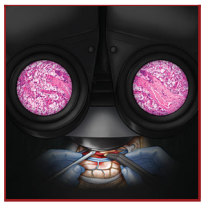

Pathological Features of Tumors of the Nervous System in Hereditary Cancer Predisposition Syndromes: A Review

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Hereditary cancer predisposition syndromes (HCS) become more recognizable as the knowledge about them expands, and genetic testing becomes more affordable. In this review, we discussed the known HCS that predispose to central and peripheral nervous system tumors. Different genetic phenomena were highlighted, and the important cellular biological alterations were summarized. Genetic mosaicism and germline mutations are features of HCS, and recently, they were described in normal population and as modifiers for the genetic landscape of sporadic tumors. Description of the tumors arising in these conditions was augmented by representative cases explaining the main pathological findings. Clinical spectrum of the syndromes and diagnostic criteria were tabled to outline their role in defining these disorders. Interestingly, precision medicine has found its way to help these groups of patients by offering targeted preventive measures. Understanding the signaling pathway alteration of mammalian target of rapamycin (mTOR) in tuberous sclerosis helped introducing mTOR inhibitors as a prophylactic treatment in these patients. More research to define the germline genetic alterations and resulting cellular signaling perturbations is needed for effective risk-reducing interventions beyond prophylactic surgeries.

KEY WORDS: Hereditary, Germline, Mosaicism, Neurofibromatosis, NF1, NF2, P53, RB1, MEN1, PTEN, mTOR, VHL, ATM

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Hereditary cancer predisposition syndrome (HCS) is a condition of increasing risk of developing cancer resulting from inherited gene mutation. The first described germline genetic variants predisposing individuals to cancer was *BRCA1*.[1] Currently, exome/whole genome sequencing allows novel genes discovery in these disorders. Many exclusive solo cancer susceptibility genes have been identified; however, epidemiological studies elucidated that susceptibility to specific tumors could be attributed to mutations in group of different genes. Conversely, some independent syndromes appeared to be manifestations of different mutations in the same gene. Development of each syndrome requires a loss of tumor-suppressor proteins – hypothesis described by Knudson[2] in retinoblastoma. Knudson's[2] "two-hit" hypothesis postulates one allele loss in germline followed by second

ABBREVIATIONS: AD, autosomal dominant; **AR,** Autosomal recessive; **ASA,** acetylsalicylic acid; **AT,** ataxia-telangiectasia; **ATM,** AT mutated; **AT/RT,** atypical teratoid/rhabdoid tumor; **CMMRD,** constitutional MMR deficiency syndrome; **CNC,** Carney complex; **CNS,** central nervous system; **CPC,** choroid plexus carcinoma; **CS,** Cowden syndrome; **DNT,** dysembryoplastic neuroepithelial tumor; **GEMM,** genetically engineered mouse model; **GFAP,** Glial fibrillary acidic protein; **HAT,** histone acetyltransferase; **HCS,** hereditary cancer predisposition syndrome; **H&E,** Hematoxylin and eosin stain; **HIF,** hypoxia-inducible factor; **IHC,** Immunohistochemistry; **LFS,** Li-Fraumeni syndrome; **LS,** Lynch syndrome; **MMR,** mismatch repair; **mTOR,** mammalian target of rapamycin; **MYC,** myelocytomatosis oncogene; **NBS,** Nijmegen breakage syndrome; **OPG,** optic pathway glioma; **PA,** pituitary adenomas; **PHTS,** PTEN hamartoma tumor syndrome; **RB,** Retinoblastoma; **RTPS,** rhabdoid tumor predisposition syndrome; **SEGA,** subependymal giant cell astrocytoma; **SGBS,** Simpson-Golabi-Behmel syndrome; **SHH,** sonic hedgehog; **SMO,** the signal transducer Smoothened; **TSC,** tuberous sclerosis complex; **VCP,** valosin-containing protein; **VHL,** Von Hippel-Lindau; **WHO,** World Health Organization

allele loss causes multiple tumors. However, the phenomenon of gene dosage sensitivity suggests that haploinsufficiency can explain tumorigenesis.[3-5]

Germline mosaicism is a feature of HCS. Mosaicism could be somatic, germline, or mixed gonadal/somatic. Naturally, an average of 2:1 asymmetry of early human embryonic cells contributes to adult tissues.[6] Segmental syndrome/mosaicism results in some cells having 2 normal genes and other cells containing pathogenic variants in 1 copy of the same gene. People with segmental syndrome do not have affected parents. Originally, segmental syndrome is proven by molecular analysis in many cutaneous traits then expanded to hereditary cancer syndrome. Rare individuals were described having only germline mosaicism without apparent somatic features.[7,8]

Germline mutations are traditionally viewed as HCS hallmark; however, increasing evidence shows a key role of inherited germline genetic variation in nonhereditary cancer risk.[9] Recent studies suggest that germline variants affect somatic mutation profiles in individuals having sporadic cancer.[10,11] For example, selective amplification of germline variants like *AGK*, *DGKB*, *EGFR*, *INSR*, *KIT*, and *RELN* are associated with increased glioblastoma risk.[12]

Studying HCS requires experimental models in addition to natural history and genetics studies of affected families. Modeling human cancers was achieved by genetically engineered mouse models (GEMMs) either by the traditional, mosaic, conditional, chimeric, or nongermline GEMMs. Furthermore, induced pluripotent stem cells technology introduces a feasible way of studying HCS.[13,14]

Central nervous system (CNS) is affected by several HCS either predominantly or as a bystander. Some HCS were previously grouped under the term "Phakomatoses" because of the involvement of the eye lesions; however, it is no longer used because of lack of such lesions in many HCS. Common syndromes that predominantly involve the CNS include neurofibromatosis (NF) types 1 and 2, Von Hippel-Lindau (VHL) disease, and tuberous sclerosis complex (TSC), whereas syndromes having mostly extra-neural manifestations include Cowden, Li-Fraumeni, Turcot, and Gorlin syndromes. There is cellular, molecular, and clinical overlap between NF1, NF2, and schwanommatosis.[15]

Noteworthy, recent advances in understating HCS improved personalized risk assessment and develop novel interventions to prevent or intercept cancer. For example, precision prevention for *BRCA1*-mutation carriers moved toward receptor activator of NF-κB (RANK) activation interference.[16] Further studies are needed to expand our knowledge of germline alterations for developing and implementing effective risk-reducing interventions beyond prophylactic surgical approaches.

