Title
Melanoma pathology: new approaches and classification*

Journal
British Journal of Dermatology, 185(2)

ISSN
0007-0963

Authors
Yeh, I
Bastian, BC

Publication Date
2021-08-01

DOI
10.1111/bjd.20427

Peer reviewed

HHS Public Access

Author manuscript

Br J Dermatol. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Br J Dermatol. 2021 August ; 185(2): 282–293. doi:10.1111/bjd.20427.

Melanoma Pathology 2.0 – New Approaches and Classification

Iwei Yeh,

Boris C. Bastian

Department of Dermatology and Pathology, University of California, San Francisco, CA, USA

Abstract

Cancer is caused by the accumulation of pathogenic alterations of the genome and epigenome that result in permanent changes that disrupt cellular homeostasis. The genes that become corrupted in this process vary among different tumor types, reflecting specific vulnerabilities and dependencies of the cell from which the cancer originated. This also applies to 'melanoma', a cancer that constitutes not one, but multiple diseases that can be separated based on their cell of origin, etiology, clinical appearance and course, and response to treatment.

We review the current classification of melanoma within distinct evolutionary pathways and the associated genetic alterations. In addition, we review the application of molecular diagnostics to the diagnosis of melanocytic tumors in the context of histopathologic assessment.

Introduction

The spectrum of genetic alterations in melanocytic neoplasms varies depending on when in life and at which anatomic site the tumors arise. This is strikingly illustrated by the fact that mutations in *BRAF* or *NRAS* are common in melanomas on sun-exposed skin and mucosa[1,2] but are virtually absent in those of the uveal tract[3,4]. The latter invariably have mutations in the Gαq signaling pathway instead. These differences likely reflect differences in the cells of origin from which these neoplasms arise and/or their microenvironment that likely lead to different vulnerabilities of the cells for transformation. The absence of one type of mutation in one tumor type does not mean that the mutation does not arise in the cell of origin but indicates that it does not provide a selective advantage in that cell type. The patterns of somatic mutations in melanomas, and cancers in general, thus reflect the complex interplay between the processes that generate mutations, the starting state of the cell in which they occur, and the homeostatic rules that constrain that cell.

Without exception, melanomas harbor multiple genetic alterations that corrupt more than one pathway. This reflects the existence of tumor suppressive mechanisms, usually multiple, in long-lived organisms such as humans. Tumor progression to melanoma typically occurs in discrete steps, as the pathways required for full transformation are incrementally corrupted. This can result in partially transformed neoplasms, in which progression is temporarily or permanently halted. Examples include the melanocytic nevus, a clonal proliferation of melanocytes that have acquired a mutation that promotes proliferation but have retained

The authors have no conflicts of interest to disclose.

tumor suppressive mechanisms resulting in a stable state. In most nevi this mutation is BRAF V600E, which strongly activates the MAPK pathway[6,7]. Other nevus-initiating mutations affect other signaling components of the MAPK pathway and, as these mutations are sufficient for pathway activation, usually only one of them is present in a given nevus. The occasional progression of such a nevus results from one of the constituent cells acquiring an additional mutation that overrides the proliferation-constraining mechanism. This typically involves inactivation of *CDKN2A* or mutation of the *TERT* promoter, highlighting oncogene-induced and replicative senescence as important factors that help keep these benign neoplasms in check.

Some not overtly malignant melanocytic tumors harbor additional pathogenic alterations that resulted in a second round of clonal expansion. This points to the redundancy of tumor suppressor mechanisms, as backup mechanisms apparently become engaged when one senescence mechanism becomes corrupted. Genetically intermediate melanocytic tumors are now designated melanocytomas in the revised WHO Classification[8]. Their risk of malignant transformation likely is higher than their corresponding nevus stage but remains to be quantified.

Pathways to melanoma defined in the 2018 WHO Classification of Skin Tumors

The framework outlined above has been the basis of a two-dimensional classification schema in which different melanoma subtypes are distinguished along one axis and their respective precursor stages on the other[9] and serves as the foundation for the revised melanoma classification in the 2018 WHO Classification of Skin Tumors[8,10].

Classification of melanomas according to their evolutionary pathways attempts to integrate our understanding of causal mechanisms, clinical and histopathological presentation, diagnosis, prognosis and will be a work in progress for some time (Table 1). Here we provide a brief review of these pathways.

Pathway 1: Low cumulative sun damage melanoma (low-CSD, superficial spreading melanoma)

The degree of solar elastosis in the dermis reflects the degree of sun exposure and corresponds with patient age, pigmentary phenotype and anatomic site. Melanomas that arise in a background of low cumulative sun-damage (low-CSD) typically arise on the trunk and extremities of adults between age 20 and 60[11]. Most of these melanomas harbor a BRAF V600E mutation (Figure 1). The defining feature, low cumulative sun-damage, is assessed by the degree of solar elastosis[11]. Most low-CSD melanomas are superficial spreading melanomas.

Common or conventional nevi are the main precursor for this melanoma subtype. These nevi typically arise in the first two decades of life and the majority harbor BRAF V600E mutations with a minority harboring NRAS mutations instead. Different types of melanocytomas can develop within these nevi through additional mutations. Deep penetrating melanocytoma (formerly nevus) is defined by additional mutations that activate

the beta-catenin pathway[12]. *BAP1*-inactivated melanocytoma (previously classified as a Spitz tumor) is defined by inactivation of the tumor suppressor gene *BAP1* [13–15]. *PRKAR1A*-inactivated melanocytomas are a subset of pigmented epithelioid melanocytoma, formerly referred to as epithelioid blue nevus[16]. These melanocytomas are usually clinically stable but can progress to melanoma through further genetic alterations[17,18]. Assessment of the presence of additional mutations such as in *CDKN2A* or the promoter of *TERT* and chromosomal copy number aberrations can assist with differentiating melanocytoma and low-CSD melanoma.

Within the new paradigm of nevus -> melanocytoma -> low-CSD melanoma, it seems likely that some dysplastic nevi will turn out to be additional forms of melanocytoma that harbor additional progression events beyond the initiating mutation. Clinically, dysplastic nevi present as broad (> 5 mm) irregularly bordered and pigmented macules and thin papules[19]. Their histopathologic features include a broad intraepidermal component of single melanocytes and nests of them, nests of melanocytes bridging adjacent rete ridges, and fibroplasia and an inflammatory response in the superficial dermis. In some families, an increased number of dysplastic nevi is associated with a germline alteration such as inactivating mutations in *CDKN2A*[20]. This explains why the presence of multiple dysplastic nevi is associated with an *increased melanoma risk for the patient*; it indicates the presence of a germline that interferes with the suppression of melanocyte transformation in all of the patient's melanocytes. However, it is to be expected that dysplastic nevi may result from an *acquired* mutation that would be present in cells of that dysplastic nevus and inform on the *progression risk of the individual dysplastic nevus* but not reflect any germline predisposition to melanoma in the patient. Disentangling these factors holds the promise to solve the Gordian knot that the conflicting definitions for dysplastic nevi have tied and assist with their evidence-based clinical management.

Pathway 2: High cumulative sun damage melanoma (high-CSD, lentigo maligna melanoma)

Melanomas on skin with marked solar elastosis (high-CSD melanomas) tend to have a lentiginous or single cell growth pattern in the epidermis in contrast to the often pagetoid growth pattern of low-CSD melanomas. They typically have an extended radial growth phase, with a large patch of in situ melanoma developing before an invasive component forms (Figure 2). Both clinically and histopathologically, their borders may be difficult to demarcate and recurrence after excision is more common than for low-CSD melanoma.

High-CSD melanomas typically do not harbor *BRAF* V600E mutations but instead harbor other MAPK kinase pathway mutations such as *BRAF* V600K, *NRAS* or *KIT* mutations, or inactivation of the negative regulators of Ras, *NF1* or *RASA2*. A pre-existing nevus is typically absent and melanoma in situ is considered the predominant precursor lesion.

Pathway 3: Desmoplastic melanoma

Desmoplastic melanoma is defined by a dermal component with a predominance of spindled, unpigmented melanocytes interspersed between thickened collagen bundles resembling a scar. When the desmoplastic component represents >90% of the tumor, it is classified as "pure" as opposed to "mixed" [21,22]. The pure subtype of desmoplastic

melanoma infrequently metastasizes to the lymph nodes and has improved survival compared to other forms of cutaneous melanoma of similar tumor thickness. Local complications include extension along nerves due to neurotropism.

Most desmoplastic melanomas can be regarded as a variant of high-CSD melanoma, but they occasionally can arise in other settings. The high-CSD desmoplastic melanomas have an extremely high burden of UV-induced mutations[23]. *NF1* inactivating mutations often occur with other weakly activating mutations in the MAP-kinase pathway, but BRAF V600E or RAS mutations are infrequent[24,25]. Promoter mutations in NFKBIE, encoding NF-κB inhibitor ε, are enriched in desmoplastic melanomas.

