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Molecular pathology of skin adnexal tumors

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ABSTRACT

Aims

Tumors of the cutaneous adnexa arise from, or differentiate toward, structures in normal skin such as hair follicles, sweat ducts/glands, sebaceous glands, or a combination of these elements. This class of neoplasms includes benign tumors and highly aggressive carcinomas. Adnexal tumors often present as solitary sporadic lesions, but can herald the presence of an inherited tumor syndrome such as Muir-Torre Syndrome, Cowden Syndrome, or CYLD Cutaneous Syndrome. In contrast to squamous cell carcinoma and basal cell carcinoma, molecular changes in adnexal neoplasia have been poorly characterized, and there are few published reviews on the current state of knowledge.

Methods and Results

We reviewed findings in peer-reviewed literature on molecular investigations of cutaneous adnexal tumors published through June 2021.

Conclusions

Recent discoveries have revealed diverse oncogenic drivers and tumor suppressor alterations in this class of tumors, implicating pathways including Ras/MAPK, PI3K, YAP/TAZ, beta-catenin, and NF-kappaB. These observations have identified novel markers, such as NUT for poroma and

porocarcinoma, and PLAG1 for mixed tumors. Here, we provide a comprehensive overview and update of the molecular findings associated with adnexal tumors of the skin.

INTRODUCTION

Tumors of the cutaneous adnexa are lesions that arise from, or differentiate toward, structures in normal skin such as regions of hair follicles, sweat ducts/glands, sebaceous glands, or a combination of these elements.[1-3] This class of neoplasms includes benign tumors and highly aggressive carcinomas. Adnexal tumors often present as solitary sporadic lesions, but in some cases can herald the presence of an inherited tumor syndrome.[1-4] In contrast to cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), molecular changes in adnexal neoplasia have been poorly characterized. However, recent discoveries have revealed diverse oncogenic drivers and tumor suppressor alterations in this class of tumors.[3] Here, we provide a comprehensive overview and update of the molecular genetics and genomics associated with adnexal tumors of the skin.

Tumors with Sebaceous Differentiation

I. General Features

Sebaceous neoplasia exists on a spectrum from benign (sebaceous adenoma, sebaceoma) to malignant (sebaceous carcinoma, SC). These lesions present as a painless nodule with a predilection for the periocular region. SC has potential for recurrence and metastasis.[2, 4, 5]

II. Histopathology

Sebaceous differentiation is characterized by multiple clear cytoplasmic vacuoles lending a microvesicular appearance and scalloping of the nucleus. Sebaceous adenoma is well-circumscribed, with abnormal architecture but retained polarization (central sebocytes surrounded by unusually prominent peripheral basaloid germinative cells) (Fig 1A). Sebaceoma is circumscribed, with loss of polarization (mingling of sebocytes and basaloid cells) and >50%

basaloid cells (Fig 1B). In SC, malignant findings can include atypia, infiltrative growth, and pagetoid scatter within the overlying epidermis; sebaceous differentiation may be extensive, or focal and subtle (Fig 1C).[1, 2, 5]

III. Molecular Features

Sebaceous tumors can be sporadic or syndromic. Muir-Torre Syndrome (MTS) is a subtype of Lynch Syndrome/ Hereditary Non-Polyposis Colon Cancer associated with germline mutation of MMR genes including *MLH1, MSH2*, and *MSH6*, manifested by sebaceous tumors and internal carcinomas (Tables 1, 2).[5] Immunohistochemistry is highly sensitive for detecting loss of MMR protein expression related to MTS (Fig 1D), although this approach can display limited specificity for distinguishing sporadic from syndromic tumors (as low as 48%) when risk factors for MTS are not considered in case selection.[6] MUTYH-associated polyposis syndrome, associated with germline mutation of the DNA damage repair gene *MUTYH* (previously known as *MYH*), can also be associated with sebaceous neoplasms.[5, 7]

Sporadic cutaneous (extraocular) SC can be divided into 3 molecular categories: MMR-deficient, UV-damaged, and pauci-mutational (Table 2).[8] Highly recurrent mutations vary by subtype. *TP53* mutations are a frequent finding in MMR and UV-damaged tumors.[8, 9] Of note, ocular SC has similarities to extraocular SC but also displays distinct drivers in some tumors, including HPV or loss of *ZNF750*.[5, 10, 11]

Sporadic sebaceous adenomas and sebaceomas are less well characterized, but show similar aberrations to SC, including mutations of MMR genes, *HRAS/KRAS*, and/or *TP53* (Table 2).[9, 12]

Tumors with Follicular Differentiation

Fibrofolliculoma/Trichodiscoma

I. General Features

Fibrofolliculoma/trichodiscoma display hair follicle and stromal differentiation. The tumor classically presents on the nose, and can be associated with Birt-Hogg-Dube syndrome.[1, 4]

II. Histopathology

Tumors are characterized by a stromal nodule with collagenous, mucinous, and fibroblastic elements. In fibrofolliculoma, this is accompanied by a central distorted follicular infundibulum. Trichodiscoma consists predominantly of loose edematous stroma, often with an epidermal collarette or distorted sebaceous units at the periphery.[1]

III. Molecular Features

Fibrofolliculoma/trichodiscoma can be sporadic, or associated with Birt-Hogg Dube syndrome linked to germline mutation in the folliculin (*FLCN)* gene that regulates the mammalian target of rapamycin complex 1 (mTORC1) signaling cascade (Tables 1, 3).[1]

The spindle cell-predominant variant of trichodiscoma (SCPT) lacks association with Birt-Hogg-Dube syndrome, and can bear close resemblance to spindle cell lipoma.[13] Evaluation for *RB1* deletion (present in spindle cell lipoma, absent in SCPT) is helpful in this distinction.[14]

Pilomatricoma and Pilomatrical Carcinoma

I. General Features

Pilomatricoma and pilomatrical carcinoma differentiate toward hair matrix.[1] Tumors are typically found as large nodules on the head and neck (Fig 2A). Pilomatricoma is a relatively common tumor that usually arises on younger adults, whereas pilomatrical carcinoma is rare and tends to present after middle age. Multiple pilomatricomas may be associated with inherited tumor syndromes, as discussed below. Pilomatrical carcinoma can be associated with recurrence, metastasis, and death, although the risk of aggressive disease is unclear.[1-3]

II. Histopathology

Pilomatricoma is a well-circumscribed dermal tumor lesion composed of peripheral basophilic cells that transition into centrally located shadow cells, accompanied by frequent calcification and rupture reaction (Figure 2A, B). The “proliferating pilomatricoma” subtype can display cytologic atypia and high mitotic rate, but lacks infiltrative growth or significant tumor necrosis.

Pilomatrical carcinoma displays asymmetric, infiltrative growth; tumor necrosis; and a predominance of basophilic cells.[1-3]

III. Molecular Features

Pilomatricoma and pilomatrical carcinoma harbor *CTNNB1* mutations resulting in constitutive activation of the Wnt/beta-catenin pathway, with associated immunophenotypic findings (Table 3, Fig 2C-G).[15-17] Subclonal trisomy 18 (including the anti-apoptotic gene *BCL2*) has also been demonstrated.[18]

Familial multiple pilomatricoma can be associated with a germline gain-of-function missense variant of *PLCD1* that stimulates the protein kinase C pathway.[19] Multiple pilomatricomas may also arise in association with germline *APC* variants.[20] In mismatch repair deficiency or myotonic dystrophy, hypermutation phenotypes lead to secondary somatic mutations of *CTNNB1* that result in formation of multiple pilomatricomas (Table 3, Fig 2G).[21, 22]

Pilomatrical carcinomas usually arise *de novo* rather than from a preexisting pilomatricoma, and genetic events that might trigger progression of pilomatricoma to pilomatrical carcinoma have not been identified. Pilomatrical carcinosarcoma can show clonal similarity between epithelial and mesenchymal components.[23]

Trichoblastoma (including Trichoepithelioma) and Trichoblastic Carcinoma/Carcinosarcoma

I. General Features

Trichoblastoma recapitulates primitive hair follicle (hair germ) and follicular mesenchyme, and typically presents as a solitary nodule on the head and neck, or in association with nevus sebaceus. Malignant forms are rare, and include trichoblastic carcinoma and carcinosarcoma.[1, 3, 4]

II. Histopathology

Trichoblastoma is a circumscribed tumor in the deep dermis and/or subcutis, consisting of uniform basaloid cells arranged in retiform or racemiform patterns, accompanied by fine fibroblastic stroma (follicular mesenchyme). There is no significant tumor retraction or atypia,

unlike BCC. Variant morphologies include lymphadenoma, trichoepithelioma, and desmoplastic trichoepithelioma. Cells are positive for BerEp4, with scattered CK20-positive Merkel cells by immunohistochemistry in most cases.[1, 3]

Trichoblastic carcinoma displays diagnostic features of trichoblastoma accompanied by epithelial atypia including pleomorphism with hyperchromasia, mitotic figures, and crowding. Carcinosarcoma demonstrates malignant atypia of both epithelial and stromal components.[1, 2]

III. Molecular Features

Activating mutations in *HRAS* have been described in a subset (11%) of trichoblastomas (Table 3).[24] No classical *PTCH1* mutations have been found in conventional trichoblastoma, unlike in BCC.[3, 25]

The trichoepithelioma subtype can occur sporadically or in the setting of *CYLD* cutaneous syndrome and related entities (Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma), associated with germline variants in *CYLD* on chromosome 16q12-q13 (Tables 1, 3).[26-29] The product of *CYLD* is a deubiquitinase, the loss of which results in aberrant activation of the NF-κB signaling pathway.[30] Other syndromic associations include Rombo Syndrome (possibly associated with *MYH9* germline variants) and Bazex–Dupré–Christol Syndrome (*ACTRT1* germline variants).[31, 32] The dominant driver of sporadic trichoepithelioma remains unknown; occasional cases display somatic mutations in *PTCH1* or *CTNNB1* (Table 3).[33, 34]

Molecular findings in two cases of trichoblastic carcinosarcoma implicated inactivating tumor suppressor mutations (*TP53*, *CDKN2A*), and oncogene activation (*TERT* promoter mutation, and subclonal *CTNNB1* mutation) (Table 3).[35, 36]