NEUROFIBROMATOSIS TYPE 1

NF1 (Tables 1 and 2) increases risk for neurofibroma, optic gliomas, and malignant peripheral nerve sheath tumors (MPNSTs).

The cutaneous, intraneural, diffuse, and plexiform neurofibromas (Figure 1A-1C) are commonly encountered. The plexiform variant involving multiple nerve trunks that appear early first 2 yr of life causes significant physical disfigurement. Plexiform neurofibromas have 10% lifetime risk of progression into MPNST (Figure 1D and 1E). In localized pediatric MPNST, NF1 is associated with worse survival.

NF1 develop low-grade tumors of the optic nerves, chiasm, tracts, and radiations, termed optic pathway gliomas (OPGs), which can cause vision loss. OPGs (Figure 1F) are seen in 15% to 20% of children with NF1. The second common brain tumor is the brainstem glioma, representing 18% of NF1-associated brain neoplasms. Glioblastomas could also be seen.

NF1 is caused by *NF1* germline mutations. Neurofibromin is a cytoplasmic protein that negatively regulates the RAS signaling. The *NF1* mutations are frequently seen in multiple malignancies not typically associated with NF1. Intriguingly, mouse models showed that Nf1+/− microenvironment accelerates benign tumors formation but impairs further progression to malignancy.[17] In the brain, neurofibromin acts with valosin-containing protein (VCP)/P97 to control endoplasmic reticulum formation and consequent protein synthesis. Additionally, VCP/P97 regulates dendritic spine formation and brain function.[18]

NF1 gliomas have specific genomic signatures. Pediatric low-grade gliomas typically exhibit mutations of the MAPK pathway, whereas high-grade gliomas are characterized by loss-of-function mutations in *ATRX*, *TP53*, and *CDKN2A*. Children with NF1 develop diffuse midline gliomas that carry worse prognosis than sporadic cases, independent of histone H3 lysine27-to-methionine (H3K27M) mutation. NF1 gliomas also reduce deoxyribonucleic acid (DNA) methylation of immune genes, which explain tumor-infiltrating lymphocytes.[19]

NF1 microdeletion syndrome is severe phenotype of NF1 characterized by mental retardation, developmental delay, cardiac anomalies, and dysmorphic features.[20] Patients have a 1.4-Mb heterozygous 17q11.2 deletion encompassing *NF1*.

Legius syndrome is an autosomal dominant (AD) disorder that results from loss-of-function *SPRED1* germline mutations and mimics NF1 clinically. It consists of multiple café-au-lait spots, axillary freckling, and macrocephaly but lack neurofibromas, typical osseous lesions, and OPGs.[21]

Melanoma-astrocytoma syndrome (MAS) is a rare condition with cutaneous and neurological manifestations. It is linked to *CDKN2A* and *CDKN2B* germline mutations.

NEUROFIBROMATOSIS TYPE 2

Bilateral vestibular schwannomas are the diagnostic hallmark. Cranial and spinal meningiomas, meningioangiomatosis, spinal ependymoma, and other gliomas are frequently seen. Tumors frequently demonstrate a saltatory growth pattern with unpredictable progression.[22]

NF2-associated schwannomas (Figure 2A) appear early in life (third decade) than sporadic cases. Though the vestibular branch of 8th cranial nerve is usually involved, 5th cranial nerve and

TABLE 1. Overview of Clinical Features of HCS

Disorder	Inheritance	Incidence	Penetrance	Non-neoplastic features	Neoplastic features	Diagnosis
Ataxia-telangiectasia	AR	1 in 20 000 to 100 000	Complete (100%)	Cerebellar ataxia, abnormal eye movements, other neurologic abnormalities, oculocutaneous telangiectasias, and immune deficiency. Associated features include pulmonary disease and radiation sensitivity	Lymphoma, leukemia, breast cancer, astrocytoma, ganglioglioma, medulloblastoma	Clinical and laboratory criteria[88]
Carney complex	AD	Unknown	Incomplete (70%-80%)	Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal, and penile mucosa)	Cutaneous myxoma, cardiac myxoma, breast myxomatosis, acromegaly, primary pigmented nodular adrenocortical disease, large cell calcifying Sertoli cell tumor, thyroid carcinoma, psammomatous melanotic schwannomas, blue nevus, breast ductal adenoma, osteochondromyxoma	Clinicopathological criteria[89]
Cowden Syndrome	AD	1 in 200 000 to 250 000	Incomplete (80%)	Multiple hamartomas especially (facial trichilemmomas and adult cerebellar dysplastic gangliocytomas [Lhermitte-Duclos disease], intestinal hamartomatous polyps), macrocephaly, papillomatous papules, acral keratoses	Breast, thyroid, endometrial, renal, colon carcinomas, fibrocystic breast disease, lipomas, intracranial vascular venous and cavernous angiomas	International Cowden Consortium diagnostic criteria[90] Pilarski et al diagnostic criteria[91]
Familial adenomatous polyposis	AD	1 in 8000 to 18 000	Unknown (expected to be low)		Adenomatous colorectal polyps, medulloblastoma, colorectal carcinomas, osteomas, thyroid cancers and hepatoblastomas.	Genetic testing
Hereditary retinoblastoma	AD	1 in 37 000	Complete (100%)[a]		Retinoblastoma, osteosarcoma, soft tissue sarcomas (particularly leiomyosarcoma) and melanoma	Clinically