Pathway 4: Spitz melanoma (Malignant Spitz Tumor)

Spitz tumors were first recognized as distinct from cutaneous melanoma in the 1940s[26]. They tend to arise during childhood and characteristically have epithelioid melanocytes with abundant cytoplasm and large nuclei, pagetoid scatter of melanocytes within the epidermis and limited maturation of dermal melanocytes. The set of initiating mutations in Spitz nevi includes activating *HRAS* mutations, activating gene fusions of receptor tyrosine kinases (*ALK*, *ROS1*, *NTRK1/2/3*, *RET*, *MET*, *MERTK*) and serine/threonine kinases (*BRAF*, *RAF1*, *MAP3K8*) with a broad range of partner genes[27–33].

In the WHO classification, Spitz tumor refers to a spectrum of progression states ranging from nevus to melanoma that, in addition to the histopathological findings, is defined by the initiating oncogenic alterations listed above. This new convention is intended to separate Spitz melanoma from what has been called spitzoid melanoma, a mainly cytologically defined presentation of melanoma that mostly consists of other types of cutaneous melanomas. While this is a step forward in defining Spitz tumors and their progression, there is additional unresolved complexity, which is due to the fact that the various initiating alterations are associated with differences in histopathological appearance[34–39] and perhaps risk of progression to melanoma.

Genetic alterations associated with evolution to Spitz melanoma include inactivation of *CDKN2A*, *PTEN*, and *TP53* and promoter mutations in TERT[40–42], similar to other subtypes of melanoma. Spitz tumors with homozygous deletion of *CDKN2A* but without additional driver alterations such as TERT promoter mutation appear to have indolent behavior[43] and should be considered intermediate Spitz tumors, with the nomenclature Spitz melanocytoma preferred to the previously used term atypical Spitz tumor. Spitz melanocytomas can spread to regional nodes frequently but exceedingly rarely lead to distant metastases or fatal outcomes[44]. Spitz melanomas tend to occur in younger patients and likely have a better outcomes than other melanomas (Figure 3)[45].

Pathway 5: Acral Melanoma

Melanomas on the non-hair bearing (glabrous) skin of the hands and feet including the nail unit are referred to as acral melanomas. Recent genetic data indicate that a subset of melanomas on these sites represent low-CSD melanomas, defined by the presence of *BRAF* V600E and their pattern of DNA copy number changes[46,47]. Similar to their non-acral counterparts, acral melanoma of this subset tend to occur in younger patients with European

ancestry and may arise from a pre-existing nevus. We postulate that most BRAF V600E mutant acral melanomas are biologically similar from those on non-acral skin.

The remaining acral melanomas, most of which have MAPK activating mutations other than BRAF V600E, clinically and histopathologically fall into the category of acral lentiginous melanoma (ALM) and have distinctive genetic features that separate them from high- and low-CSD melanomas[48–51]. They have a low point-mutation burden and instead harbor many focal amplifications and deletions, and structural rearrangements. They have a lentiginous or single cell growth pattern with a broad radial growth phase that may be present for many years before progression to invasive melanoma and often show extension along eccrine ducts (Figure 4). Recent studies in mice identified a melanocyte precursor cell within eccrine glands that may be the cell of origin of acral lentiginous melanoma[52]. The *in situ* phase often fades into an area colonized by *field cells*, neoplastic melanocytes that appear close to normal in cytomorphology and are equidistantly spaced in the basilar epidermis with no notable increase in density. They share, however, copy number changes including pathogenic amplifications with the adjacent manifest in situ and invasive melanoma and are considered a very subtle and early form of melanoma in situ[53]. The field cells can extend several centimeters, explaining why the peripheral margins of acral melanoma in situ can be difficult to assess and partial biopsies have to be assessed with caution. The presence of the occult field cells likely also explains an increased local recurrence rate after surgical excision.

Acral lentiginous melanoma harbors a diversity of genetic driver alterations, many of which are promising drug targets, including *KIT* mutations, non-V600E *BRAF* mutations, and kinase fusions. It can be difficult to distinguish BRAF V600E mutant acral melanoma from ALM by histopathologic and clinical features alone. Molecular testing for V600E and other BRAF mutations should be performed when BRAF targeted therapy is clinically indicated.

Pathway 6: Mucosal Melanoma

Mucosal melanomas arise from melanocytes in the sinonasal and genitourinary mucosa. Due to their internal location, mucosal melanomas are often diagnosed either as large primary tumors or metastases. Similar to acral melanomas, mucosal melanomas harbor a low point mutation burden and also harbor many focal amplifications and deletions and structural rearrangements[51,54–56]. BRAF V600E mutations are uncommon. There are indications of differences to acral melanoma and perhaps variation among mucosal melanomas in that genitourinary mucosal melanomas more commonly have hotspot mutations in *SF3B1* as compared to sinonasal ones[54]. Furthermore, some mucosal melanomas have GNAQ mutations, further indicating a possible relationship between this category of melanocytic neoplasms thought to originate from dermal rather than epithelial melanocytes[57,58]. Similar to acral lentiginous melanoma, mucosal melanomas have diverse driver alterations, including some that could be targeted therapeutically. *SPRED1* was recently identified as a tumor suppressor in mucosal melanoma and it is often inactivated in the setting of mutant *KIT*[55].

Pathway 7: Melanoma arising in congenital nevus

Congenital nevi are defined as nevi that are present at birth, but nevi that arise shortly after birth are often subsumed under this term. However, there may be differences between bona fide congenital nevi, which are often very large and those arising after birth because, giant congenital nevi are most frequently caused by mutations in *NRAS*, whereas smaller congenital nevi more commonly harbor *BRAF* V600E mutations[59,60]. This suggests that the cell of origin of giant congenital nevi can be more effectively transformed by *NRAS* mutation whereas the cell of origin of conventional acquired nevi are more effectively transformed by *BRAF* mutations, supporting the idea that their cells of origin may differ.

The risk of melanoma arising within a congenital nevus increases with the size of the nevus, likely reflecting the total number of melanocytes with the initiating mutation. The risk of melanoma developing in a congenital nevus is estimated to be up to 2.5-8% in giant congenital melanocytic nevi greater than 20 cm in diameter[61,62].

Rapidly growing nodules within a giant congenital nevus are not uncommon[63]. Most are benign, even if the densely cellular nodules may appear worrisome histopathologically. Assessment of copy number in these tumors can be helpful as proliferative nodules typically harbor copy number gains and losses of entire chromosomes, while melanomas harbor copy number gains and losses of parts of chromosomes (Figure 5)[64]. Specific secondary alterations apart from copy number changes to explain the development of these atypical proliferative nodules have not yet been identified.

Pathway 8 and 9: Melanoma arising in Blue Nevus and Uveal Melanoma

Melanoma in blue nevi and uveal melanoma arise from melanocytes that are not associated with any epithelium and share similar genetic alterations. They both harbor activating mutations in the Gαq pathway, predominantly in *GNAQ* and *GNA11* but rarely in their upstream receptor *CYSLTR1* [65–68] or their downstream effector *PLCB4*[69]. They do not harbor a UV signature[3,4,65,66,69,70]. Mutations in the Gαq pathway are sufficient to form blue nevi in the skin and uveal nevi in the eye. Progression to melanoma occurs through a distinct set of additional genetic alterations, which include bi-allelic inactivation of *BAP1*, hotspot mutations in *SF3B1* (similar to a subset of mucosal melanomas), or mutations in *EIF1AX*[71–73]. Specific DNA copy number changes are also shared by both types of melanoma and include monosomy 3, resulting in loss of heterozygosity of *BAP1*, and gain of 8q, which contains the oncogene *MYC*[74,75]. Uveal melanomas are divided into low risk (class 1) and high-risk (class 2) tumors by their expression profiles[76]. Class 2 signatures are associated with *BAP1* inactivation and portend a higher rate of liver metastasis and lethal outcome[77,78]. Uveal melanomas disseminate hematologically with a propensity to metastasize to the liver[79,80]. Blue nevus like melanomas often disseminate through lymphatics, similar to other cutaneous melanomas although cases with a heavy burden of liver metastasis have been reported, suggesting that some may display a similar liver tropism[75,81].

Blue nevi may originate from melanocytes that developed via the ventromedial pathway in which stem cells from the neural crest migrate along developing nerves and can give rise to

Schwann cells or melanocytes[82]. This may explain the sometimes segmental distribution of blue nevi (Nevus of Ito and Ota), which are often associated with perineural involvement.

Melanomas arising in blue nevus need to be distinguished from other highly pigmented melanomas (i.e. with β-catenin activation or *PRKAR1A*-inactivation). If a remnant of blue nevus cannot be clearly identified, the presence of an activating Gαq mutation or BRAF V600E mutation can help classify lesions into the blue or low-CSD pathway, respectively.