Trichilemmoma and Trichilemmal Carcinoma

I. General Features

Trichilemmoma differentiates toward the hair follicle outer root sheath, and presents as a solitary lesion (most commonly on the central face) or within nevus sebaceus. Multiple trichilemmomas occur in Cowden syndrome (Table 1).[1, 3, 4]

Trichilemmal carcinomas tend to develop as solitary nodules on sun-exposed skin. Small studies suggest a favorable prognosis, with potential for rare metastasis.[37] The existence of trichilemmal carcinoma as a distinct entity from SCC has been debated.[1]

II. Histopathology

Trichilemmomas are lobular tumors connected to the epidermis, composed of monomorphic clear cells and squamous cells, bordered by peripheral palisading and well-defined hyaline basement membrane material. Trichilemmal carcinoma displays cytologic and architectural similarity to trichilemmoma, with additional findings including infiltrative growth, cytologic atypia, prominent nucleoli, and frequent mitoses.[3]

III. Molecular Features

Multiple trichilemmomas are included in the diagnostic criteria for Cowden syndrome, which is part of the *PTEN* hamartoma tumor syndrome associated with *PTEN* loss (10q23.31) resulting in disinhibition of the PI3-kinase pathway (Table 1).[3, 4] Trichilemmomas arising sporadically or within nevus sebaceus can harbor *HRAS* mutations, and lack alteration of *PTEN* (Table 3).[38, 39] Thus, PTEN protein expression can distinguish sporadic from syndromic cases.[39]

NGS profiling of 4 trichilemmal carcinomas revealed frequent *TP53* mutation, with variable additional alterations (Table 3).[40] With the exception of *TP53* mutation, these mutations were substantially different from recurrent changes previously described for SCC.[41]

Other Follicular Tumors

Molecular findings in additional follicular tumors, including basaloid follicular hamartoma, and trichilemmal cysts and tumors, are shown in Tables 1 and 3.[3, 4, 42-47] Of note, one case of malignant proliferating trichilemmal tumor displayed an identical *ALPK1* hotspot mutation to those described for spiradenomas (see below)[43, 48]. As of this writing, the molecular genetics of many follicular tumors (such as trichofolliculoma, pilar sheath acanthoma, melanocytic matricoma, and tumor of the follicular infundibulum) remain undescribed.

Sweat Gland Tumors

Eccrine sweat glands are distributed throughout the body, and consist of a deep secretory coil that secretes sweat through a long duct onto the epidermal surface. In contrast, apocrine sweat glands are confined to specific body sites (including axilla, perineum, and eyelids) and are associated with hair follicles. Of note, adnexal tumors with mixed follicular and glandular differentiation have been historically designated as apocrine, even in the absence of specific apocrine morphology.[1, 3]

Cylindroma, Spiradenoma, Spiradenocylindroma, and the malignancies arising from these entities

I. General Features

Cylindromas, spiradenomas, and spiradenocylindromas are solitary when sporadic, but can be multiple when associated with CYLD cutaneous syndrome.[4] Malignant forms are typically several centimeters in size and can grow rapidly from existing benign lesions. The prognosis of malignant lesions has been correlated to histologic grade, with low-grade tumors metastasizing less frequently than high-grade tumors.[2, 3, 49]

II. Histopathology

Spiradenomas are characterized by well-circumscribed round dermal nodules consisting of two cell populations (small monomorphous basaloid cells, and larger clear cells), prominent infiltrating lymphocytes, and intratumoral basement membrane material and lumen formation (Fig 3A). Cylindromas have numerous basaloid nests interconnecting in a "jigsaw puzzle" pattern, with basement membrane material surrounding individual nests (Fig 3B). Many lesions have hybrid features (spiradenocylindromas).[1, 3]

Diagnosis of malignant counterparts (cylindrocarcinoma, spiradenocarcinoma) relies upon identification of a benign precursor (Fig 3C). Diagnostic features include cytologic atypia (which may be low-grade or high-grade), mitotic figures, and (for spiradenocarcinoma) loss of lymphocytes within the tumor (Fig 3D). Ki67 is typically elevated in malignant lesions, and Myb expression may be lost.[1-3, 49]

III. Molecular Features

Cylindromas are associated with CYLD cutaneous syndrome and related syndromes (familial cylindromatosis, Brooke-Spiegler Syndrome), characterized by germline mutation of the *CYLD* gene resulting in aberrant activation of the NF-κB pathway (Table 1, Fig 3E-H).[29, 30, 50] Sporadic cylindromas can also harbor *CYLD* mutations (Table 4).[29, 48] Alternatively, *MYB-NFIB* fusions have been reported in cylindromas (Table 4, Fig 3F,G),[51] although the incidence is unclear as this finding was not further demonstrated in a subsequent genomic study.[48] *c-MYB (MYB)* is a transcription factor associated with regulation of cell cycle, cell survival, and differentiation.[52] Interestingly, Myb expression occurs in *CYLD*-mutant cylindromas lacking the MYB fusion,[48, 53] suggesting that Myb may act downstream of NF-kB in such tumors (Fig 3H).[54]Additional mutations have been described in the epigenetic modifiers *BCOR* and *DNMT3A*, that are more traditionally associated with hematologic malignancy.[48, 55]

Spiradenomas and spiradenocarcinomas are also associated with loss-of function mutations in *CYLD,* or gain-of-function mutations in *ALPK1*, resulting in NF-κB activation (Fig 3H).[48] *TP53* mutations are restricted to malignant tumors (spiradenocarcinoma/cylindrocarcinoma), supporting a role in progression from benign precursors (Table 4, Fig 3H).[48, 56-58]

Digital Papillary Adenocarcinoma

I. General Features

Digital Papillary Adenocarcinoma (DPA) is an adnexal neoplasm presenting as a slow-growing nodule in acral locations, with high rates of recurrence (up to 21%) and metastasis to lungs or lymph nodes (26-50% of cases).[1-3, 59]

II. Histopathology

DPA is composed of multiple dermal nodules of mild-to-moderately atypical cuboidal cells lining cystic spaces with papillary invaginations. Cribriform or solid growth may also be present.[1, 3]

III. Molecular Features

Driving mutations in DPA remain poorly understood. Somatic mutations in *BRAF* V600E[60, 61] and *TP53*[56, 62] occur in a minority of cases (Table 4).

Endocrine mucin-producing sweat gland carcinoma

I. General Features

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a low-grade neuroendocrine tumor, analogous to solid papillary carcinoma of the breast. EMPSGC presents as a slow-growing nodule that may clinically mimic a cyst. Metastasis has not been reported, however, there can be local recurrence with incomplete excision.[2, 63, 64]

II. Histopathology

Tumors are composed of nodules of low-grade neuroendocrine cells displaying varying architecture including solid, cystic, papillary, or cribriform patterning. There may be associated mucinous carcinoma. Immunohistochemically, the tumor is positive for markers including cytokeratins, horomone receptors (AR, ER, and PR), neuroendocrine markers, and MUC2.[1, 64, 65]

III. Molecular Features

A recent next generation sequencing study analyzed three cases of EMPSGC and identified heterogeneous mutations affecting DNA damage response/repair (e.g. *BRD4, PPP4R2*, and *RTEL1*) and tumor-suppressor pathway (e.g. *BRD4, TP53, TSC1*, and *LATS2*) (Table 4).[65] A separate case series described deletion on chromosome 6.[66] Other limited molecular studies have been negative for driver alterations.[67, 68]

Hidradenoma and Hidradenocarcinoma

I. General Features

Hidradenoma and hidradenocarcinoma are tumors with sweat duct secretory features. The typical presentation is as a solitary nodule.[4] Malignant transformation is rare. Metastasis has been reported for both low and high-grade hidradenocarcinomas.[1-3]

II. Histopathology

Hidradenoma is a dermal tumor with solid and cystic configuration, composed of variable proportions of clear, polygonal, oncocytic, epidermoid, squamoid, and mucinous cells. There is ductal formation and associated hyalinized stroma. When significant atypia, infiltration, and mitoses are present, the lesion is best characterized as hidradenocarcinoma.[1, 3]

III. Molecular Features

Approximately half of hidradenomas harbor the t(11;19) translocation resulting in the fusion of *CRTC1* (previously known as *TORC1* or *MECT1*) and *MAML2* (Table 4).[69, 70] *CRTC1-MAML2* fusions activate the cAMP Response Element Binding Protein (CREB) pathway to promote tumorigenesis. Fusions of *CRTC3-MAML2* or *EWSR1-POU5F1* have also been described.[71, 72] The poroid variant of hidradenoma displays genetic features of poroma (discussed below).

Hidradenocarcinomas can also display *CRTC1-MAML2* fusions.[73] In addition, *AKT1* mutation, *PIK3CA* mutation, and *ERBB2* (Her2/neu) amplification have been described in single cases.[56, 73] *TP53* mutations occur, although these are not universal (Table 4).[56, 58, 62, 73, 74]

Microcystic Adnexal Carcinoma (MAC)

I. General Features

Microcystic adnexal carcinoma (MAC) is a malignant sweat duct neoplasm usually presenting as a firm plaque. Tumors are locally aggressive, with frequent recurrence after excision, but rarely metastasize. Although multiple tumors can occur, a syndromic association has not been demonstrated.[1-4]

II. Histopathology

MAC is an infiltrative carcinoma with superficial keratinizing cysts, deeper infiltrative bilayered strands with sweat duct differentiation, minimal cytologic atypia, and fibrotic to hyalinized stroma.[1-3]

III. Molecular Features

In a study of 18 tumors, approximately 39% of MACs harbored mutually exclusive alterations including either inactivation in *TP53* (22%), or insertions affecting *JAK1* (17%) associated with increased phospho-STAT3 expression by immunohistochemistry.[75] Case reports have also described alterations of genes including *TP53, CDKN2A,* and *CDKN2B*,[74, 76] and deletion of 6q (Table 4).[77] There is no known syndromic association for multiple MACs; however, benign proliferations similar to MAC have been linked to elastin abnormalities and germline *MYH9* variants.[31, 78]

Poroma and Porocarcinoma

I. General Features

Poromas display dermal sweat duct differentiation. Clinically, poromas are solitary papules with a sessile, pedunculated, or papillomatous appearance.[4] Porocarcinomas are often ulcerated nodules, that present *de novo* or as transformation of an existing poroma. Porocarcinomas carry significant risk of local recurrence/regional metastasis (up to 20%) and distant metastasis (up to 12%).[1-3, 79, 80]