TABLE 1. Continued

Disorder	Inheritance	Incidence	Penetrance	Non-neoplastic features	Neoplastic features	Diagnosis
Li-Fraumeni Syndrome	AD	1 in 5000 to 20 000	100% in women, 73% in men		Soft tissue sarcomas, breast carcinoma, osteosarcomas, brain tumors, adrenocortical carcinoma	Classical LFS[92] Chompret criteria[93] LFS-like syndrome[94]
Melanoma-astrocytoma syndrome	AD	<1:1 million	Unknown		Cutaneous malignant melanoma, astrocytoma, neurofibroma, schwannoma, and meningioma	Genetic testing
Multiple endocrine neoplasia type 1	AD	1:30 000	Complete (100%)		Tumors of the parathyroid glands, anterior pituitary, and enteropancreatic	Occurrence of two or more primary MEN1 tumor types
Neurofibromatosis type 1	AD	1 in 2600 to 3000	Complete (100%)	Café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), osseous lesions including sphenoid wing dysplasia, spinal scoliosis, osteopenia, osteoporosis and short stature, vascular deformities including fibromuscular dysplasia of the renal arteries, stenosis of the internal carotid and other cerebral arteries	Neurofibroma, OPGs, MPNST, gastrointestinal stromal tumors, medullary thyroid carcinomas, pheochromocytomas, rhabdomyosarcomas, juvenile xanthogranulomas, glomus tumors, myelomonocytic leukemia, breast cancer	NIH diagnostic criteria[95]
Neurofibromatosis type 2	AD	1 in 25 000		Some dysplastic/developmental lesions including meningioangiomatosis, glial and retinal hamartomas and neuropathies	Bilateral vestibular schwannomas, schwannomas in other cranial, spinal and peripheral nerves, cranial and spinal meningiomas, and spinal ependymoma; other gliomas	Revised Manchester criteria[96,97]
Nevoid basal cell carcinoma syndrome	AD	1 in 31 000 to 164 000	Incomplete 97%	Developmental abnormalities including jaw cysts, intracranial ectopic calcification, Palmar-plantar pits, vertebral anomalies, bifid ribs, macrocephaly, dysmorphic facies, ocular anomalies	Basal cell carcinomas, ovarian tumors, medulloblastoma, meningioma, fetal rhabdomyoma and rhabdomyosarcoma, cardiac fibroma, lymphomesenteric cysts, non-Hodgkin lymphoma, Hodgkin lymphoma, melanoma, chronic lymphoid leukemia, soft tissue leiomyosarcoma, breast carcinoma, lung carcinoma, and sinonasal undifferentiated carcinoma	Consensus statement from the first international colloquium on NBCCS[98]

TABLE 1. Continued

Disorder	Inheritance	Incidence	Penetrance	Non-neoplastic features	Neoplastic features	Diagnosis
Nijmegen breakage syndrome	AR	Unknown		Progressive microcephaly, growth retardation, immunodeficiency	Lymphoid malignancy, medulloblastomas	Clinical and genetic testing
Noonan syndrome	AD	1 in 1000 to 2500	Incomplete	Facial features, developmental delay, short stature, congenital heart disease, renal anomalies, lymphatic malformations, bleeding difficulties	DNT, subependymoma, glioneural tumor, gliomas	Clinical and genetic testing
Rhabdoid tumor predisposition syndrome	AD	1:1 million	Unknown (probably incomplete)	Coffin-Siris syndrome, Nicolaides-Baraitser syndrome	Rhabdoid tumor either within the cranium as AT/RT or extracranially, especially in the kidney, as malignant rhabdoid tumor, multifocal rhabdoid tumor, schwannoma, meningioma	Genetic testing
Rubinstein-Taybi syndrome	AD	1 in 125 000	Complete (100%)	Multiple congenital anomalies, postnatal growth deficiency, microcephaly, specific facial characteristics, broad thumbs and big toes, and mental retardation	Medulloblastomas, meningiomas, oligodendrogliomas	Clinical diagnosis
Schwannomatosis	AD	1 in 126 000	Incomplete[b]		Multiple peripheral schwannomas, multiple meningiomas	Criteria for definite schwannomatosis[99]
Simpson-Golabi-Behmel syndrome	X-linked			Males with fetal macrosomia, postnatal overgrowth, macrocephaly, organomegaly, facial features, extremities abnormalities, supernumerary nipples, cardiac, skeletal, gastrointestinal, and genitourinary malformations	Wilms tumor, liver tumors, sellar-suprasellar cyst, dysmorphic pituitary gland, cyst of the septum pellucidum	Clinical diagnostic criteria not established

TABLE 1. Continued

Disorder	Inheritance	Incidence	Penetrance	Non-neoplastic features	Neoplastic features	Diagnosis
Tuberous Sclerosis Complex	AD	1 in 5000 to 10 000	Complete (100%)	Several hamartomas involving neural and non-neural tissues. Disorders involving the CNS include tubers (cortical hamartomas) and subcortical glioneuronal nodules, subependymal glial nodules (candle gutterings)	SEGAs, angiofibromas (adenoma sebaceum), subungual fibromas, cardiac rhabdomyomas, intestinal polyps, pulmonary lymphangioleiomyomatosis, renal angiomyolipomas	International TSC Consensus Conference[100]
Von-Hippel-Lindau disease	AD	1 in 36 000	Complete (100%)		Renal cell carcinoma, hemangioblastoma of the CNS and retina, pheochromocytoma, pancreatic cysts and cystadenomas of the epididymis and broad ligament, endolymphatic sac tumors of the middle ear	Mainly genetic testing after diagnosis of a single manifestation of VHL disease
Werner syndrome	AR	1 in 200 000		Bilateral cataracts, graying and loss of hair, scleroderma-like skin changes, diabetes mellitus, osteoporosis	Thyroid follicular carcinomas, malignant melanoma, meningioma, soft tissue sarcomas, primary bone tumors, leukemia/myelodysplasia	Clinical and genetic testing if clinical features are inconclusive[102]

[a]There are familial cases of "low-penetrance" phenotype with less severe RB1 mutations (eg, in-frame, missense, and promoter region).
[b]Lesser in LZTR1 variant.
AD, autosomal dominant; AR, autosomal recessive; GFAP, Glial fibrillary acidic protein; NIH, National institutes of Health.

