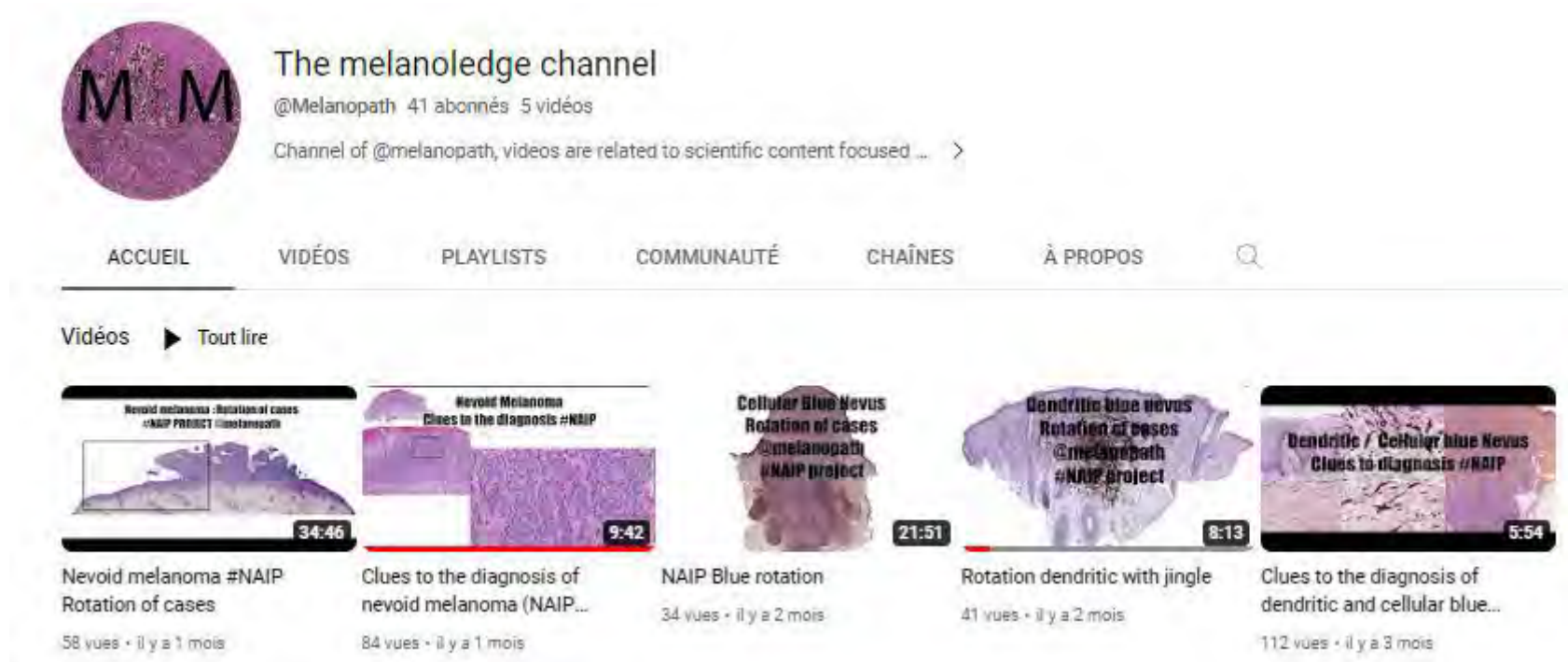
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Molecular pathology of melanocytic tumors

X/Twitter: [@melanopath](#)

Youtube : Formations et enseignement Centre Léon Bérard

The melanoledge channel ([dendritic and cellular blue nevus, PKC fused](#))



The screenshot displays the YouTube channel page for 'The melanoledge channel'. The channel's profile picture is a circular image with a purple background and the letters 'M M'. The channel name is 'The melanoledge channel', with the handle '@Melanopath', 41 subscribers, and 5 videos. A description states: 'Channel of @melanopath, videos are related to scientific content focused ...'. Below the channel information are navigation tabs: ACCUEIL, VIDÉOS, PLAYLISTS, COMMUNAUTÉ, CHAÎNES, and À PROPOS. The 'VIDÉOS' tab is selected, showing a list of five videos. Each video thumbnail includes a title, a duration, and view statistics.

Video Title	Duration	Views	Time
Nevoid melanoma #NAIP Rotation of cases	34:46	58 vues	il y a 1 mois
Clues to the diagnosis of nevoid melanoma (NAIP...	9:42	84 vues	il y a 1 mois
NAIP Blue rotation	21:51	34 vues	il y a 2 mois
Rotation dendritic with jingle	8:13	41 vues	il y a 2 mois
Clues to the diagnosis of dendritic and cellular blue...	5:54	112 vues	il y a 3 mois