II. Histopathology

Poromas are nodular tumors with broad connection to the epidermis, composed of two cell types: poroid and cuticular cells (Fig 4A, B). Poroid cells are small, monomorphous, round cells with uniform ovoid nuclei and little cytoplasm. Cuticular cells have a centrally placed nucleus with abundant eosinophilic cytoplasm. Ductal differentiation manifests as small vacuoles or true ducts. Variants include purely dermal tumors (dermal duct tumor), intraepidermal lesions (hidroacanthoma simplex), or those with hybrid features with hidradenoma (poroid hidradenoma). Porocarcinomas demonstrate similar morphology, accompanied by infiltration and cytologic atypia.[1-3]

Molecular Features

Poromas and porocarcinomas harbor activating mutations in *HRAS*,[81, 82] or fusions of YAP/TAZ including *YAP1-MAML2, YAP1-NUTM1,* or (rarely) *WWTR1-NUTM1* fusions (Table 4).[83-85] *YAP* is a key transcriptional regulator controlling essential functions such as proliferation and

apoptosis, that is negatively regulated by the Hippo pathway.[86, 87] Notably, immunohistochemical expression of the fusion partner NUT represents a highly specific marker for poromas and porocarcinomas, although sensitivity is limited for classic poromas (approximately 17-20%), with higher sensitivity in poroid hidradenomas (93%) and porocarcinomas (50-58%)(Fig 4C).[83-85, 88, 89]

Porocarcinomas have also been reported to harbor other oncogene mutations (including *EGFR, ERBB2, FGFR3, KRAS, NRAS,* or *PIK3CA*), or *EWSR1* rearrangement (Table 4).[74, 81-83, 90] Mutations in tumor suppressor genes (*TP53*, *RB1*, *CDKN2A*) may be restricted to porocarcinomas rather than poromas (Table 4, Fig 4D), although reports have been mixed.[81-83] Aberrant immunohistochemical expression of p53, Rb, and p16 is a sensitive and specific finding for porocarcinoma relative to poroma.[91]

Syringocystadenoma Papilliferum and Syringocystadenocarcinoma Papilliferum

I. General Features

Syringocystadenoma papilliferum (SCAP) may occur in isolation or in association with nevus sebaceus (discussed below). Clinically, SCAPs are solitary papules, predominantly on the head and neck.[4] Malignant lesions (syringocystadenocarcinoma papilliferum, or verrucous carcinoma arising in SCAP) are rare. Complete surgical excision of carcinomas is typically curative.[1, 3]

II. Histopathology

Syringocystadenoma papilliferum (SCAP) is a benign apocrine neoplasm associated with the epidermis or hair follicle, composed of papillary and cystic structures formed by a double layer of columnar luminal cells and ovoid basal cells (Fig 5A). The surrounding stroma is rich in plasma cells (Fig 5B). There may be overlying verrucous epidermal hyperplasia.[1, 3]

Syringocystadenocarcinoma papilliferum are similar to SCAP, with overtly malignant cytologic features including atypia, mitoses, loss of polarity, and areas of infiltrative growth.[1, 3]

III. Molecular Features

Mutations of *BRAF V600E* (approximately 52%)[24, 92] and *HRAS* (approximately 26%)[24, 93, 94] are the most commonly identified drivers associated with SCAP (Table 4). *BRAF* V600E mutation is detectable in both the glandular and verrucous (keratinocytic) components of the tumor (Fig 5C).[95] A SCAP arising within nevus sebaceus was found to harbor a *PIK3CA* mutation not present in the precursor lesion.[93]

Genomic events in malignant tumors are poorly understood. Verrucous carcinomas arising in SCAP demonstrate corresponding *BRAF* mutations.[96] One metastatic tumor classified as syringocystadenocarcina papilliferum demonstrated multiple mutations including *TP53* and *PIK3CA* E453K (Table 4),[97] although *TP53* mutation may not be consistently present in these tumors.[58]

Other Sweat Gland Tumors

Molecular findings in additional sweat gland tumors are listed in Table 4, including adenoid cystic carcinoma, apocrine carcinoma, hidradenoma papilliferum, hidrocystoma, mammary analog secretory carcinoma, mucoepidermoid carcinoma, tubular adenoma, signet-ring/histiocytoid carcinoma, syringoma, and syringofibroadenoma.[1-4, 98-102] As of this writing, there are no well-characterized genomic aberrations in many sweat gland neoplasms, including mucinous carcinoma, cribriform carcinoma, or squamoid eccrine ductal carcinoma.

TUMORS WITH MIXED DIFFERENTIATION

Although many adnexal tumors can display mixed differentiation in a subset of cases, multilineage differentiation is a consistent feature of mixed tumor and nevus sebaceus (Table 5).

Mixed tumor (chondroid syringoma) and malignant mixed tumor

I. General Features

Mixed tumor (chondroid syringoma) is a benign neoplasm analogous to pleomorphic adenoma of the salivary gland. The tumor presents as a large solitary nodule, with no predilection for

anatomic location. Benign mixed tumor has an uneventful course. Malignant mixed tumors are rare, arise from benign mixed tumors, and have metastatic potential.[1, 3, 4]

II. Histopathology

Apocrine mixed tumors have a prominent glandular component, arranged as tubules and cysts with two cell layers, as well as myoepithelial and mesenchymal (chondromyxoid) components (Fig 6A, B). Major subtypes are eccrine mixed tumor (EMT) and apocrine mixed tumor (AMT). EMTs have simple ductal structures in a chondromyxoid stroma, whereas glands are larger and more extensive in AMT. Malignant mixed tumor arises from a pre-existing benign mixed tumor, and can resemble adenocarcinoma, myoepithelial carcinoma, sarcomatoid carcinoma, or not otherwise specified (NOS).[1, 3]

III. Molecular Features

Benign and malignant cutaneous mixed tumors harbor *PLAG1* rearrangements (Table 5),[103] with potentially different fusion partners (*NDRG1* and *TRPS1*)[104] from *PLAG1* fusions in pleomorphic adenomas in the salivary gland.[105] PLAG1 immunohistochemistry can thus be useful for identifying mixed tumors in cases with partial sampling or poor differentiation (Fig 6C)[103, 105] although this marker may be less sensitive for the eccrine subtype.[106] *PFH1-TFE3* fusion was reported in one case of malignant mixed tumor (Table 5), a fusion also associated with ossifying fibromyxoid tumors.[107]

CONCLUSION

Our understanding of the molecular alterations in cutaneous adnexal neoplasms has advanced greatly in recent years. However, the rarity and diversity of these tumors has made large-scale definitive studies challenging; for many tumor types, molecular data is based only on case reports or small series. Further, there is little understanding of germline and somatic events related to adnexal tumorigenesis in populations of non-European descent. Finally, additional investigations of tumor progression, and functional characterization of potential driver genes, are necessary to place genomic findings in biological context. Together with the many recent

advances described in this review, such studies will significantly improve diagnosis, prognostication, and management of these challenging tumors.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Kazakov D, McKee P, Michal M, and Kacerovska D, *Cutaneous Adnexal Tumors*. 2012, Lippincott Williams and Wilkins: Philadelphia, United States.
2. Elder D E, Massi D, Scolyer R A, and Willemze R, eds. *WHO Classification of Skin Tumors*. 4 ed. 2018, International Agency for Research on Cancer: Lyon, France.
3. Hile G and Harms P W. Update on molecular genetic alterations of cutaneous adnexal neoplasms. *Surgical Pathology Clinics* 2021; 14: 251-272.
4. Bolognia J L, Schaffer J V, and Cerroni L, eds. *Dermatology*. 2018, Elsevier: China.
5. North J P. Molecular Genetics of Sebaceous Neoplasia. *Surg Pathol Clin* 2021; 14: 273-284.
6. Roberts M E, Riegert-Johnson D L, Thomas B C et al. Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms. *J Genet Couns* 2013; 22: 393-405.

7. Ponti G, Ponz de Leon M, Maffei S et al. Attenuated familial adenomatous polyposis and Muir-Torre syndrome linked to compound biallelic constitutional MYH gene mutations. *Clin Genet* 2005; 68: 442-7.
8. North J P, Golovato J, Vaske C J et al. Cell of origin and mutation pattern define three clinically distinct classes of sebaceous carcinoma. *Nat Commun* 2018; 9: 1894.
9. Harvey N T, Tabone T, Erber W, and Wood B A. Circumscribed sebaceous neoplasms: a morphological, immunohistochemical and molecular analysis. *Pathology* 2016; 48: 454-62.
10. Tetzlaff M T, Curry J L, Ning J et al. Distinct Biological Types of Ocular Adnexal Sebaceous Carcinoma: HPV-Driven and Virus-Negative Tumors Arise through Nonoverlapping Molecular-Genetic Alterations. *Clin Cancer Res* 2019; 25: 1280-1290.
11. Tetzlaff M T, Singh R R, Seviour E G et al. Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. *J Pathol* 2016; 240: 84-95.
12. Georgeson P, Walsh M D, Clendenning M et al. Tumor mutational signatures in sebaceous skin lesions from individuals with Lynch syndrome. *Mol Genet Genomic Med* 2019; 7: e00781.
13. Kutzner H, Requena L, Rutten A, and Mentzel T. Spindle cell predominant trichodiscoma: a fibrofolliculoma/trichodiscoma variant considered formerly to be a neurofollicular hamartoma: a clinicopathological and immunohistochemical analysis of 17 cases. *Am J Dermatopathol* 2006; 28: 1-8.
14. Michalova K, Kutzner H, Steiner P et al. Spindle Cell Predominant Trichodiscoma or Spindle Cell Lipoma With Adnexal Induction? A Study of 25 Cases, Revealing a Subset of Cases With RB1 Heterozygous Deletion in the Spindle Cell Stroma. *Am J Dermatopathol* 2019; 41: 637-643.
15. Chan E F, Gat U, McNiff J M, and Fuchs E. A common human skin tumour is caused by activating mutations in beta-catenin. *Nat Genet* 1999; 21: 410-3.
16. Tumminello K and Hosler G A. CDX2 and LEF-1 expression in pilomatrical tumors and their utility in the diagnosis of pilomatrical carcinoma. *Journal of Cutaneous Pathology* 2018; 45: 318-324.
17. Lazar A J, Calonje E, Grayson W et al. Pilomatrix carcinomas contain mutations in CTNNB1, the gene encoding beta-catenin. *J Cutan Pathol* 2005; 32: 148-57.
18. Agoston A T, Liang C, Richkind K E, Fletcher J A, and Vargas S O. Trisomy 18 is a consistent cytogenetic feature in pilomatricoma. *Mod Pathol* 2010; 23: 1147.