TABLE 2. Immunophenotype and Differential Diagnosis of Nervous System Tumors Associated With HCS[a]

Tumor	Immunophenotype	Important differential diagnosis
Astrocytoma	GFAP+, S100+, Olig2 + IDH1R132H + and ATRX loss (in IDH1-mutant tumors)	Pilocytic astrocytoma DD varies with location and may rest upon clinical and radiological parameters Diffuse astrocytoma (grade 2) Reactive conditions (clinical and neuroradiological imaging) Oligodendroglioma (monotonous round nuclei, 1p/19q codeletion) Anaplastic astrocytoma (grade 3) Glioblastoma (necrosis and microvascular proliferation) Oligodendroglioma (monotonous round nuclei, 1p/19q codeletion) Glioblastoma (grade 4) Metastatic neoplasm (not infiltrative, cohesive cells) Oligodendroglioma (Monotonous round nuclei, 1p/19q codeletion) PCNSL (CD45+, CD43+)
Atypical teratoid/rhabdoid tumor	INI1 loss	Medulloblastoma (synaptophysin+, retained INI1)
Choroid plexus carcinoma	No specific IHC, CK+	Papillary tumor of the pineal region Papillary endolymphatic sac tumor (component of VHL) AT/RT (INI1 loss) Small blue cell tumors (CK−) Anaplastic ependymoma (GFAP+, CK−) Germ cell tumors (SALL4+, OCT3/4+)
Dysplastic cerebellar gangliocytomas	Synaptophysin+, NFTP+, NeuN+	Conventional gangliocytoma (abrupt interface with white matter) Astrocytoma (synaptophysin−)
Ependymoma	GFAP+, S100+, EMA+ (dot-like intracytoplasmic)	Schwannoma (strong S100+, GFAP−) Meningioma (EMA+, GFAP−) Pilocytic astrocytoma Diffuse astrocytoma Neurocytoma (synaptophysin+) Small blue cell tumors (GFAP−)
Hemangioblastoma	Inhibin+	Metastatic clear cell carcinoma (PAX8+, Inhibin−)
Malignant peripheral nerve sheath tumor	Diffuse H3K27me3 loss	Synovial Sarcoma (NY-ESO+) Leiomyosarcoma (Desmin+, SMA+) Metastatic spindle cell melanoma (S100+, SOX10+) Neurotrophic melanoma (S100+, SOX10+)
Medulloblastoma	Synaptophysin+, contain stellate reactive GFAP + astrocytes	AT/RT (INI1 loss) Ependymoma (GFAP+) Metastatic small cell carcinoma (TTF1+) Neurocytoma (cytologically bland)

TABLE 2. Continued

Tumor	Immunophenotype	Important differential diagnosis
Meningioma	Membranous EMA+, SSTR2A+, CK+ (secretory subtype), PR+, GFAP−	Schwannoma (diffuse S100+, EMA−) SFT (STAT6+, CD34+, EMA−) Metastatic carcinoma (BerEP4+) Astroblastoma (Intra-axial, GFAP+) Melanocytoma (MelanA+, MiTF+, EMA−)
Neuroblastoma	Synaptophysin+, NFTP+	Glioma (GFAP+) Neurocytoma (cytologically bland)
Neurofibroma	Mixed population of S100 + and CD34+	Schwannoma (more uniform and pronounced S100+, CD34−) Low-grade MPNST (cellular, atypia, mitosis, focal S100 + or S100−) Ganglioneuroma (dysmorphic ganglion cells) DFSP (cellular, storiform growth pattern, S100−, uniform CD34 + involving all cells) NSM (lobulated, hypocellular, no association with nerve) Spindle cell lipoma (posterior neck location, S100−) Perineuroma (GLUT1+)
Oligodendroglioma	No specific IHC, Olig2+	Reactive processes Infiltrating astrocytoma Clear cell ependymoma (compact noninfiltrating architecture, EMA+) DNT (seizure history, compatible imaging, nodular architecture, floating neurons) PCNSL (CD45+, CD43+)
Retinoblastoma	CRX+, NSE+	Medulloepithelioma Nematode endophthalmitis Persistent hyperplastic primary vitreous Coat's disease
Schwannoma	Diffuse S100+, variable GFAP	Neurofibroma (mixed population of S100 + and CD34+) NSM (lobulated, hypocellular, does not exhibit Antoni A and B pattern) MPNST (invade surrounding tissue, no hyaline vessels, monotonous growth, focal S100 + or S100−) Leiomyoma (no association with nerve, S100−, SMA+) Meningioma (patchy S100+, EMA+, Reticulin−) Pilocytic astrocytoma (Reticulin−)
Subependymal giant cell astrocytoma	S100+, focal weakly GFAP+	Gemistocytic astrocytoma Tumors with ganglion cells

[a] Although IHC offers rapid method of confirming the diagnosis of tumors, DNA methylation-based assay could be helpful to decipher the cases when IHC and DNA sequencing for mutations fail to reach a definite diagnosis.[103]

IHC, Immunohistochemistry.