Final thoughts on the WHO pathway classification

We anticipate that this classification will continue to evolve as additional knowledge is uncovered. Criteria to classify individual lesions into respective pathways have to be refined and may change. In fact, as discussed above, since the development of this classification, additional data suggests that a subset of acral melanomas likely belong in the low-CSD pathway. As compared to previous classifications, the genetic drivers and level of cumulative sun-damage as assessed by the degree of solar elastosis in the skin of the primary melanoma are given more weight and classification has become less dependent on other histopathologic features.

Nodular melanoma refers to melanomas in vertical growth phase that do not have an associated benign precursor or radial growth phase. Rather than constituting a melanoma type/pathway on their own, nodular melanomas occur in most of the above pathways. They do not seem to show discernible differences in genetic alterations from other melanomas in their respective pathway, but it has been proposed that they arise through an ‘inverted’ sequential order in which pathogenic mutations arise[83]. The initial mutations would not lead to neoplastic proliferation but once such ‘poised’ melanocytes acquire oncogenic drivers in the MAPK pathway they would be fully transformed, skipping over earlier progression stages.

Molecular diagnostics

Molecular diagnostics in melanoma are used for both diagnosis and treatment selection. Histopathologic and genetic features that define the boundaries between nevus, melanocytoma, and melanoma are still being delineated. At the current time, the integration of molecular diagnostics with clinical and histopathologic features of a tumor is critical to providing the best diagnosis.

Immunohistochemistry

A mutation-specific antibody has been developed for BRAF V600E[84]. It does not recognize V600K/D/R or other BRAF mutants. Mutation specific antibodies for RAS exist for RAS Q61R and RAS Q61L that recognize specific Q61 but not Q61H mutant forms of H-, K-, and NRAS and other important variants such as those at codons 12 or 13[85,86]. With appropriate validation, mutation-specific antibodies have good sensitivity and specificity and short turn-around time.

To detect or screen for kinase fusions, immunohistochemistry to detect the kinase domain of the native protein can be used. The kinase domain is present in the normal and the

chimeric protein generated by structural rearrangements, but as the normal proteins of ALK and ROS1 are not expressed in normal melanocytes, immunoreactivity with either antibody in a melanocytic tumor is indicative of the respective kinase fusion. A caveat is alternative transcript initiation of *ALK* (ALK^{ATI}) that results in the expression of a truncated form of ALK, which can lead to immunoreactivity in the absence of a fusion[87]. The normal protein of other kinase genes are often expressed in normal melanocytes, making immunohistochemistry less suitable to detect rearrangements. While immunohistochemistry for the kinase domain of NTRK1/2/3 using the pan-Trk antibody can be used to screen for NTRK1/2/3 fusions, only very strong homogeneous expression predicts an underlying fusion[89]. Depending on the fusion partner, the antibodies against kinase domains can demonstrate different staining patterns. ETV6-NTRK3 has mostly nuclear expression whereas MYO5A-NTRK3 has mostly cytoplasmic expression[39]. Immunohistochemistry currently is not useful to detect BRAF or MAP3K8 fusions.

In deep penetrating melanocytoma, a range of different mutations result in β-catenin accumulation, which can be detected by immunohistochemistry. Conventional melanocytic nevi express β-catenin in a gradient pattern with higher expression levels in neoplastic melanocytes near the epidermis and other epithelial structures. However, in deep penetrating melanocytoma, there is strong uniform beta-catenin expression from top to bottom, sometimes with notable nuclear staining[12,90].

Immunohistochemistry can also be used to infer loss of tumor suppressors. Tumor suppressor proteins that can be evaluated by immunohistochemistry include BAP1, PRKAR1A, p16, and NF1. However, missense mutations can disrupt protein function but maintain immunoreactivity and thus lead to false negative results (i.e. positive immunoreactivity despite loss of a functional protein). In addition, the absence of expression of a tumor suppressor may indicate that the tumor suppressor has not been induced, rather than inactivated genetically.

Using immunohistochemistry to assess for molecular alterations in melanocytic tumors requires an understanding of the expected staining patterns and should be integrated with clinical and histopathologic features.

DNA and RNA based mutation detection

For detecting mutations in DNA, multiple platforms are in use, including Sanger sequencing, allele-specific PCR assays, and targeted next-generation sequencing (NGS). Each method has its advantages and disadvantages. Laboratories are gradually shifting to targeted NGS as the range of relevant genetic alterations in cancer expands. Depending on the targeted NGS platform, other genetic alterations including DNA copy number changes and loss of heterozygosity can also be identified.

Identification of structural rearrangements such as kinase fusions requires specific techniques as the genomic breakpoints usually occur in intronic regions that can span hundreds of kilobases. NGS of DNA can detect fusions if entire introns are targeted for capture, but RNA sequencing is a more robust and cost-effective method of detection. Detection of fusion transcripts by RT-PCR is highly sensitive and specific, but RT-PCR

assays must be designed to detect specific fusions and is not practical for detecting the broad spectrum of kinase fusions that occur in melanocytic neoplasms.

Most melanomas demonstrate multiple DNA copy number changes, with some differences in pattern among those that develop within different pathways. A small number of specific gains or losses can be assessed by fluorescence in situ hybridization (FISH). The advantage of FISH is that it allows for assessment of tumors with heterogenetic subclones, small size or significant inflammation. Copy number changes, and depending on the platform also allelic imbalance, can be assessed by comparative genomic hybridization (CGH) with the advantage of providing an assessment of the entire genome but at the cost of lower sensitivity if the tumor cell content is low or there is significant tumor heterogeneity.

While nevi typically do not demonstrate copy number alterations, Spitz nevi with HRAS mutations often demonstrate copy gain of chromosome 11p, which contains the mutant HRAS. Spitz nevi with kinase rearrangements may demonstrate copy number alterations of the chromosomal regions that flank the rearranged genes.

Gene Expression Profiling

Gene expression tests for melanocytic tumors aim to assist with diagnosis or prognosis. The expression of specific transcripts is measured across all cells in the tumor, including neoplastic melanocytes, stromal cells and inflammatory cells. MyPath melanoma (Myriad Genetics, Salt Lake City Utah) provides a numerical score binned into ranges that correspond with likely benign, indeterminate or malignant based on the expression of 23 genes[91]. Sensitivity and specificity are 91.5% (CI 86.4-95.2%) and 92.5% (CI 90.0-94.5%) respectively. Initial findings suggest that the test has different performance across different subtypes of nevi and melanoma[92,93] and may have decreased performance for indeterminate or intermediate tumors[94]. The clinical utility of this test remains uncertain.

There are multiple prognostic gene expression tests for cutaneous melanoma. Improved risk-stratification can guide the use of sentinel lymph node biopsy, surveillance, and adjuvant therapy. However, these tests have not been assessed in clinical trials to determine what clinical utility they provide beyond AJCC staging parameters, and the Melanoma Prevention Working Group does not recommend their routine use[95].

Future directions

The pace of technologic development has led to a remarkable expansion of our understanding of the genetic progression of cancer and melanoma and melanocyte biology and resulted in improved treatments and refined diagnostic methods. One of the critical hurdles ahead is the development of prognostic biomarkers that can identify patients with primary melanomas at high risk of progression so that they can receive the appropriate adjuvant therapies while their residual tumor burden is still at a minimum.

Acknowledgements

We thank A. Hunter Shain and Meng Wang for their helpful comments on the manuscript. The authors are supported by funding from the National Cancer Institute (R35CA220481).