19. Liu K, Luo J, Ma T et al. Germline Mutation of PLCD1 Contributes to Human Multiple Pilomatricomas through Protein Kinase D/Extracellular Signal-Regulated Kinase1/2 Cascade and TRPV6. *J Invest Dermatol* 2021; 141: 533-544.
20. Trufant J, Kurz W, Frankel A et al. Familial multiple pilomatrixomas as a presentation of attenuated adenomatosis polyposis coli. *J Cutan Pathol* 2012; 39: 440-3.
21. Chmara M, Wernstedt A, Wasag B et al. Multiple pilomatricomas with somatic CTNNB1 mutations in children with constitutive mismatch repair deficiency. *Genes Chromosomes Cancer* 2013; 52: 656-64.
22. Rubben A, Wahl R U, Eggermann T, Dahl E, Ortiz-Bruchle N, and Cacchi C. Mutation analysis of multiple pilomatricomas in a patient with myotonic dystrophy type 1 suggests a DM1-associated hypermutation phenotype. *PLoS One* 2020; 15: e0230003.
23. Luong T M H, Akazawa Y, Mussazhanova Z et al. Cutaneous pilomatrical carcinosarcoma: a case report with molecular analysis and literature review. *Diagn Pathol* 2020; 15: 7.
24. Shen A S, Peterhof E, Kind P et al. Activating mutations in the RAS/mitogen-activated protein kinase signaling pathway in sporadic trichoblastoma and syringocystadenoma papilliferum. *Hum Pathol* 2015; 46: 272-6.
25. Hafner C, Schmiemann V, Ruetten A et al. PTCH mutations are not mainly involved in the pathogenesis of sporadic trichoblastomas. *Hum Pathol* 2007; 38: 1496-500.
26. Hu G, Onder M, Gill M et al. A novel missense mutation in CYLD in a family with Brooke-Spiegler syndrome. *J Invest Dermatol* 2003; 121: 732-4.
27. Salhi A, Bornholdt D, Oeffner F et al. Multiple familial trichoepithelioma caused by mutations in the cylindromatosis tumor suppressor gene. *Cancer Res* 2004; 64: 5113-7.
28. Zhang X J, Liang Y H, He P P et al. Identification of the cylindromatosis tumor-suppressor gene responsible for multiple familial trichoepithelioma. *J Invest Dermatol* 2004; 122: 658-64.
29. Bignell G R, Warren W, Seal S et al. Identification of the familial cylindromatosis tumour-suppressor gene. *Nat Genet* 2000; 25: 160-5.
30. Brummelkamp T R, Nijman S M, Dirac A M, and Bernards R. Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-kappaB. *Nature* 2003; 424: 797-801.
31. Fewings E, Ziemer M, Hortnagel K et al. Malta (MYH9 Associated Elastin Aggregation) Syndrome: Germline Variants in MYH9 Cause Rare Sweat Duct Proliferations and Irregular Elastin Aggregations. *J Invest Dermatol* 2019; 139: 2238-2241 e6.

32. Park H S, Papanastasi E, Blanchard G et al. ARP-T1-associated Bazex-Dupre-Christol syndrome is an inherited basal cell cancer with ciliary defects characteristic of ciliopathies. *Commun Biol* 2021; 4: 544.
33. Vorechovsky I, Unden A B, Sandstedt B, Toftgard R, and Stahle-Backdahl M. Trichoepitheliomas contain somatic mutations in the overexpressed PTCH gene: support for a gatekeeper mechanism in skin tumorigenesis. *Cancer Res* 1997; 57: 4677-81.
34. Kazakov D V, Sima R, Vanecek T et al. Mutations in exon 3 of the CTNNB1 gene (beta-catenin gene) in cutaneous adnexal tumors. *Am J Dermatopathol* 2009; 31: 248-55.
35. Kim C, Brown A, and Osipov V. Trichoblastic carcinosarcoma in a 34-year-old woman with histopathologic and molecular analysis, including re-demonstration of a CDKN2A p.(R58*) mutation. *J Cutan Pathol* 2021; 48: 334-339.
36. Giang J, Biswas A, Mooyaart A L, Groenendijk F H, Dikrama P, and Damman J. Trichoblastic carcinosarcoma with panfollicular differentiation (panfollicular carcinosarcoma) and CTNNB1 (beta-catenin) mutation. *J Cutan Pathol* 2021; 48: 309-313.
37. Zhuang S M, Zhang G H, Chen W K et al. Survival study and clinicopathological evaluation of trichilemmal carcinoma. *Mol Clin Oncol* 2013; 1: 499-502.
38. Tsai J H, Huang W C, Jhuang J Y et al. Frequent activating HRAS mutations in trichilemmoma. *Br J Dermatol* 2014; 171: 1073-7.
39. Al-Zaid T, Ditelberg J S, Prieto V G et al. Trichilemmomas show loss of PTEN in Cowden syndrome but only rarely in sporadic tumors. *Journal of Cutaneous Pathology* 2012; 39: 493-499.
40. Ha J H, Lee C, Lee K S et al. The molecular pathogenesis of Trichilemmal carcinoma. *BMC Cancer* 2020; 20: 516.
41. Pickering C R, Zhou J H, Lee J J et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res* 2014; 20: 6582-92.
42. Horer S, Marrakchi S, Radner F P W et al. A Monoallelic Two-Hit Mechanism in PLCD1 Explains the Genetic Pathogenesis of Hereditary Trichilemmal Cyst Formation. *J Invest Dermatol* 2019; 139: 2154-2163 e5.
43. Gallant J N, Sewell A, Almodovar K et al. Genomic landscape of a metastatic malignant proliferating tricholemmal tumor and its response to PI3K inhibition. *NPJ Precis Oncol* 2019; 3: 5.
44. Besagni F, Dika E, Ricci C et al. Basaloid follicular hamartomas in pediatric Basal Cell Nevus Syndrome: A diagnostic challenge. *J Dermatol* 2021.

45. Seo S H, Lee S E, and Kim S C. Happle-Tinschert Syndrome: A Case Report of Unilateral Segmentally Arranged Basaloid Follicular Hamartoma with Scoliosis and Review of Literature. *Ann Dermatol* 2020; 32: 159-163.
46. Shevchenko A, Durkin J R, and Moon A T. Generalized basaloid follicular hamartoma syndrome versus Gorlin syndrome: A diagnostic challenge. *Pediatr Dermatol* 2018; 35: e396-e397.
47. Grachtchouk V, Grachtchouk M, Lowe L et al. The magnitude of hedgehog signaling activity defines skin tumor phenotype. *EMBO J* 2003; 22: 2741-51.
48. Rashid M, van der Horst M, Mentzel T et al. ALPK1 hotspot mutation as a driver of human spiradenoma and spiradenocarcinoma. *Nat Commun* 2019; 10: 2213.
49. van der Horst M P, Marusic Z, Hornick J L, Luzar B, and Brenn T. Morphologically low-grade spiradenocarcinoma: a clinicopathologic study of 19 cases with emphasis on outcome and MYB expression. *Mod Pathol* 2015; 28: 944-53.
50. Verhoef S, Schrander-Stumpel C T, Vuzevski V D et al. Familial cylindromatosis mimicking tuberous sclerosis complex and confirmation of the cylindromatosis locus, CYLD1, in a large family. *J Med Genet* 1998; 35: 841-5.
51. Fehr A, Kovacs A, Loning T, Frierson H, Jr., van den Oord J, and Stenman G. The MYB-NFIB gene fusion-a novel genetic link between adenoid cystic carcinoma and dermal cylindroma. *J Pathol* 2011; 224: 322-7.
52. Ramsay R G and Gonda T J. MYB function in normal and cancer cells. *Nat Rev Cancer* 2008; 8: 523-34.
53. Rajan N, Andersson M K, Sinclair N et al. Overexpression of MYB drives proliferation of CYLD-defective cylindroma cells. *J Pathol* 2016; 239: 197-205.
54. Corda G and Sala A. Cutaneous cylindroma: it's all about MYB. *J Pathol* 2016; 239: 391-3.
55. Davies H R, Hodgson K, Schwalbe E et al. Epigenetic modifiers DNMT3A and BCOR are recurrently mutated in CYLD cutaneous syndrome. *Nat Commun* 2019; 10: 4717.
56. Le L P, Dias-Santagata D, Pawlak A C et al. Apocrine-eccrine carcinomas: molecular and immunohistochemical analyses. *PLoS One* 2012; 7: e47290.
57. Kazakov D V, Grossmann P, Spagnolo D V et al. Expression of p53 and TP53 mutational analysis in malignant neoplasms arising in preexisting spiradenoma, cylindroma, and spiradenocylindroma, sporadic or associated with Brooke-Spiegler syndrome. *Am J Dermatopathol* 2010; 32: 215-221.