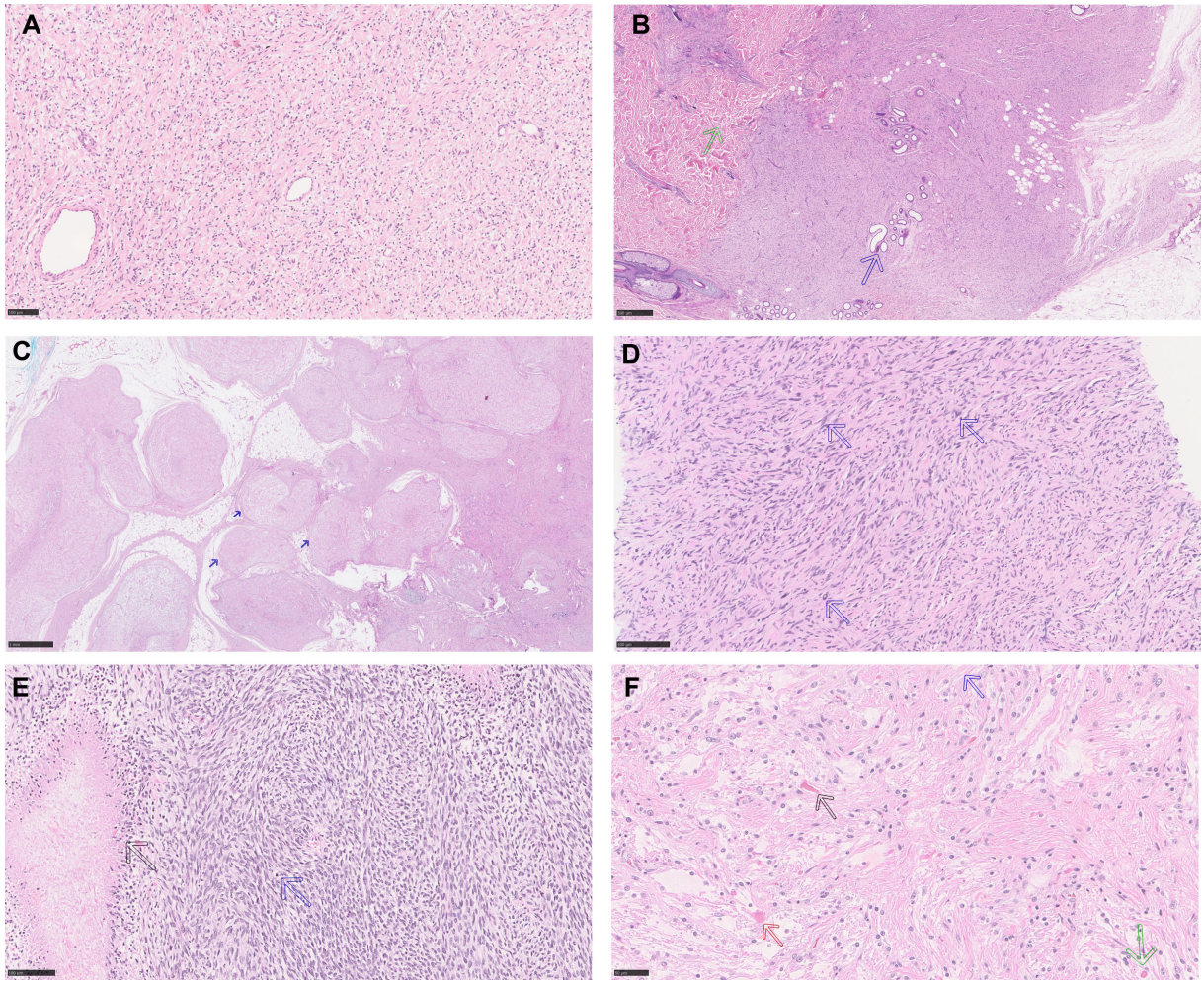

FIGURE 1. *Tumors of NF1 (H&E staining).* **A**, *Neurofibroma: benign hypocellular neoplasm composed of cells having thin, spindly nuclei in a collagenous background. Mitotic figures are rare.* **B**, *Diffuse neurofibroma: ill-defined subcutaneous proliferation (green arrow points to normal subcutaneous collagen). Blue arrow points to tumor cells entrapping adnexal structures.* **C**, *Plexiform neurofibroma: multinodular/serpentine growth pattern better appreciated grossly or on low magnification histology. Blue arrows point to multiple intraneural neurofibromas.* **D**, *Atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP): the lesion shows nuclear atypia (blue arrows) with loss of neurofibroma architecture and high cellularity, which are worrisome for malignancy transformation in plexiform neurofibromas. The term ANNUBP for lesions displaying at least 2 of these features (nuclear atypia with loss of neurofibroma architecture, high cellularity, and/or mitotic activity > 1/50 but <3/10 high-power fields) was proposed at a consensus at the National institutes of Health. Such diagnosis should prompt additional sampling, clinical correlation, and expert pathology consultation.*[101] *No mitotic figures are seen in this picture.* **E**, *MPNST: the lesion showed high-grade sarcoma with fascicular or storiform fibrosarcoma-like pattern, prominent nuclear atypia, tumor necrosis (black arrow), and mitosis (blue arrow points to a cell in prophase).* **F**, *OPG: it is pilocytic astrocytoma, WHO grade 1 (most common type of OPGs) that composed of astrocytes with bipolar thin hair-like (piloid) processes (blue arrow on top). Rosenthal fibers (black arrow in the middle), eosinophilic granular bodies (red arrow at the bottom), and hyaline globule (green arrow at the bottom) are commonly present.*

spinal nerve dorsal roots can be affected. The vestibular tumors in NF2 are polyclonal and more difficult to treat than sporadic tumors because of their multifocal nature.

Plexiform schwannoma (Figure 2B) could be associated with NF2 and no malignant transformation is reported. Schwannoma/neurofibroma hybrid nerve sheath tumors have been described in the settings of NF2. Hybrid tumors show highly ordered cellular components (Antoni-A) with loose myxoid components (Antoni-B) in addition to areas of wavy nuclei interspersed with collagen fibers (neurofibroma).

Malignant transformation in schwannoma often has epithelioid appearance but sometimes develops angiosarcoma. Collection of epithelioid cells in schwannoma suggests early malignant transformation.