References

1. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002; 417:949–54. [PubMed: 12068308]
2. Akbani R, Akdemir KC, Aksoy BA, et al. Genomic Classification of Cutaneous Melanoma. Cell 2015; 161:1681–96. [PubMed: 26091043]
3. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature 2009; 457:599–602. [PubMed: 19078957]
4. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med 2010; 363:2191–9. [PubMed: 21083380]
5. Huang JL-Y, Urtatiz O, Van Raamsdonk CD. Oncogenic G Protein GNAQ Induces Uveal Melanoma and Intravasation in Mice. Cancer Res 2015; 75:3384–97. [PubMed: 26113083]
6. Pollock PM, Harper UL, Hansen KS, et al. High frequency of BRAF mutations in nevi. Nat Genet 2003; 33:19–20. [PubMed: 12447372]
7. Yeh I, von Deimling A, Bastian BC. Clonal BRAF mutations in melanocytic nevi and initiating role of BRAF in melanocytic neoplasia. J Natl Cancer Inst 2013; 105:917–9. [PubMed: 23690527]
8. Elder DE, Massi D, Scolyer R, Willemze R. WHO Classification of Skin Tumours, 4th Edition. Lyon, France, IARC Press, 2018.
9. Bastian BC. The Molecular Pathology of Melanoma: An Integrated Taxonomy of Melanocytic Neoplasia. Annual Review of Pathology: Mechanisms of Disease 2014; 9:239–71.
10. Elder DE, Bastian BC, Cree IA, et al. The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma: Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway. Archives of Pathology & Laboratory Medicine 2020; 144:500–22. [PubMed: 32057276]
11. Landi MT, Bauer J, Pfeiffer RM, et al. MC1R Germline Variants Confer Risk for BRAF-Mutant Melanoma. Science 2006; 313:521–2. [PubMed: 16809487]
12. Yeh I, Lang UE, Durieux E, et al. Combined activation of MAP kinase pathway and β-catenin signaling cause deep penetrating nevi. Nat Commun 2017; 8:644. [PubMed: 28935960]
13. Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet 2011; 43:1018–21. [PubMed: 21874003]
14. Wiesner T, Murali R, Fried I, et al. A Distinct Subset of Atypical Spitz Tumors is Characterized by BRAF Mutation and Loss of BAP1 Expression. The American Journal of Surgical Pathology 2012; 36:818–30. [PubMed: 22367297]
15. Yeh I, Mully TW, Wiesner T, et al. Ambiguous melanocytic tumors with loss of 3p21. Am J Surg Pathol 2014; 38:1088–95. [PubMed: 24705312]
16. Cohen JN, Joseph NM, North JP, et al. Genomic Analysis of Pigmented Epithelioid Melanocytomas Reveals Recurrent Alterations in PRKAR1A, and PRKCA Genes. The American Journal of Surgical Pathology 2017; 41:1333–46. [PubMed: 28796000]
17. Ardakani NM, Palmer DLG, Wood BA. BAP1 deficient malignant melanoma arising from the intradermal component of a congenital melanocytic naevus. Pathology 2015; 47:707–10. [PubMed: 26517632]
18. Cohen JN, Yeh I, Mully TW, et al. Genomic and Clinicopathologic Characteristics of PRKAR1A-inactivated Melanomas: Toward Genetic Distinctions of Animal-type Melanoma/ Pigment Synthesizing Melanoma. Am J Surg Pathol 2020. doi:10.1097/PAS.0000000000001458.
19. Reimer RR, Clark WH, Greene MH, et al. Precursor lesions in familial melanoma. A new genetic preneoplastic syndrome. JAMA 1978; 239:744–6. [PubMed: 621895]
20. Hussussian CJ, Struewing JP, Goldstein AM, et al. Germline p16 mutations in familial melanoma. Nat Genet 1994; 8:15–21. [PubMed: 7987387]
21. Hawkins WG, Busam KJ, Ben-Porat L, et al. Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. Ann Surg Oncol 2005; 12:207–13. [PubMed: 15827812]

22. Scolyer RA, Thompson JF. Desmoplastic Melanoma: A Heterogeneous Entity in Which Subclassification as “Pure” or “Mixed” May Have Important Prognostic Significance. Ann Surg Oncol 2005; 12:197–9. [PubMed: 15827808]
23. Shain AH, Garrido M, Botton T, et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. Nat Genet 2015; 47:1194–9. [PubMed: 26343386]
24. Gutzmer R, Herbst RA, Mommert S, et al. Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in desmoplastic neurotropic melanoma. Hum Genet 2000; 107:357–61. [PubMed: 11129335]
25. Davison JM, Rosenbaum E, Barrett TL, et al. Absence of V599E BRAF mutations in desmoplastic melanomas. Cancer 2005; 103:788–92. [PubMed: 15641040]
26. Spitz S Melanomas of Childhood. Am J Pathol 1948; 24:591–609. [PubMed: 18859360]
27. Bastian BC, LeBoit PE, Pinkel D. Mutations and copy number increase of HRAS in Spitz nevi with distinctive histopathological features. Am J Pathol 2000; 157:967–72. [PubMed: 10980135]
28. Botton T, Yeh I, Nelson T, et al. Recurrent BRAF kinase fusions in melanocytic tumors offer an opportunity for targeted therapy. Pigment Cell Melanoma Res 2013; 26:845–51. [PubMed: 23890088]
29. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. Nat Commun 2014; 5:3116. [PubMed: 24445538]
30. Yeh I, Botton T, Talevich E, et al. Activating MET kinase rearrangements in melanoma and Spitz tumours. Nat Commun 2015; 6:7174. [PubMed: 26013381]
31. Yeh I, Tee MK, Botton T, et al. NTRK3 kinase fusions in Spitz tumours. J Pathol 2016; 240:282–90. [PubMed: 27477320]
32. VandenBoom T, Quan VL, Zhang B, et al. Genomic Fusions in Pigmented Spindle Cell Nevus of Reed: The American Journal of Surgical Pathology 2018; :1.
33. Newman S, Fan L, Pribnow A, et al. Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas. Nature Medicine 2019; :1.
34. Busam KJ, Kutzner H, Cerroni L, Wiesner T. Clinical and pathologic findings of Spitz nevi and atypical Spitz tumors with ALK fusions. Am J Surg Pathol 2014; 38:925–33. [PubMed: 24698967]
35. Yeh I, de la Fouchardiere A, Pissaloux D, et al. Clinical, histopathologic, and genomic features of Spitz tumors with ALK fusions. Am J Surg Pathol 2015; 39:581–91. [PubMed: 25602801]
36. Yeh I, Busam KJ, McCalmont TH, et al. Filigree-like Rete Ridges, Lobulated Nests, Rosette-like Structures, and Exaggerated Maturation Characterize Spitz Tumors With NTRK1 Fusion. Am J Surg Pathol 2019; 43:737–46. [PubMed: 30844834]
37. Amin SM, Haugh AM, Lee CY, et al. A Comparison of Morphologic and Molecular Features of BRAF, ALK, and NTRK1 Fusion Spitzoid Neoplasms. Am J Surg Pathol 2017; 41:491–8. [PubMed: 27776007]
38. Houlier A, Pissaloux D, Masse I, et al. Melanocytic tumors with MAP3K8 fusions: report of 33 cases with morphological-genetic correlations. Mod Pathol 2020; 33:846–57. [PubMed: 31719662]
39. de la Fouchardière A, Tee MK, Peternel S, et al. Fusion partners of NTRK3 affect subcellular localization of the fusion kinase and cytomorphology of melanocytes. Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc 2020. doi:10.1038/s41379-020-00678-6.
40. Lu C, Zhang J, Nagahawatte P, et al. The Genomic Landscape of Childhood and Adolescent Melanoma. Journal of Investigative Dermatology 2015; 135:816–23. [PubMed: 25268584]
41. Lee CY, Sholl LM, Zhang B, et al. Atypical Spitzoid Neoplasms in Childhood: A Molecular and Outcome Study. The American Journal of Dermatopathology 2017; 39:181–6. [PubMed: 27391457]
42. Raghavan SS, Peternel S, Mully TW, et al. Spitz melanoma is a distinct subset of spitzoid melanoma. Mod Pathol 2020. doi:10.1038/s41379-019-0445-z.
43. Lee S, Barnhill RL, Dummer R, et al. TERT Promoter Mutations Are Predictive of Aggressive Clinical Behavior in Patients with Spitzoid Melanocytic Neoplasms. Scientific Reports 2015; 5:11200. [PubMed: 26061100]