58. Biernat W, Peraud A, Wozniak L, and Ohgaki H. p53 mutations in sweat gland carcinomas. *Int J Cancer* 1998; 76: 317-20.
59. Suchak R, Wang W L, Prieto V G et al. Cutaneous digital papillary adenocarcinoma: a clinicopathologic study of 31 cases of a rare neoplasm with new observations. *Am J Surg Pathol* 2012; 36: 1883-91.
60. Trager M H, Jurkiewicz M, Khan S, Niedt G W, Geskin L J, and Carvajal R D. A Case Report of Papillary Digital Adenocarcinoma With BRAFV600E Mutation and Quantified Mutational Burden. *Am J Dermatopathol* 2020.
61. Bell D, Aung P, Prieto V G, and Ivan D. Next-generation sequencing reveals rare genomic alterations in aggressive digital papillary adenocarcinoma. *Ann Diagn Pathol* 2015; 19: 381-4.
62. Dias-Santagata D, Lam Q, Bergethon K et al. A potential role for targeted therapy in a subset of metastasizing adnexal carcinomas. *Mod Pathol* 2011; 24: 974-82.
63. Emanuel P O, de Vinck D, Waldorf H A, and Phelps R G. Recurrent endocrine mucin-producing sweat gland carcinoma. *Ann Diagn Pathol* 2007; 11: 448-52.
64. Agni M, Raven M L, Bowen R C et al. An Update on Endocrine Mucin-producing Sweat Gland Carcinoma: Clinicopathologic Study of 63 Cases and Comparative Analysis. *Am J Surg Pathol* 2020; 44: 1005-1016.
65. Mathew J G, Bowman A S, Saab J, Busam K J, Nehal K, and Pulitzer M. Next Generation Sequencing analysis suggests varied multistep mutational pathogenesis for Endocrine Mucin Producing Sweat Gland Carcinoma with comments on INSM1 and MUC2 suggesting a conjunctival origin. *J Am Acad Dermatol* 2021.
66. Qin H, Moore R F, Ho C Y, Eshleman J, Eberhart C G, and Cuda J. Endocrine mucin-producing sweat gland carcinoma: A study of 11 cases with molecular analysis. *J Cutan Pathol* 2018.
67. Held L, Ruetten A, Kutzner H, Palmedo G, John R, and Mentzel T. Endocrine mucin-producing sweat gland carcinoma: Clinicopathologic, immunohistochemical, and molecular analysis of 11 cases with emphasis on MYB immunoexpression. *J Cutan Pathol* 2018.
68. Cornejo K M, Hutchinson L, Meng X, O'Donnell P, and Deng A. Endocrine Mucin-Producing Sweat Gland Carcinoma of the Eyelid: A Report of a Case With Molecular Analysis. *Am J Dermatopathol* 2016; 38: 636-8.
69. Behboudi A, Winnes M, Gorunova L et al. Clear cell hidradenoma of the skin-a third tumor type with a t(11;19)--associated TORC1-MAML2 gene fusion. *Genes Chromosomes Cancer* 2005; 43: 202-5.

70. Winnes M, Molne L, Suurkula M et al. Frequent fusion of the CRTC1 and MAML2 genes in clear cell variants of cutaneous hidradenomas. *Genes Chromosomes Cancer* 2007; 46: 559-63.
71. Kuma Y, Yamada Y, Yamamoto H et al. A novel fusion gene CRTC3-MAML2 in hidradenoma: histopathological significance. *Hum Pathol* 2017; 70: 55-61.
72. Moller E, Stenman G, Mandahl N et al. POU5F1, encoding a key regulator of stem cell pluripotency, is fused to EWSR1 in hidradenoma of the skin and mucoepidermoid carcinoma of the salivary glands. *J Pathol* 2008; 215: 78-86.
73. Kazakov D V, Ivan D, Kutzner H et al. Cutaneous hidradenocarcinoma: a clinicopathological, immunohistochemical, and molecular biologic study of 14 cases, including Her2/neu gene expression/amplification, TP53 gene mutation analysis, and t(11;19) translocation. *Am J Dermatopathol* 2009; 31: 236-47.
74. Cavalieri S, Busico A, Capone I et al. Identification of potentially druggable molecular alterations in skin adnexal malignancies. *J Dermatol* 2019; 46: 507-514.
75. Chan M P, Plouffe K R, Liu C J et al. Next-generation sequencing implicates oncogenic roles for p53 and JAK/STAT signaling in microcystic adnexal carcinomas. *Mod Pathol* 2020; 33: 1092-1103.
76. Chen M B and Laber D A. Metastatic Microcystic Adnexal Carcinoma with DNA Sequencing Results and Response to Systemic Antineoplastic Chemotherapy. *Anticancer Res* 2017; 37: 5109-5111.
77. Wohlfahrt C, Ternesten A, Sahlin P, Islam Q, and Stenman G. Cytogenetic and fluorescence in situ hybridization analyses of a microcystic adnexal carcinoma with del(6)(q23q25). *Cancer Genet Cytogenet* 1997; 98: 106-10.
78. Schaller J, Rytina E, Rutten A, Hendricks C, Ha T, and Requena L. Sweat duct proliferation associated with aggregates of elastic tissue and atrophodermia vermiculata: a simulator of microcystic adnexal carcinoma. Report of two cases. *J Cutan Pathol* 2010; 37: 1002-9.
79. Robson A, Greene J, Ansari N et al. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. *Am J Surg Pathol* 2001; 25: 710-20.
80. A N, S H, R S, In G, Miller K, and Wysong A. Eccrine Porocarcinoma: New Insights and a Systematic Review of the Literature. *Dermatol Surg*; 44: 1247-1261.
81. Harms P W, Hovelson D H, Cani A K et al. Porocarcinomas harbor recurrent HRAS-activating mutations and tumor suppressor inactivating mutations. *Hum Pathol* 2016; 51: 25-31.
82. Bosic M, Kirchner M, Brasanac D et al. Targeted molecular profiling reveals genetic heterogeneity of poromas and porocarcinomas. *Pathology* 2018; 50: 327-332.

83. Sekine S, Kiyono T, Ryo E et al. Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. *J Clin Invest* 2019; 129: 3827-3832.
84. Macagno N, Kervarrec T, Sohier P et al. NUT Is a Specific Immunohistochemical Marker for the Diagnosis of YAP1-NUTM1-rearranged Cutaneous Poroid Neoplasms. *Am J Surg Pathol* 2021.
85. Parra O, Kerr D A, Bridge J A, Loehrer A P, and Linos K. A case of YAP1 and NUTM1 rearranged porocarcinoma with corresponding immunohistochemical expression: Review of recent advances in poroma and porocarcinoma pathogenesis with potential diagnostic utility. *J Cutan Pathol* 2021; 48: 95-101.
86. Varelas X. The Hippo pathway effectors TAZ and YAP in development, homeostasis and disease. *Development* 2014; 141: 1614-26.
87. Harvey K F, Zhang X, and Thomas D M. The Hippo pathway and human cancer. *Nat Rev Cancer* 2013; 13: 246-57.
88. Prieto-Granada C, Morlote D, Pavlidakey P et al. Poroid adnexal skin tumors with YAP1 fusions exhibit similar histopathologic features: A series of six YAP1-rearranged adnexal skin tumors. *J Cutan Pathol* 2021.
89. Russell-Goldman E, Hornick J L, and Hanna J. Utility of YAP1 and NUT immunohistochemistry in the diagnosis of porocarcinoma. *J Cutan Pathol* 2021; 48: 403-410.
90. Antonescu C R, Zhang L, Chang N E et al. EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. *Genes Chromosomes Cancer* 2010; 49: 1114-24.
91. Zahn J, Chan M P, Wang G et al. Altered Rb, p16, and p53 expression is specific for porocarcinoma relative to poroma. *Journal of Cutaneous Pathology* 2019; 46: 659-664.
92. Watanabe Y, Shido K, Niihori T et al. Somatic BRAF c.1799T>A p.V600E Mosaicism syndrome characterized by a linear syringocystadenoma papilliferum, anaplastic astrocytoma, and ocular abnormalities. *Am J Med Genet A* 2016; 170A: 189-94.
93. Kim J T, Newsom K J, and Shon W. Detection of somatic mutations in secondary tumors associated with nevus sebaceus by targeted next generation sequencing. Comment on Kitamura et al. *Int J Dermatol* 2018; 57: 120-122.
94. Levinsohn J L, Tian L C, Boyden L M et al. Whole-exome sequencing reveals somatic mutations in HRAS and KRAS, which cause nevus sebaceus. *J Invest Dermatol* 2013; 133: 827-830.

95. Friedman B J, Sahu J, Solomides C C, Connolly D M, and Lee J B. Contiguous verrucous proliferations in syringocystadenoma papilliferum: A retrospective analysis with additional evaluation via mutation-specific BRAFV600E immunohistochemistry. *J Cutan Pathol* 2018; 45: 212-216.
96. Alegria-Landa V, Jo-Velasco M, Santonja C et al. Syringocystadenoma papilliferum associated with verrucous carcinoma of the skin in the same lesion: Report of four cases. *J Cutan Pathol* 2020; 47: 12-16.
97. Altunel E, Perepletchikov A, and Kozyreva O. Metastatic Syringocystadenocarcinoma Papilliferum: A Case Report, Tumor Genomic Profiling, and Literature Review. *Case Rep Oncol Med* 2020; 2020: 9056209.
98. Pfarr N, Allgauer M, Steiger K et al. Several genotypes, one phenotype: PIK3CA/AKT1 mutation-negative hidradenoma papilliferum show genetic lesions in other components of the signalling network. *Pathology* 2019; 51: 362-368.
99. Pfarr N, Sinn H P, Klauschen F et al. Mutations in genes encoding PI3K-AKT and MAPK signaling define anogenital papillary hidradenoma. *Genes Chromosomes Cancer* 2016; 55: 113-9.
100. Wu W M and Lee Y S. Autosomal dominant multiple syringomas linked to chromosome 16q22. *Br J Dermatol* 2010; 162: 1083-7.
101. Liau J Y, Tsai J H, Huang W C, Lan J, Hong J B, and Yuan C T. BRAF and KRAS mutations in tubular apocrine adenoma and papillary eccrine adenoma of the skin. *Hum Pathol* 2018; 73: 59-65.
102. Goto K, Kukita Y, Honma K et al. Signet-ring cell/histiocytoid carcinoma of the axilla: a clinicopathologic and genetic analysis of 11 cases, review of the literature, and comparison with potentially related tumours. *Histopathology* 2021.
103. Bahrami A, Dalton J D, Krane J F, and Fletcher C D M. A subset of cutaneous and soft tissue mixed tumors are genetically linked to their salivary gland counterpart. *Genes Chromosomes & Cancer* 2012; 51: 140-148.
104. Panagopoulos I, Gorunova L, Andersen K et al. NDRG1-PLAG1 and TRPS1-PLAG1 Fusion Genes in Chondroid Syringoma. *Cancer Genomics Proteomics* 2020; 17: 237-248.
105. Matsuyama A, Hisaoka M, and Hashimoto H. PLAG1 expression in cutaneous mixed tumors: an immunohistochemical and molecular genetic study. *Virchows Arch* 2011; 459: 539-45.
106. Russell-Goldman E, Dubuc A, and Hanna J. Differential Expression of PLAG1 in Apocrine and Eccrine Cutaneous Mixed Tumors: Evidence for Distinct Molecular Pathogenesis. *Am J Dermatopathol* 2020; 42: 251-257.