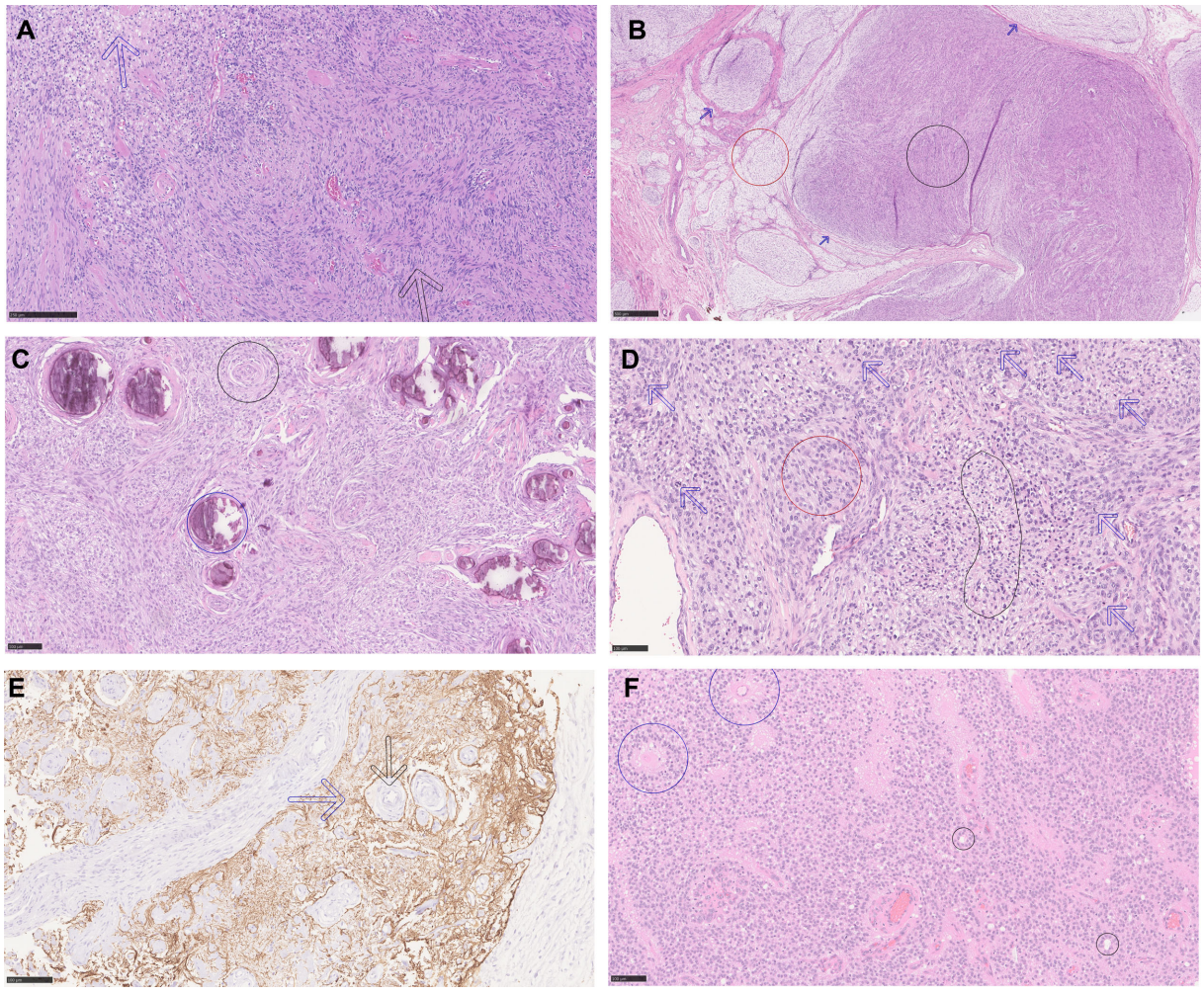

FIGURE 2. *Tumors of NF2 (H&E staining).* **A**, *Schwannoma: lesion is composed of mildly atypical Schwann cells arranged in fascicles. Hypercellular areas (Antony A, black arrow on the right) with nuclear palisading giving rise to Verocay bodies are seen intermixed with hypocellular areas (Antony B, blue arrow on the left). Some schwannomas may show increased proliferative activity; however, this is not considered a sign of aggressive behavior. This lesion does not show mitosis.* **B**, *Plexiform schwannoma: tumor is formed of multiple round to oval nodules (blue arrows) composed of spindled Schwann cells. There is syncytial growth pattern (black circle on the right) and amorphous-appearing pool of cellular processes (Verocay bodies, red circle on the left).* **C**, *Meningioma: the lesion is composed of atypical meningothelial cells arranged in sheets and lobules with scattered cellular whorls (black circle on top) and calcified psammoma bodies (blue circle at the bottom). It is WHO grade 1 tumor. Multiple meningiomas or meningiomatosis is a feature of NF2, and they are usually psammomatous, fibroblastic, meningothelial, or transitional types.* **D** *showed anaplastic meningioma (WHO grade 3). Red circle highlights sheet of atypical meningothelial cells with many mitotic figures (blue arrows) and tumor necrosis (black line in the middle).* **E**, *Meningioangiomatosis: it is a malformative cortical lesion that is characterized by plaque like proliferation of perivascular meningothelial and fibroblast like cells. Meningeal cells encircle intracortical vessels (black arrow, cells are negative for Glial fibrillary acidic protein (GFAP)), where brain parenchyma stains positive for GFAP (blue arrow). Brain invasion was in question, but the bland cytology of the lesion argued against it (GFAP IHC).* **F**, *Spinal ependymoma: the tumor shows true rosettes (black circles on the right) and perivascular pseudo-rosettes (blue arrows on the left) with hypercellular sheet-like growth pattern in between.*

Multiple meningiomas (Figure 2C-2E) (meningiomatosis) occur throughout the cranial and spinal neuraxis and maybe the presenting feature of NF2. There are 2 main hypotheses for their development, one that supports the independent tumorigenesis of these neoplasms and the other suggests the propagation of tumor cells of a unique clone through cerebrospinal fluid.

Gliomas in NF2 consist predominantly of spinal and cauda equina ependymomas (Figure 2F). These are usually multiple and slowly growing.

Glial hamartias are clusters of atypical glial cells that occur in the cortices and basal ganglia. These are common and pathognomonic features of NF2.

NF2 results from mutation in the NF2. Merlin exists in 2 forms: inactivated (unphosphorylated) and activated (phosphorylated). Once Merlin gets activated in the presence of WNT or transmembrane proteins (cadherins, integrins, and CD44), inhibits mammalian target of rapamycin (mTOR), is imported to the nucleus and suppresses the Hippo pathway (YAP/TAZ) through binding of the transcription factor CRL4.[23]

The discovery of LZTR1-associated schwannomatosis showed substantial diagnostic overlap with NF2, particularly in those with unilateral vestibular schwannoma and other nondermal schwannomas.

Schwannomatosis is characterized by multiple peripheral schwannomas in the absence of other diagnostic features of NF2. Bilateral vestibular schwannomas are not encountered and multiple meningiomas could happen. Unlike NF2, somatic mutations of *NF2* not germline mutations are frequently seen resulting from *SMARCB1* or *LZTR1* germline mutations.

LZTR1 inhibits RAS signaling through ubiquitination of RAS by cullin 3 ubiquitin ligase complexes. *LZTR1* mutations result in incomplete degradation of Ras-GTPase RIT1 and dysregulated growth factor signaling responses.[24] LZTR1 loss in Schwann cells drives dedifferentiation and proliferation.[25]

FAMILIAL MULTIPLE MENINGIOMAS

It is an AD disorder defined by the presence of at least 2 lesions that appear simultaneously or at different intracranial locations, without the association of NF. Heterozygous loss-of-function germline mutations in *SMARCE1* – SWI/SNF complex – predisposes to spinal and intracranial clear-cell meningiomas.[26] Swedish study showed concordance in histology for meningioma in mother-offspring.[27]

CARNEY COMPLEX

It is associated with clinically aggressive psammomatous melanotic schwannoma (Figure 3).

Carney complex (CNC) is linked in 40% of familial cases to mutations in tumor-suppressor gene *PRKAR1*. Protein kinase alpha is a ubiquitous cAMP-dependent kinase that binds to A-kinase anchoring proteins and allows cAMP-responsive events to occur within specific compartments of the cells and to cluster with other classes of signaling enzymes.[28] Missense mutation in *PRKAR1* results in decrease in the cellular pool of the regulatory subunits (RIα) allowing the catalytic (C) subunit to roam unregulated increasing the kinase activity.