44. Lallas A, Kyrgidis A, Ferrara G, et al. Atypical Spitz tumours and sentinel lymph node biopsy: a systematic review. The Lancet Oncology 2014; 15:e178–83. [PubMed: 24694641]
45. Paradela S, Fonseca E, Pita-Fernández S, Prieto V g. Spitzoid and non-spitzoid melanoma in children. A prognostic comparative study. Journal of the European Academy of Dermatology and Venereology 2013; 27:1214–21. [PubMed: 22928628]
46. Yeh I, Jorgenson E, Shen L, et al. Targeted genomic profiling of acral melanoma. J Natl Cancer Inst 2019. doi:10.1093/jnci/djz005.
47. Newell F, Wilmott JS, Johansson PA, et al. Whole-genome sequencing of acral melanoma reveals genomic complexity and diversity. Nature Communications 2020; 11:5259.
48. Arrington JH, Reed RJ, Ichinose H, Krementz ET. Plantar lentiginous melanoma: a distinctive variant of human cutaneous malignant melanoma. Am J Surg Pathol 1977; 1:131–43. [PubMed: 602975]
49. Coleman WP, Loria PR, Reed RJ, Krementz ET. Acral Lentiginous Melanoma. Arch Dermatol 1980; 116:773–6. [PubMed: 7396539]
50. McGovern VJ, Cochran AJ, Van der Esch EP, et al. The classification of malignant melanoma, its histological reporting and registration: a revision of the 1972 Sydney classification. Pathology 1986; 18:12–21. [PubMed: 3725419]
51. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005; 353:2135–47. [PubMed: 16291983]
52. Okamoto N, Aoto T, Uhara H, et al. A melanocyte–melanoma precursor niche in sweat glands of volar skin. Pigment Cell Melanoma Res 2014; 27:1039–50. [PubMed: 25065272]
53. North JP, Kageshita T, Pinkel D, et al. Distribution and significance of occult intraepidermal tumor cells surrounding primary melanoma. J Invest Dermatol 2008; 128:2024–30. [PubMed: 18323782]
54. Hintzsche JD, Gorden NT, Amato CM, et al. Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. Melanoma Res 2017; 27:189–99. [PubMed: 28296713]
55. Ablain J, Xu M, Rothschild H, et al. Human tumor genomics and zebrafish modeling identify SPRED1 loss as a driver of mucosal melanoma. Science 2018. doi:10.1126/science.aau6509.
56. Newell F, Kong Y, Wilmott JS, et al. Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. Nat Commun 2019; 10:3163. [PubMed: 31320640]
57. Lyu J, Wu Y, Li C, et al. Mutation scanning of BRAF, NRAS, KIT, and GNAQ/GNA11 in oral mucosal melanoma: a study of 57 cases. J Oral Pathol Med 2016; 45:295–301. [PubMed: 26399561]
58. Sheng X, Kong Y, Li Y, et al. GNAQ and GNA11 mutations occur in 9.5% of mucosal melanoma and are associated with poor prognosis. European Journal of Cancer 2016; 65:156–63. [PubMed: 27498141]
59. Bauer J, Curtin JA, Pinkel D, Bastian BC. Congenital melanocytic nevi frequently harbor NRAS mutations but no BRAF mutations. J Invest Dermatol 2007; 127:179–82. [PubMed: 16888631]
60. Ichii-Nakato N, Takata M, Takayanagi S, et al. High frequency of BRAFV600E mutation in acquired nevi and small congenital nevi, but low frequency of mutation in medium-sized congenital nevi. J Invest Dermatol 2006; 126:2111–8. [PubMed: 16691193]
61. Kinsler VA, O'Hare P, Bulstrode N, et al. Melanoma in congenital melanocytic naevi. Br J Dermatol 2017; 176:1131–43. [PubMed: 28078671]
62. Krengel S, Hauschild A, Schäfer T. Melanoma risk in congenital melanocytic naevi: a systematic review. Br J Dermatol 2006; 155:1–8.
63. Herron MD, Vanderhooft SL, Smock K, et al. Proliferative nodules in congenital melanocytic nevi: a clinicopathologic and immunohistochemical analysis. Am J Surg Pathol 2004; 28:1017–25. [PubMed: 15252307]
64. Bastian BC, Xiong J, Frieden IJ, et al. Genetic changes in neoplasms arising in congenital melanocytic nevi: differences between nodular proliferations and melanomas. Am J Pathol 2002; 161:1163–9. [PubMed: 12368190]
65. Moore AR, Ceraudo E, Sher JJ, et al. Recurrent activating mutations of G-protein-coupled receptor CYSLTR2 in uveal melanoma. Nat Genet 2016; 48:675–80. [PubMed: 27089179]

66. Möller I, Murali R, Müller H, et al. Activating cysteinyl leukotriene receptor 2 (CYSLTR2) mutations in blue nevi. Mod Pathol 2016. doi:10.1038/modpathol.2016.201.

67. van de Nes JAP, Koelsche C, Gessi M, et al. Activating CYSLTR2 and PLCB4 Mutations in Primary Leptomeningeal Melanocytic Tumors. Journal of Investigative Dermatology 2017; 137:2033–5. [PubMed: 28499758]

68. Goto K, Pissaloux D, Paindavoine S, et al. CYSLTR2-mutant Cutaneous Melanocytic Neoplasms Frequently Simulate 'Pigmented Epithelioid Melanocytoma,' Expanding the Morphologic Spectrum of Blue Tumors: A Clinicopathologic Study of 7 Cases. Am J Surg Pathol 2019. doi:10.1097/PAS.0000000000001299.

69. Johansson P, Aoude LG, Wadt K, et al. Deep sequencing of uveal melanoma identifies a recurrent mutation in PLCB4. Oncotarget 2015. doi:10.18632/oncotarget.6614.

70. Shain AH, Bagger MM, Yu R, et al. The genetic evolution of metastatic uveal melanoma. Nat Genet 2019; 51:1123–30. [PubMed: 31253977]

71. Harbour JW, Onken MD, Roberson EDO, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science 2010; 330:1410–3. [PubMed: 21051595]

72. Harbour JW, Roberson EDO, Anbunathan H, et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. Nature Genetics 2013. doi:10.1038/ng.2523.

73. Martin M, Maßhöfer L, Temming P, et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat Genet 2013; 45:933–6. [PubMed: 23793026]

74. White JS, McLean IW, Becker RL, et al. Correlation of comparative genomic hybridization results of 100 archival uveal melanomas with patient survival. Cancer Genet Cytogenet 2006; 170:29–39. [PubMed: 16965952]

75. Costa S, Byrne M, Pissaloux D, et al. 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. Am J Surg Pathol 2016; 40:368–77. [PubMed: 26645730]

76. Onken MD, Worley LA, Ehlers JP, Harbour JW. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. Cancer Res 2004; 64:7205–9. [PubMed: 15492234]

77. Field MG, Kuznetsov JN, Bussies PL, et al. BAP1 loss is associated with DNA methylomic repatterning in highly aggressive Class 2 uveal melanomas. Clin Cancer Res 2019. doi:10.1158/1078-0432.CCR-19-0366.

78. Tschentscher F, Hüsing J, Hölter T, et al. Tumor classification based on gene expression profiling shows that uveal melanomas with and without monosomy 3 represent two distinct entities. Cancer Res 2003; 63:2578–84. [PubMed: 12750282]

79. Raivio I Uveal melanoma in Finland. An epidemiological, clinical, histological and prognostic study. Acta Ophthalmol Suppl 1977; :1–64.

80. Kath R, Hayungs J, Bornfeld N, et al. Prognosis and treatment of disseminated uveal melanoma. Cancer 1993; 72:2219–23. [PubMed: 7848381]

81. Dai J, Tetzlaff MT, Schuchter LM, et al. Histopathologic and mutational analysis of a case of blue nevus-like melanoma. J Cutan Pathol 2016; 43:776–80. [PubMed: 27152652]

82. Adameyko I, Lallemend F, Aquino JB, et al. Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. Cell 2009; 139:366–79. [PubMed: 19837037]

83. Shain AH, Bastian BC. From melanocytes to melanomas. Nat Rev Cancer 2016; 16:345–58. [PubMed: 27125352]

84. Capper D, Preusser M, Habel A, et al. Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. Acta Neuropathologica 2011; 122:11–9. [PubMed: 21638088]

85. Ilie M, Long-Mira E, Funck-Brentano E, et al. Immunohistochemistry as a potential tool for routine detection of the NRAS Q61R mutation in patients with metastatic melanoma. Journal of the American Academy of Dermatology 2015; 72:786–93. [PubMed: 25659223]

86. Kakavand H, Walker E, Lum T, et al. BRAFV600E and NRASQ61L/Q61R mutation analysis in metastatic melanoma using immunohistochemistry: a study of 754 cases highlighting potential

pitfalls and guidelines for interpretation and reporting. Histopathology 2016; 69:680–6. [PubMed: 27151331]

87. Wiesner T, Lee W, Obenauf AC, et al. Alternative transcription initiation leads to expression of a novel ALK isoform in cancer. Nature 2015; 526:453–7. [PubMed: 26444240]
88. Couts KL, Bemis J, Turner JA, et al. ALK Inhibitor Response in Melanomas Expressing EML4-ALK Fusions and Alternate ALK Isoforms. Mol Cancer Ther 2018; 17:222–31. [PubMed: 29054983]
89. Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of NTRK Fusions. Am J Surg Pathol 2017; 41:1547–51. [PubMed: 28719467]
90. de la Fouchardière A, Caillot C, Jacquemus J, et al. β-Catenin nuclear expression discriminates deep penetrating nevi from other cutaneous melanocytic tumors. Virchows Arch 2019; 474:539–50. [PubMed: 30756182]
91. Clarke LE, Warf MB, Flake DD, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. J Cutan Pathol 2015; 42:244–52. [PubMed: 25727210]
92. Clarke LE, Pimentel JD, Zalaznick H, et al. Gene expression signature as an ancillary method in the diagnosis of desmoplastic melanoma. Human Pathology 2017; 70:113–20. [PubMed: 29079183]
93. Ko JS, Clarke LE, Minca EC, et al. Correlation of melanoma gene expression score with clinical outcomes on a series of melanocytic lesions. Hum Pathol 2019; 86:213–21. [PubMed: 30566894]
94. Reimann JDR, Salim S, Velazquez EF, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. Mod Pathol 2018; 31:1733–43. [PubMed: 29955141]
95. Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. JAMA Dermatol 2020; 156:1004–11. [PubMed: 32725204]
96. Shain AH, Yeh I, Kovalyshyn I, et al. The Genetic Evolution of Melanoma from Precursor Lesions. New England Journal of Medicine 2015; 373:1926–36. [PubMed: 26559571]