107. Panagopoulos I, Gorunova L, Lund-Iversen M, Bassarova A, and Heim S. Fusion of the Genes PHF1 and TFE3 in Malignant Chondroid Syringoma. *Cancer Genomics Proteomics* 2019; 16: 345-351.

Figure Legends

Figure 1. Sebaceous tumors. (A) Sebaceous adenoma, displaying normal polarization with prominent basaloid germinative layer. (B) Sebaceoma, with predominance of basaloid cells. (C) Sebaceous carcinoma, with mitotically active atypical cells and subtle sebaceous differentiation. (D) Example of mismatch repair gene immunohistochemistry, demonstrating the most common pattern (loss of MSH2 and MSH6). A-C: Hematoxylin and eosin (magnification 400x for A, B; 200x for C). D: Immunohistochemistry with DAB brown chromogen detection (magnification 25x).

Figure 2. Pilomatricoma. (A) Circumscribed tumor in dermis or subcutis. (B) Cell types include ghost cells (bottom left), basophilic cells (top right), and transitional cells. (C) Beta-catenin expression in pilomatricomas, with nuclear and cytoplasmic staining of peripheral basaloid cells. (D) Beta-catenin staining in background epidermis, demonstrating membranous staining of keratinocytes. (E) LEF1 nuclear expression consistent with activated beta-catenin signaling in basaloid cells of pilomatricoma. (F) CDX2 expression in pilomatricomas may be downstream of Wnt/beta-catenin signaling. (G) Gene alterations in pilomatricomas implicate Wnt/beta-catenin and Protein Kinase C pathways. A,B: hematoxylin and eosin (5x and 400x), C-F: Immunohistochemistry with DAB brown chromogen (400x). FAP: familial adenomatous polyposis. GOF: gain of function variant/mutation. LOF: Loss of function.

Figure 3. Spiradenoma and cylindroma. (A) Spiradenoma displaying small monomorphous cells with duct formation and intermingled lymphocytes. (B) Cylindroma. Interlocking "jigsaw puzzle" formation with prominent basement membrane. (C) Spiradenocarcinoma. Scanning

magnification of large infiltrative tumor. Dashed circle denotes precursor spiradenoma. (D) Spiradenocarcinoma, displaying poorly-differentiated tumor cells. (E) Nuclear and cytoplasmic p65 expression in spiradenoma, correlating with NF-κB pathway activation. (F) Myb expression in cylindroma. (G) Fluorescence in situ hybridization for *MYB* (red) and *NFIB* (green) performed demonstrates fusion signals (yellow arrows) in some cylindromas. (H) Molecular drivers for spiradenomas and cylindromas implicate NF-κB and Myb, with tumor suppressor loss-of-function events (TSG LOF) associated with malignant progression. A-D: hematoxylin and eosin (A, B, D 400x; C scanning magnification). E, F: Immunohistochemistry with DAB brown chromogen (200x). GOF: gain of function variant/mutation. LOF: Loss of function variant/mutation.

Figure 4. Poroma. (A) Nodular tumor with glandular differentiation and broad connection to epidermis. (B) Tumors consist of small poroid cells and larger cuticular cells, with lumen formation. (C) When *NUTM1* is present as a fusion partner, NUT protein expression is a specific finding for poroma and related tumors. (D) Molecular drivers of poroma implicate Hippo/YAP and MAPK pathways, with tumor suppressor loss-of-function (TSG LOF) potentially related to malignant progression.

Figure 5. Syringocystadenoma papilliferum. (A) Cystic glandular proliferation with associated epidermal hyperplasia. (B) Papillary growth with plasma cell-rich stroma. (C) In the subset of tumors with *BRAF* V600E mutations, immunohistochemistry for BRAF-V600E can demonstrate presence of mutation in glandular (green arrow) and epidermal (black arrow) components.

Figure 6. Benign mixed tumor. (A) Circumscribed dermal nodule with glandular structures in chondromyxoid stroma (hematoxylin and eosin, 6x). (B) Glandular structures in myxoid stroma (hematoxylin and eosin, 100x). (C) PLAG1 immunohistochemical expression in mixed tumor (DAB chromogen, 200x).

Table 1. Syndromic Associations with Cutaneous Adnexal Tumors

Syndrome	**Gene Function**	**Cutaneous Tumors**	**Extracutaneous Neoplasms**	**Other Findings**	**Estimated Prevalence**
Bazex–Dupré–Christol (ACTRT1)	Ciliary function	BCC, less frequently trichoepitheliomas	N/A	Follicular atrophoderma, hypotrichosis, hypohidrosis, milia, facial hyperpigmentation, hair shaft anomalies	<1/1000000
Birt-Hogg-Dube (FLCN)	Inhibition of mTOR pathway	Fibrofolliculoma/trichodiscoma, acrochordon	Pulmonary cysts, renal tumors (most commonly oncocytoma or renal cell carcinoma)	Spontaneous pneumothorax	Unknown
CYLD cutaneous syndrome /Brooke-Spiegler (CYLD)	Deubiquitinase (NF-κB inhibition)	Trichoepithelioma, spiradenoma, cylindroma, spiradenocylindroma with rare malignant transformation	Membranous basal cell adenoma (salivary gland)	N/A	<1/100,000
Clouston (GJB6, GJB2)	Connexins	Syringofibroadenoma	N/A	Palmoplantar keratoderma, hypotrichosis, nail dystrophy	Unknown
Cowden (PTEN)	Inhibition of PI3K signaling	Trichilemmoma, multiple hamartomatous lesions	High risk for breast, thyroid, and endometrial carcinoma	Acral keratoses, oral papillomas	1/200000
Familial Pilomatricoma (PLCD1)	Phospholipase C (Protein kinase C, MAPK)	Multiple pilomatricomas	N/A	N/A	Unknown

FAP (APC)	Inhibition of Wnt/β-catenin signaling	Multiple pilomatricomas, epidermoid cysts, cutaneous fibromas, lipoomas	Osteomas, colorectal adenomas, desmoid tumors, adrenal adenomas, nasopharyngeal angiofibroma Increased risk for colon, thyroid, hepatobiliary, and CNS malignancies	N/A	(~1/8000).
Generalized basaloid follicular hamartoma syndrome (PTCH1)	Hedgehog signaling (less prominent activation than NBCCS)	Basaloid follicular hamartomas; less frequently acrochordons, steatocystomas	N/A	Palmoplantar pitting, hypohidrosis, hypotrichosis, alopecia	
Happle-Tinschert Syndrome (unknown)	Unknown	Unilateral segmental basaloid follicular hamartoma	N/A	Cerebral, osseous, dental abnormalities	Unknown
Muir-Torre (MMR genes: MLH1, MSH2, and MSH6)	DNA mismatch repair	Sebaceous adenoma, sebaceoma, sebaceous carcinoma, keratoacanthoma	Colonic adenocarcinoma (most common), genitourinary, breast, and hematologic malignancies	N/A	1/300
Malta	Myosin heavy chain	Syringoma, microcystic adnexal	N/A	Atrophoderma vermiculata,	Unknown

syndrome/Nicolau-Balus (MYH9, possible)		carcinoma-like lesions		milia	
NBCCS (PTCH1)	Inhibition of Hedgehog signaling	Numerous BCCs; basaloid follicular hamartomas (infrequent)	Odontogenic keratocysts, CNS tumors, ovarian cysts	Palmoplantar pits, skeletal anomalies, coarse facial features, hypertelorism, macrocephaly	~1/31000
Schimmelpenning–Feuerstein–Mims (postzygotic HRAS/KRAS)	RAS-MAPK signaling	Nevus sebaceus	CNS, ocular, and skeletal anomalies	N/A	Unknown
Schöpf-Schulz-Passarge (WNT10A)	Wnt/β-catenin signaling	Syringofibroadenoma, eyelid apocrine hidrocystoma	N/A	Palmoplantar keratoderma, telangiectasia, dental anomalies, onychodystrophy, hypotrichosis	<1/1000000
Steatocystoma multiplex (KRT17)	Keratin	Steatocystomas, eruptive vellus hair cysts	N/A	Pachyonychia congenita	Unknown

BCC: basal cell carcinoma. FAP: familial adenomatous polyposis. MMR: mismatch repair. NBCCS: nevoid basal cell carcinoma syndrome.

Table 2. Molecular Findings in Cutaneous Sebaceous Tumors

Tumor	Molecular Findings	Diagnostic Correlations
sebaceous carcinoma	**Sporadic—3 subtypes:** 1) MMR (mismatch repair genes, *HRAS/KRAS, TP53, RB1, RREB1, NOTCH1/2, FAT3, KMT2D)* 2) UV (*TP53, RREB1, NOTCH1/2, FAT3, KMT2D*) 3) Paucimutational (*HRAS, NOTCH1*) **Syndromes-2:** Mismatch repair genes (*MSH2>MLH1, MSH6*): Muir-Torre Syndrome *MUTYH*: MUTY-Associated Polyposis	UV signature correlates with poor differentiation, infiltrative growth, squamous differentiation MMR immunohistochemistry may show expression loss in syndromic or sporadic MMR-deficient tumors
sebaceous adenoma, sebaceoma	**Sporadic (subtypes not established)** *MSH2, HRAS/KRAS, TP53, CDKN2A, EGFR, CTNNB1* **Syndromes—2:** Mismatch repair genes (*MSH2>MLH1, MSH6*): Muir-Torre Syndrome *MUTYH*: MUTY-Associated Polyposis	MMR immunohistochemistry may show expression loss in syndromic or sporadic MMR-deficient tumors