CNC was previously called NAME (nevi, atrial myxoma, ephelides) and LAMB (lentigines, atrial myxoma, blue nevi) syndrome. Because of the presence of ephelides (freckles), it may seem like Peutz-Jeughers syndrome. Carney triad consists of paragangliomas, gastric stromal tumors, and pulmonary chondromas, and should not be confused with CNC.

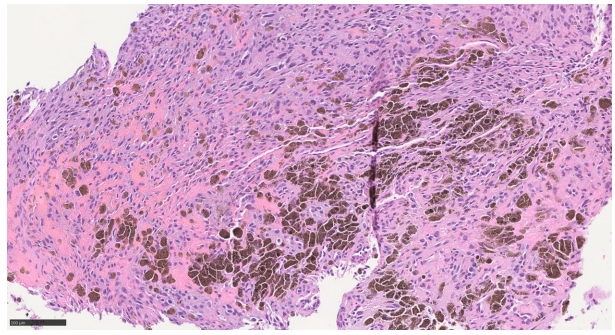

FIGURE 3. *Tumors of CNC (H&E staining). Psammomatous melanotic schwannoma in 10% of patients, a rare nerve sheath tumor that can involve the CNS and is characterized by high melanin pigmentation and psammoma bodies.*

TUBEROUS SCLEROSIS COMPLEX

CNS manifestations include tubers, subcortical glioneuronal nodules, subependymal glial nodules, and subependymal giant cell astrocytoma (SEGA).

SEGA (Figure 4A) occurs in 5% to 15% of TSC patients and is considered a major diagnostic criterion. The tumors are well circumscribed and project in the lateral ventricle. SEGA could present with intratumoral hemorrhage and acute hydrocephalus.

Cortical tubers (Figure 4B) are hamartomatous nodules that can be epileptogenic and are usually needed to be resected. Magnetic resonance imaging helps to identify them, and reflectance spectroscopy was attempted in small cohort for better localization.[29]

TSC is caused by inactivating *TSC1* and *TSC2* germline mutations. Tuberin and hamartin dimerize to suppress mTOR; that is why everolimus is used in TSC.[30] Tsc1 stabilizes Tsc2 by facilitating Hsp90-mediated folding of kinase and nonkinase clients, including Tsc2, thereby preventing their degradation.[31]

Conversely, Polo-like kinase 1 phosphorylation of TSC1 interferes with TSC1/TSC2 binding, destabilized TSC1, promoted dissociation of the TSC complex from the lysosome, and eventually leads to mTOR activation.[32] Sustained activation of mTOR in oligodendrocyte progenitors in *Tsc1* mutants leads to oligodendrocyte cell death and myelination defects.[33] Hyperactive mTOR-mediated negative feedback regulation of AKT partially contributes to the benign nature of TSC-associated tumors.[34]

VON HIPPEL-LINDAU DISEASE

VHL syndrome is divided into 4 subtypes (1, 2A, 2B, and 2C) according to the risk of developing pheochromocytoma (type 2C has only pheochromocytomas). Type 1 is more likely to develop CNS hemangioblastomas.

CNS or retinal hemangioblastomas (Figure 5) appear at early age (25-29 yr). CNS tumors developed in cerebellum, brain stem,

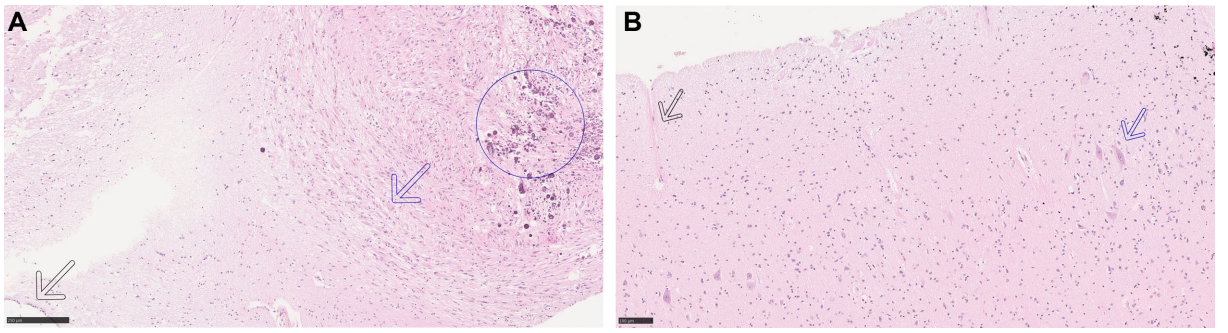

FIGURE 4. *Lesions in TSC (H&E staining).* **A**, *SEGA: lesion consists of large atypical astrocytes that have copious eosinophilic cytoplasm resembling gemistocytic astrocytes and are arranged in sheets, fascicles, and perivascular clusters (blue arrow). Stromal dystrophic calcification (blue circle) is common. Mitotic figures are rare. It is a slow growing neoplasm (WHO grade 1) arising from the subependymal layer of the lateral ventricles (black arrow points to ependymal lining of lateral ventricle).* **B**, *Cortical tubers: it is a hamartomatous nodule that can be multiple and epileptogenic. Large balloon cells displaying both glial and neuronal features are frequently encountered (blue arrow). Typically, lesion is composed of multinucleated giant cells, abnormal dysplastic neurons, and reactive gliosis, disrupting the normal cortical lamination (not shown here). Black arrow shows Virchow-Robin space.*

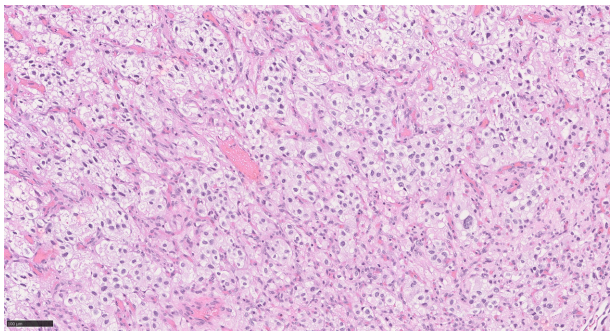

FIGURE 5. *Hemangioblastoma in VHL (H&E staining). The tumor is composed of 2 elements, large number of capillaries and small blood vessels, and collection of stromal cells with eosinophilic cytoplasm. Many stromal cells display larger, lipidized, and vacuolated cytoplasm. The cell of origin is not known. These are benign circumscribed tumors and belong to WHO grade 1.*

and spinal cord, in that order of frequency. Multifocal CNS hemangioblastomas were also reported.