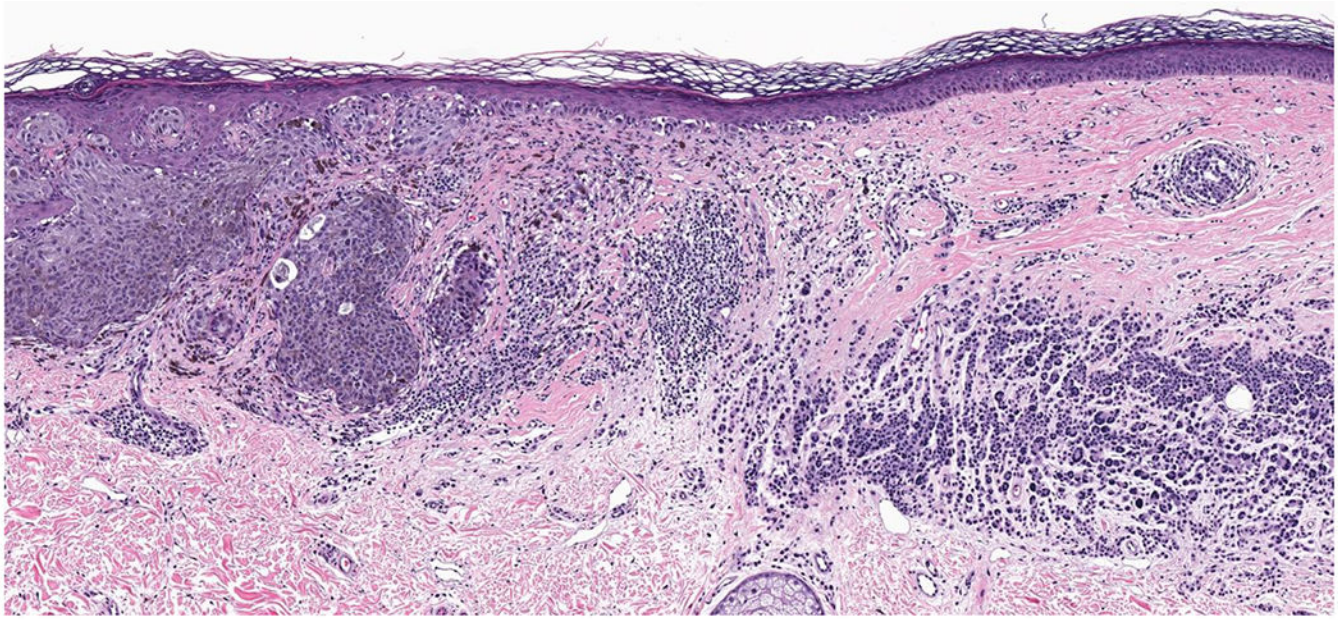

Figure 1. Low cumulative sun damage (low-CSD) melanoma arising from a nevus on the back of a 45-year-old man.

The nevus is in the mid-dermis and composed of small melanocytes that mature with descent in the dermis (lower right). The melanoma is composed of large nests of atypical melanocytes with abundant cytoplasmic pigment arrayed in the epidermis and superficial dermis (upper left). Note the minimal amount of solar elastosis in the dermis. Both the nevus and the melanoma harbor a BRAF V600E mutation while the melanoma alone harbors a TERT promoter mutation and copy number gains and losses characteristic of melanoma. This case was previously reported (case 2)[96]. Hematoxylin and eosin stained slide digitally imaged at 40x magnification.

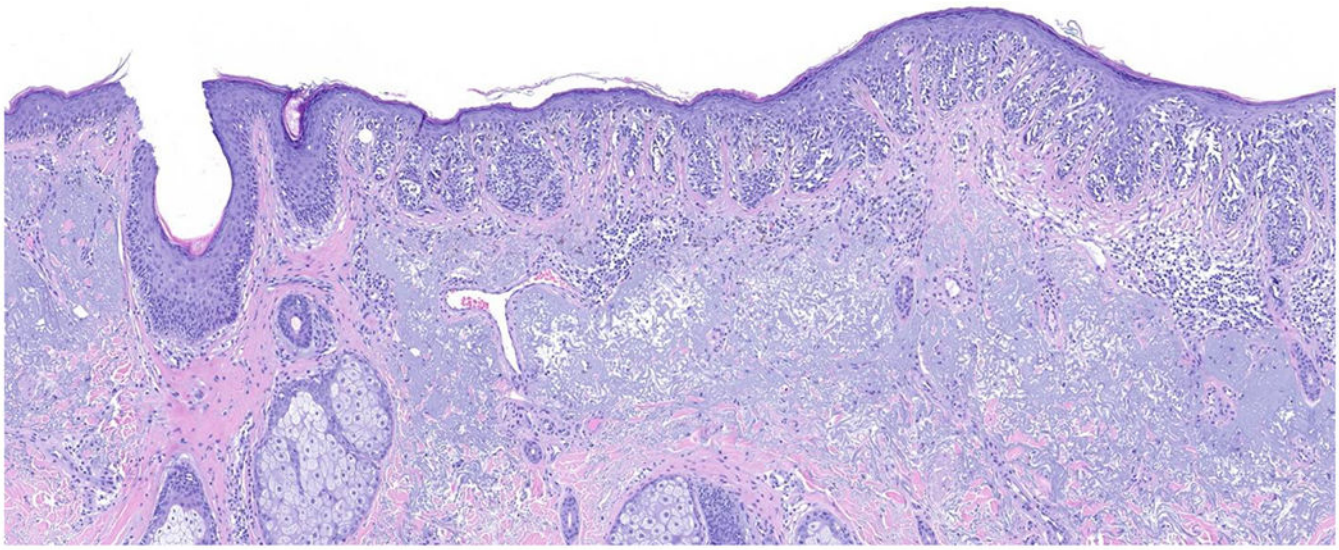

Figure 2. Melanoma in situ arising on skin with high cumulative sun damage (high-CSD).
Note the extent of solar elastosis in the dermis. There is a broad junctional proliferation of melanocytes arrayed predominantly as single cells limited to the lower epidermis (lentiginous growth pattern). Hematoxylin and eosin stained slide digitally imaged at 40x magnification.