Table 3. Molecular Findings in Cutaneous Tumors with Hair Follicle Differentiation

basaloid follicular hamartoma	**Sporadic:** unknown **Syndrome:** *PTCH1* (NBCCS, GBFHS)	
fibrofolliculoma/trichodiscoma	**Sporadic:** unknown **Syndrome:** *FLCN* (Birt-Hogg-Dube Syndrome)	No *RB1* deletion (unlike spindle cell lipoma)
pilomatricoma, pilomatrical carcinoma	**Sporadic:** *CTNNB1* activating mutation **Syndromes/Inherited**: *APC* (Familial Adenomatous Polyposis/Gardner) *PLCD1* (familial pilomatricoma) *CTNNB1* somatic mutation superimposed on germline mutation in other gene (MMR syndromes, myotonic dystrophy)	IHC: Beta-catenin (nuclear and cytoplasmic), LEF1, CDX2 expression
trichoblastoma (TB), other than trichoepithelioma	**Sporadic:** *HRAS* (subset)	
trichoblastic carcinoma	**Sporadic:** *TP53, CDKN2A, TERT* promoter*, CTNNB1*	
trichoepithelioma (TB subtype)	**Sporadic:** *PTCH1, CTNNB1* **Syndromes—2:** *CYLD* (CYLD Cutaneous Syndrome) *ACTRT1* (Bazex–Dupré–Christol Syndrome) *MYH9* (possible) (Rombo Syndrome)	
trichilemmoma	**Sporadic:** *HRAS* **Syndrome:** *PTEN* (Cowden Syndrome)	PTEN protein loss is specific to syndromic tumors
trichilemmal carcinoma	**Sporadic:** *TP53*, variable mutations and oncogenic fusions	.
trichilemmal cyst	**Sporadic:** unknown **Inherited:** *PLCD1* (familial)	
trichilemmal tumor (benign, malignant)	**Sporadic:** Aneuploidy, (1 malignant case) *PIK3CA* and *ALPK1* mutations	

GBFHS: generalized basaloid follicular hamartoma syndrome. NBCCS: Nevoid basal cell carcinoma syndrome.

Table 4. Molecular Findings in Sweat Gland Tumors

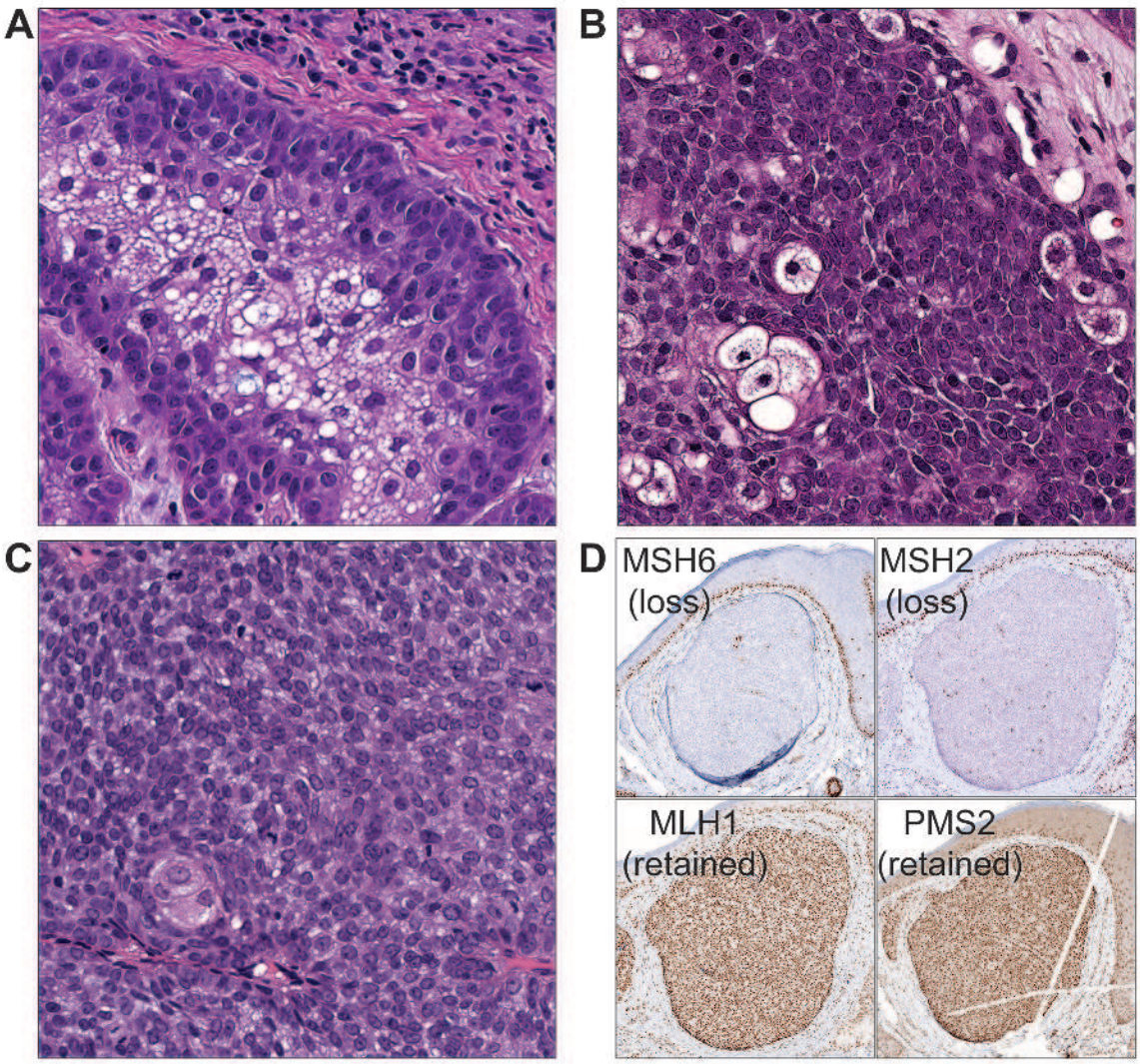
cylindroma	**Sporadic:** *CYLD* mutation, *MYB-NFIB* fusion **Syndrome:** *CYLD* (CYLD Cutaneous Syndrome)	Myb expression (not specific)
spiradenoma	**Sporadic:** *CYLD* mutation, *ALPK1* mutation **Syndrome:** *CYLD* (CYLD Cutaneous Syndrome)	Myb expression (not specific)
carcinoma ex spiradenoma, cylindroma (spiradenocarcinoma, cylindrocarcinoma)	**Sporadic or syndromic:** *TP53* (secondary mutation in addition to molecular driver of precursor benign tumor)	Loss of Myb expression may correlate with malignancy
adenoid cystic carcinoma	**Sporadic:** *MYB-NFIB* fusions, *MYBL1-NFIB* fusion	Myb expression (not specific)
apocrine carcinoma	**Sporadic:** *ERBB2* (HER2-neu) gene amplification (1 case)	
digital papillary adenocarcinoma	**Sporadic:** *BRAF* V600E (minority), *TP53* (minority)	
endocrine mucin-producing sweat gland carcinoma	**Sporadic:** heterogeneous mutations affecting DNA damage response/repair (*BRD4, PPP4R2, RTEL1*) and tumor-suppressor pathway (*BRD4, TP53, TSC1, LATS2*)	MUC2 expression suggestive of conjunctival origin
hidradenoma	**Sporadic:** *CRTC1-MAML2* fusion (rarely *CRTC3-MAML2*), *EWSR1-POU5F1* fusion	
hidradenoma papilliferum	**Sporadic:** *PIK3CA*, other PI3K pathway mutations	
hidradenocarcinoma	**Sporadic:** *CRTC1-MAML2* fusion, *ERBB2* amplification, *TP53* mutation (minority)	
hidrocystoma	**Sporadic:** unknown **Syndrome:** *WNT10A* (Schöpf-Schulz-Passarge Syndrome)	
mammary analog secretory carcinoma	**Sporadic:** *ETV6* fusions including *ETV6-NTRK3;* (rare) *NFIX-FKN1* fusion	
microcystic adnexal carcinoma	**Sporadic:** *TP53, JAK1,* paucimutational	Phospho-STAT3 and/or altered p53 expression (majority)—unlike syringoma
mucoepidermoid carcinoma	**Sporadic:** *CRTC1* rearrangements (non-*MAML2*)	
papillary eccrine adenoma (tubular	**Sporadic:** *BRAF* V600E, *KRAS*	

adenoma)		
poroma	**Sporadic:** *YAP1-MAML2, YAP1-NUTM1,* or (rarely) *WWTR1-NUTM1* fusions	NUT expression (minority)
poroid hidradenoma	**Sporadic:** *YAP1-NUTM1* (majority)	NUT expression (majority)
porocarcinoma	**Sporadic:** *YAP1-MAML2, YAP1-NUTM1* fusions; *TP53, RB1, CDKN2A, HRAS* mutation	NUT expression (majority) Aberrations of p53, Rb, and/or p16 expression
syringocystadenoma papilliferum	**Sporadic:** *BRAF* V600E, *HRAS*	
signet-ring cell/histiocytoid carcinoma	**Sporadic:** *PIK3CA* (2 cases), *CDH1* (1 case)	
syringofibroadenoma	**Sporadic:** HPV (1 of 2 cases with SCC) **Syndromes—2:** *WNT10A* (Schöpf-Schulz-Passarge Syndrome) *GJB6*, *GJB2 (*Clouston syndrome)	
syringoma	**Sporadic:** unknown **Syndromes/Inherited**: Chr 16q22 (multiple syringomas) Trisomy 21 (Downs Syndrome) *MYH9* (possible) (Nicolau-Balus Syndrome)	
tubular apocrine adenoma (tubular adenoma)	**Sporadic:** *BRAF* V600E, *KRAS*	

Table 5. Molecular Findings in Cutaneous Tumors with Multilineage Differentiation

nevus sebaceus	**Sporadic:** *HRAS, KRAS* postzygotic mutation Additional mutations in secondary tumors (trichoblastoma, SCAP, etc.) **Syndrome:** Mosaic *HRAS, KRAS, NRAS* (Schimmelpenning–Feuerstein–Mims Syndrome) *HRAS* (Costello Syndrome) *KRAS* (Noonan Syndrome) *FGFR2* (various craniosynostosis syndromes)	
mixed tumor, benign (chondroid syringoma)	**Sporadic:** *PLAG1* fusions (partners include *NDRG1*, *TRPS1*	PLAG1 is sensitive and specific marker
mixed tumor, malignant	**Sporadic:** *PLAG1* rearrangement, (single case) *PFH1-TFE3* fusion	