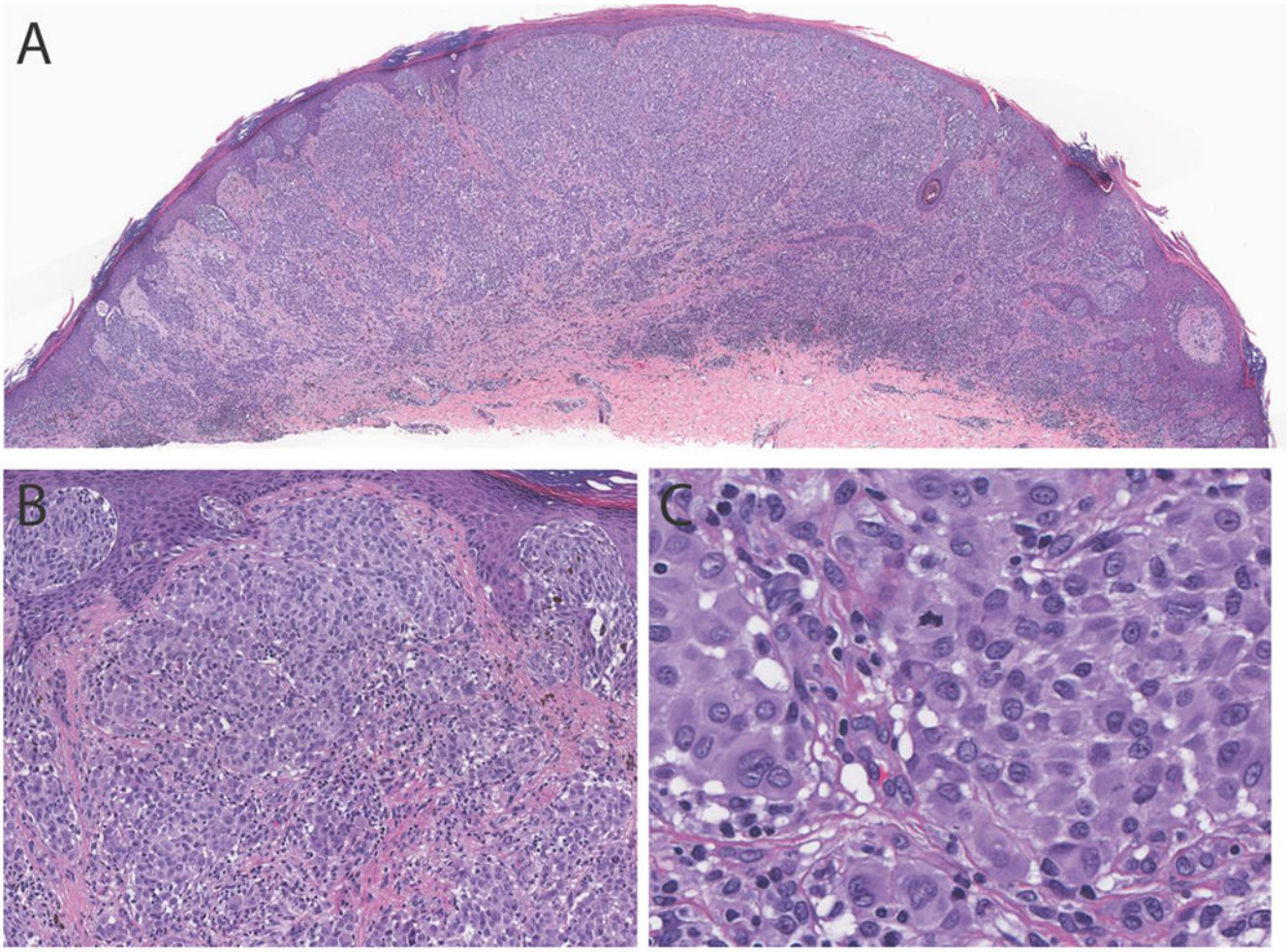

Figure 3. Spitz Melanoma with ALK fusion.

A. Low magnification view demonstrates an asymmetrically distributed compound melanocytic proliferation. Epidermal hyperplasia as is typical of Spitz nevus is present. **B.** Medium magnification view of the expansile dermal nests. **C.** High magnification view of melanocytes with expanded cytoplasm, atypical nuclei and mitotic activity. Spitzoid cytomorphology is present. This Spitz melanoma occurred on the thigh of a 23-year-old woman and demonstrated multiple copy number gains and losses including CDK4 amplification, and was previously reported (case 7)[42]. Hematoxylin and eosin stained slide digitally imaged at 40x magnification.

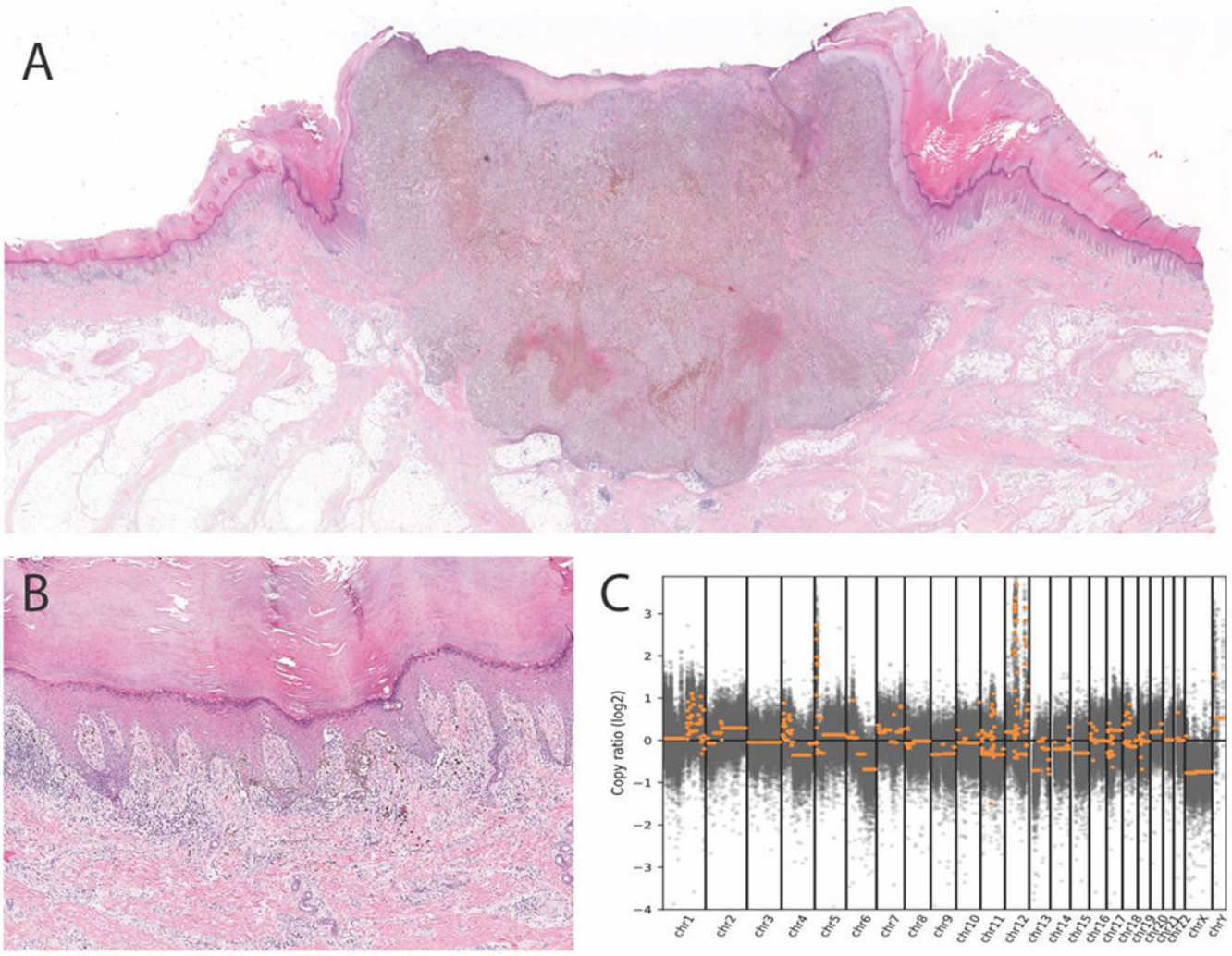

Figure 4. Acral melanoma arising within a broad patch of acral melanoma in situ.

A. Low magnification view demonstrates an ulcerated nodule of invasive melanoma arising within a melanoma in situ. **B.** Medium magnification view of the adjacent melanoma in situ shows the lentiginous growth pattern, similar to the high-CSD melanoma in situ in Figure 2. Hematoxylin and eosin stained slide digitally imaged at 40x magnification. **C.** The copy number profile shows the log2 ratio of the tumor genome compared to a normal reference on the y-axis along the genome on the x-axis. A log2 ratio of 0 represents a normal or unaltered copy number state. The acral melanoma depicted here has numerous copy number losses (chromosomal regions with log2ratio <−0.5) and gains (log2ratio>0.5) including focal amplifications of *TERT*, *CDK4* and *MDM2* (log2ratio>2).