Figure 1



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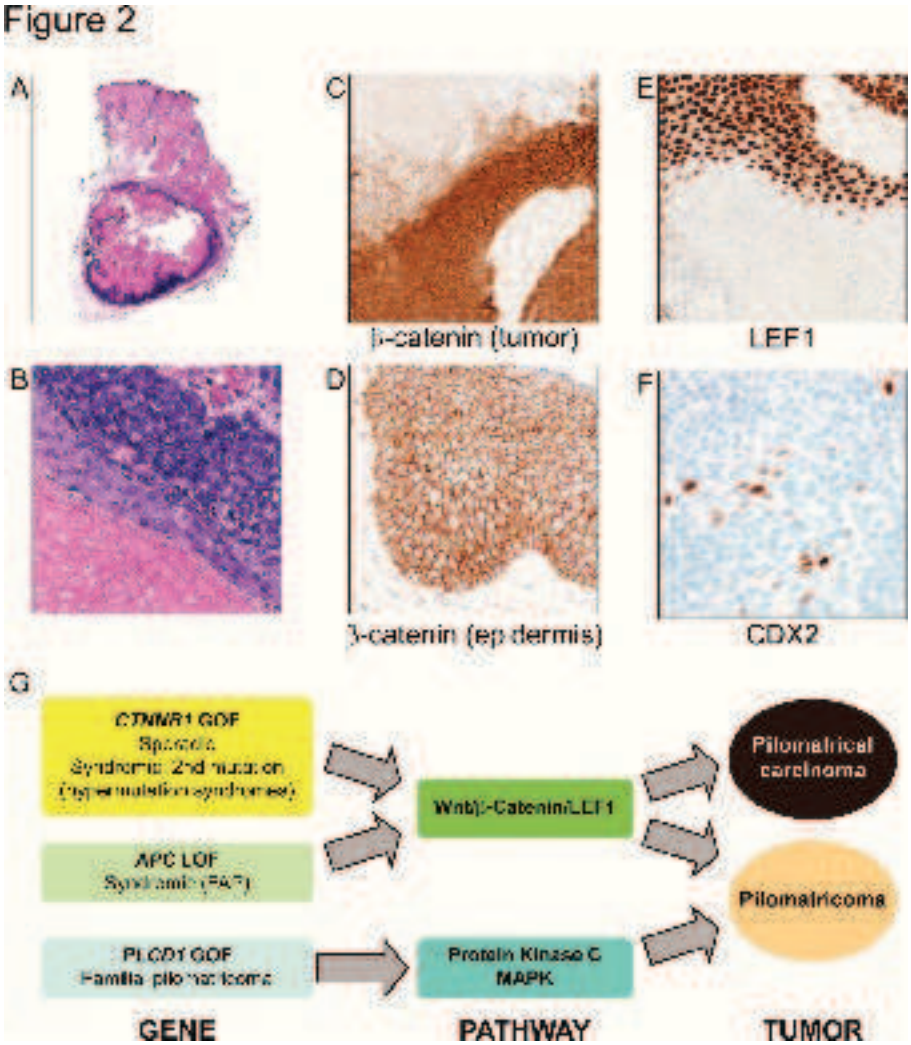

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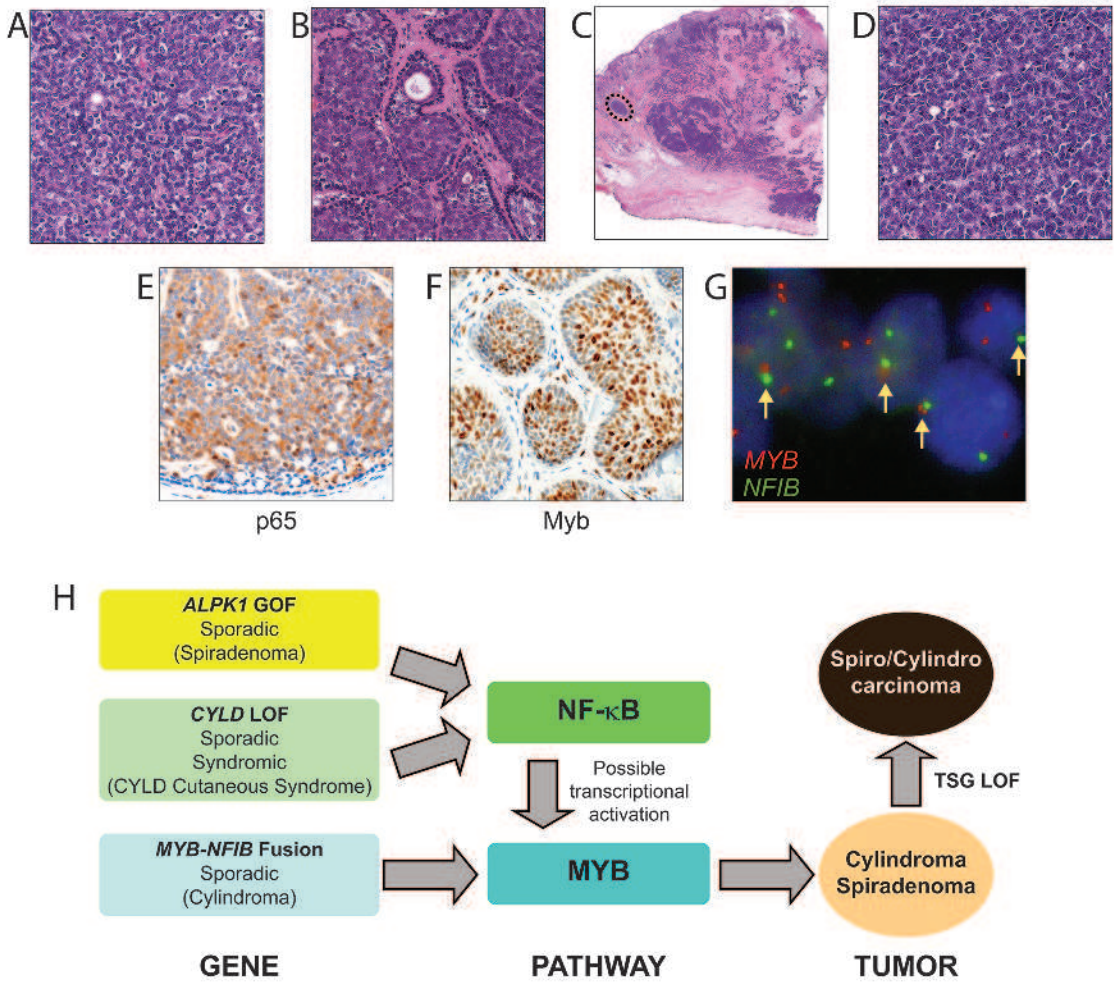
Figure 3



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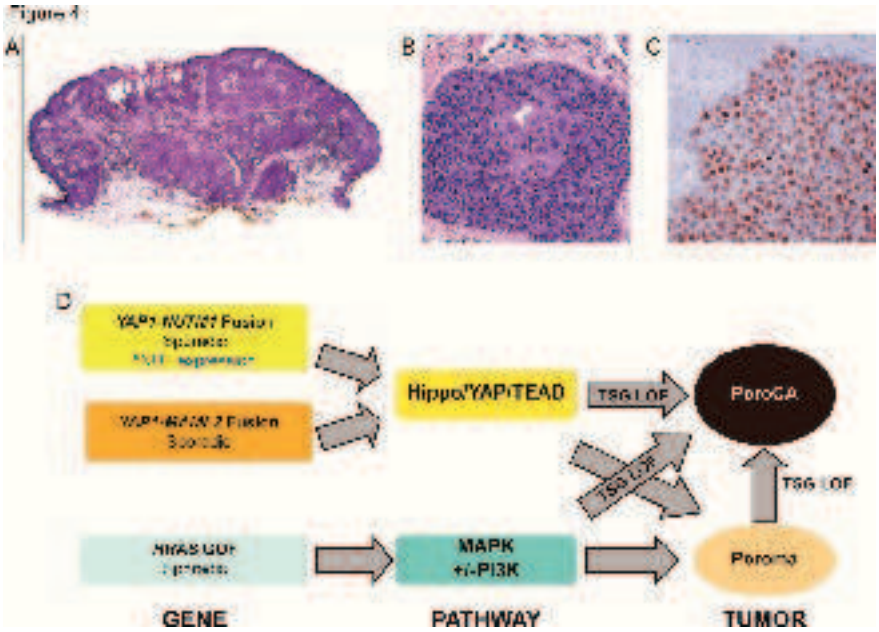

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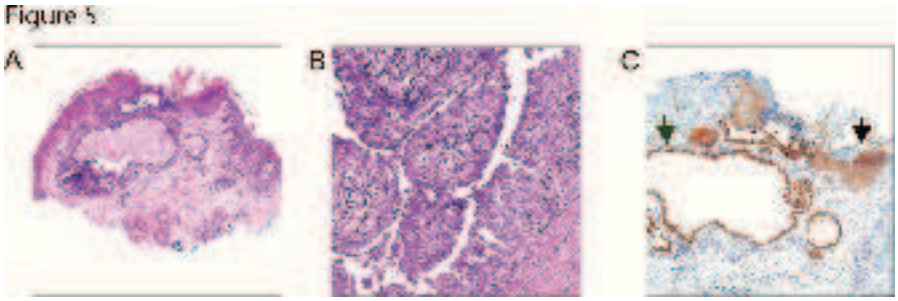

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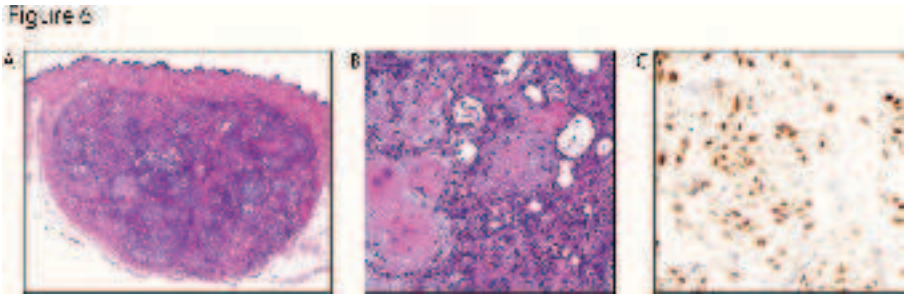

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