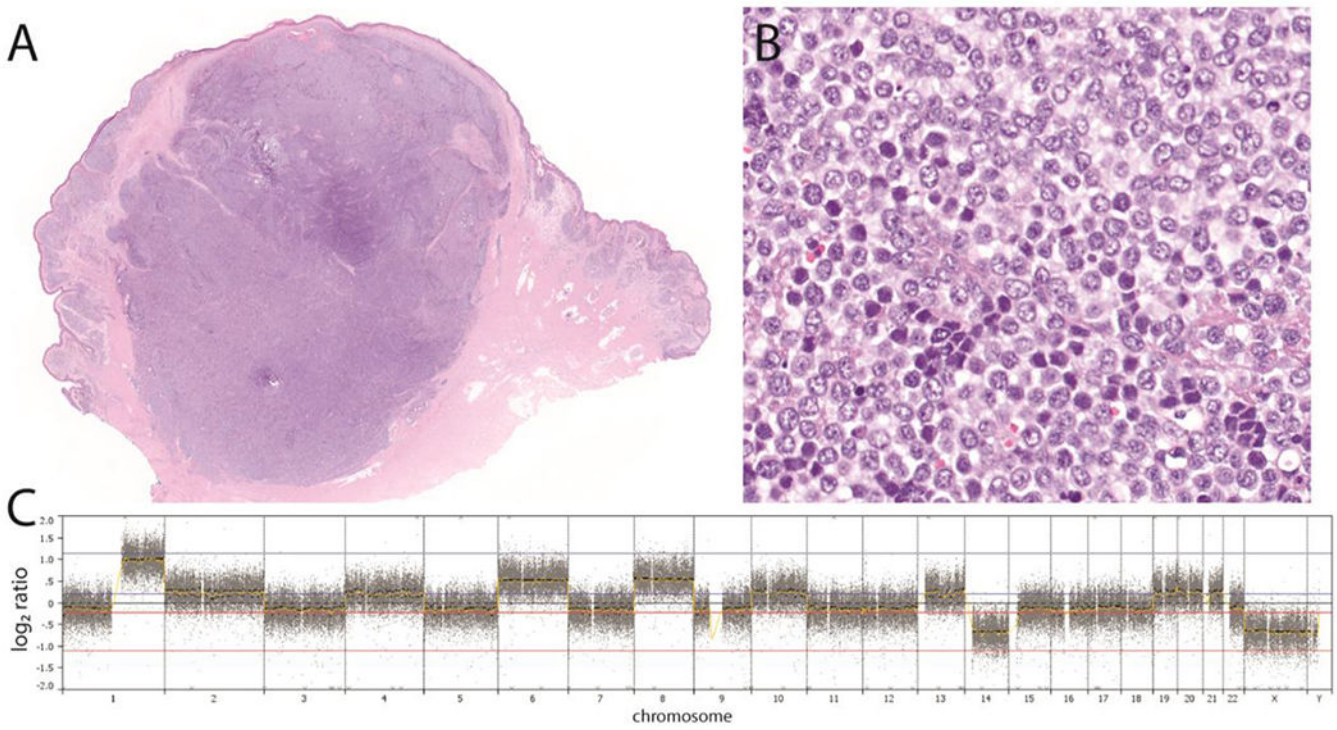

Figure 5. Pseudo-melanomatous atypical proliferative nodule arising in a congenital nevus.

A. Low magnification view shows a large nodule arising within a giant congenital nevus on the neck of a 3-year-old boy. **B.** Medium magnification view of the nodule demonstrates sheets of melanocytes with scant cytoplasm and nuclei with an open chromatin pattern. Pyknotic nuclei are present. Hematoxylin and eosin stained slide digitally imaged at 40x magnification. **C.** Copy number profile shows gains and losses of whole chromosomes. A notable exception is the copy number change of chromosome 1 which affects only the long chromosomal arm.

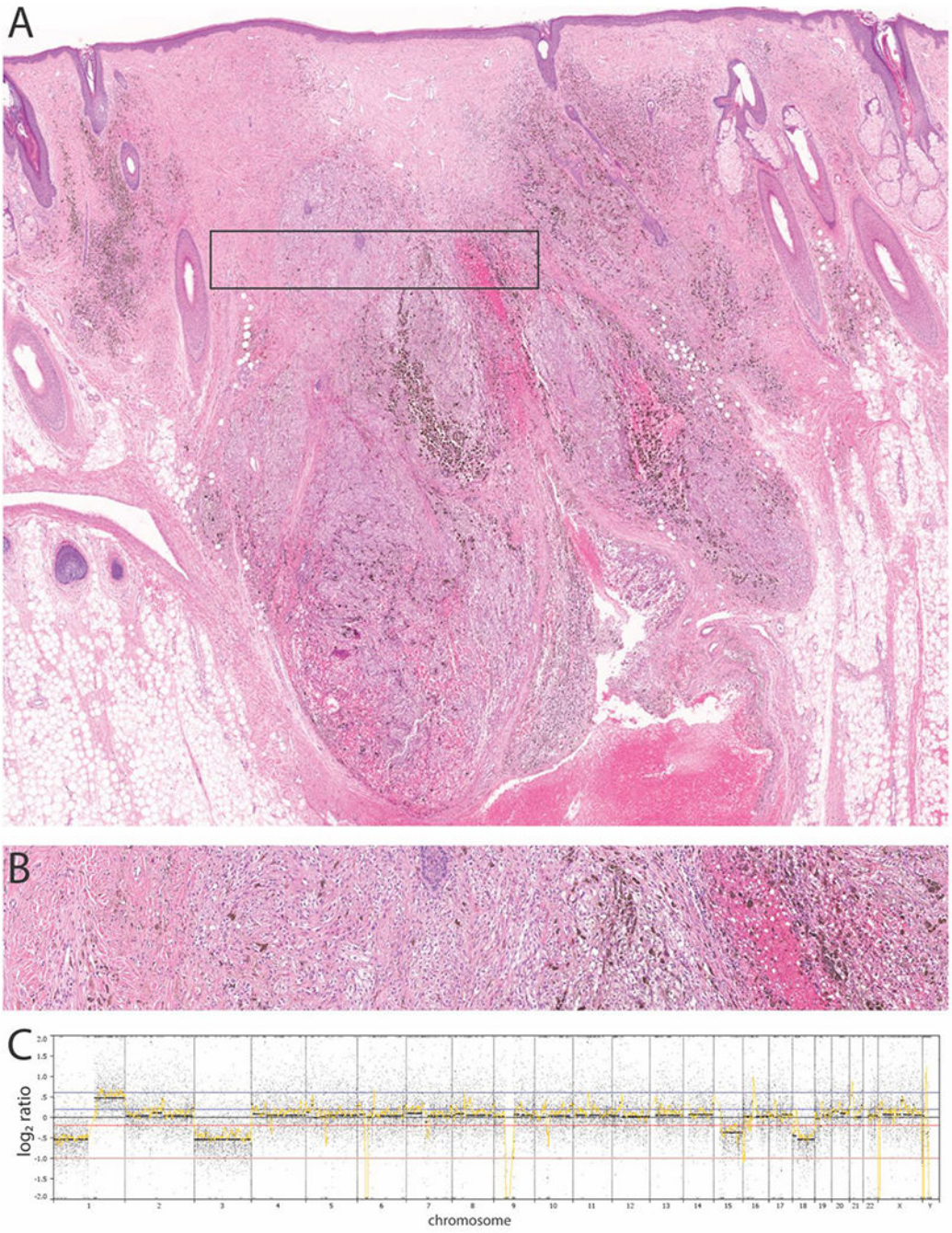

Figure 6. Melanoma arising within a blue nevus on the scalp of a 23-year-old man.

A. Low magnification view demonstrates a partly necrotic and hemorrhagic nodule that extends into the subcutis. The melanoma harbored GNA11 Q209L and SF3B1 R625C mutations. **B.** Medium magnification view of region outlined in **A** shows blue nevus on the left, melanoma centrally, and hemorrhage and necrosis on the right. Hematoxylin and eosin stained slide digitally imaged at 40x magnification. **C.** Copy number profile reveals copy gains and losses, including monosomy 3, characteristic of uveal and blue melanomas.

Table 1.

WHO pathways of melanoma development.

Adapted from [8].

	Low CSD melanoma (I)	**High CSD melanoma (II)**	**Desmoplastic melanoma (III)**	**Spitz melanoma (IV)**	**Acral melanoma (V)**	**Mucosal melanoma (VI)**	**Melanoma arising from congenital nevus (VII)**	**Melanoma arising in blue nevus (VIII) and uveal melanoma (iX)**
Nevus (common mutations)	Conventional nevus (BRAF V600E, NRAS)	No known benign precursor	No known benign precursor	Spitz nevus (HRAS, kinase fusion)	Minority arises from conventional nevus (BRAF V600E) Other benign precursors unknown	No known benign precursor	Congenital nevus (NRAS mutation, BRAF V600E)	Blue and uveal nevi (*GNAQ, GNA11, CYSTLTR1,* or *PLCB4* mutation)
Melanocytoma (common secondary mutations)	Deep penetrating melanocytoma (CTNNB1, APC) BAP1-inactivated melanocytoma PRKAR1A-inactivated melanocytoma Dysplastic nevus (TERT promoter)	Melanoma in situ (*NRAS* mutation, *BRAF* non-V600 mutation, *KIT* mutation)	Occasionally arises from melanoma in situ	Spitz melanocytoma (previously known as atypical Spitz tumor, CDKN2A inactivation)	Melanoma in situ (focal amplifications of *CCND1 and other genes*, *KIT* mutation)	Melanoma in situ (focal amplifications of *CCND1 and other genes*, *KIT* mutation)	Proliferative nodule (copy number alterations of whole chromosomes) Melanoma in situ	intermediate lesion unknown atypical blue nevus?
Mutations in Melanoma	*Mutation of TERT* promoter, *TP53*, inactivation of *CDKN2A, PTEN*	*Inactivation of NF1, CDKN2A, PTEN,* mutation *of TERT* promoter *TP53, RAC1*	*NRAS* mutation, *NF1* inactivation, amplification of *ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, MET, NFKBIE mutation, PIK3CA mutation, PTPN11 mutation*	*TERT* promoter mutation, *CDKN2A* inactivation	Amplification of *TERT, YAP1, EP300, CDK4, MDM2,* inactivation of *NF1, CDKN2A, ATRX,* mutation of *NRAS*	Amplification of *CDK4, MDM2,* inactivation of *SPRED1, NF1, ATRX,* mutation of *NRAS, SF3B1*	Mutation of *TERT* promoter	Inactivation of *BAP1,* mutation of *SF3B1, EIF1AX*