VHL is associated with inactivation *VHL* germline mutations. VHL is a tumor-suppressor protein involved in hypoxia signaling. It acts as ubiquitin E3 ligase to help the proteasomal degradation of hypoxia-inducible factors 1 and 2. These factors activate glycolysis, fatty acid metabolism, erythropoiesis, and angiogenesis. VHL is also required for proper P53 activation and mTOR regulation.

VHL-JAK-STAT signaling plays alternative pathways in hemangioblastoma to supplement VHL-hypoxia-inducible factor (HIF) pathway.[35] Jade-1 is another tumor-suppressor protein associated with histone acetyltransferase (HAT) activity and stabilized by VHL; its destabilization contributes to cancer.[36]

Independent of HIF pathway, inactivation of m^6A ribonucleic acid (RNA) demethylase Fat mass and obesity-associated protein in the presence of VHL loss reduces tumor cells growth. It was proposed as targeted therapy for drug-resistant clear-cell renal cell carcinoma in VHL.[37]

Although VHL could be caused by multiple loss-of-function mutations, C-terminal-encoding *VHL* mutations may cause polycythemia.[38]

LI-FRAUMENI SYNDROME

Among the CNS neoplasms medulloblastomas, choroid plexus carcinoma (CPC) and ependymomas predominate. However, in the young adult, astrocytomas occur commonly.

Most CPC arise in the children (14% occurring in the first year of life) in the region of the lateral ventricles (Figure 6A). Hydrocephalus and increased intracranial pressure are common because of tumors location.

Although 40% of CPCs display *TP53* germline mutations in the setting of Li-Fraumeni syndrome (LFS), 90% of *TP53* wild-type CPC harbor some dysfunction of P53 because of polymorphism like R72P variant.

Medulloblastoma (Figure 6B and 6C) predominantly affects children less than 3 yr old. They are located exclusively in the cerebellum and dorsal brainstem region. Originally, 4 histological subtypes were recognized, including classic (72% of all), desmoplastic/nodular, medulloblastoma with extensive nodularity, and large cell/anaplastic. However, World Health Organization (WHO) classification is based on their molecular characteristics because of its increasing clinical utility. Five distinct genetic subtypes are identified: WNT-activated, SHH-activated, *TP53*-mutant, *TP53* wild-type, and non-WNT/non-SHH. Massive chromosome rearrangements in a 1-step catastrophic event termed "chromothripsis" were linked to P53 status.[39]

LFS results from *TP53* germline mutations. The core P53 pathway is the response to DNA damage either by repair

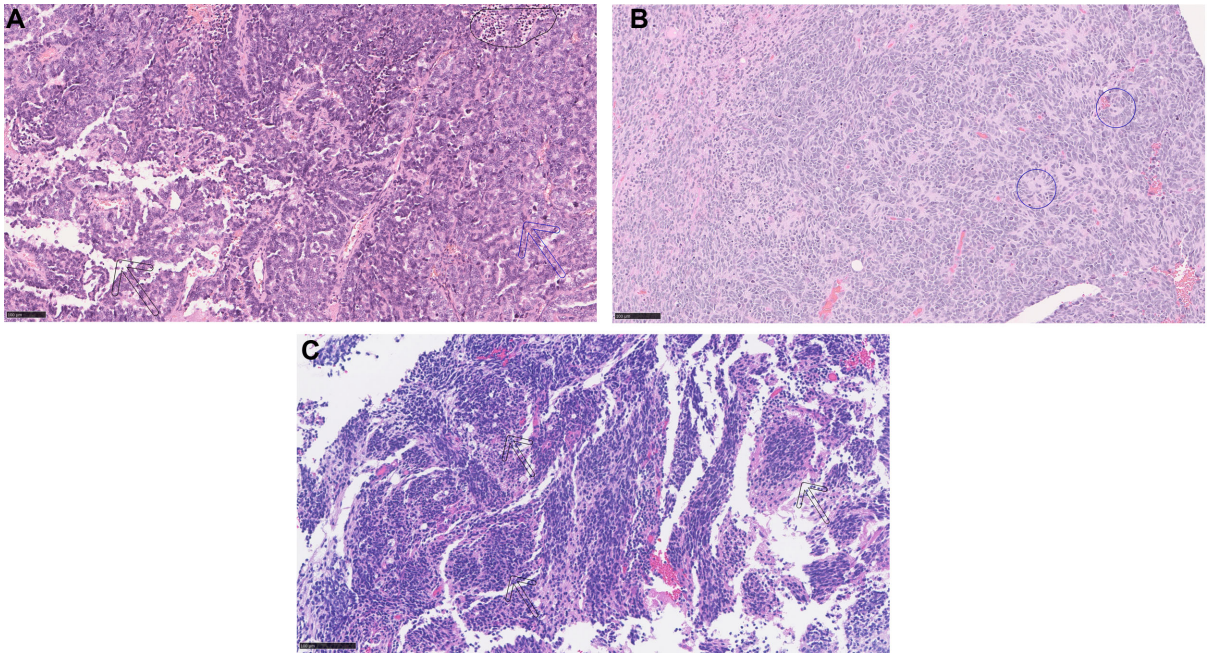

FIGURE 6. *Tumors of LFS (H&E staining).* **A**, *CPC: these tumors show a solid (blue arrow on the right) as well as vague papillary structures (black arrow on the left) with increased cell density, frequent mitotic figures and foci of necrosis (black line on top). Individual cells are epithelioid with nuclear hyperchromicity and pleomorphism. Adjacent brain invasion and metastasis via cerebrospinal fluid pathway are common. These are WHO grade 3 tumors.* **B** *and* **C**, *Medulloblastoma: these tumors are a high-grade (WHO grade 4) embryonal tumor that predominantly affects children less than 3 yr old. They are located exclusively in the cerebellum and dorsal brainstem region and consist of highly atypical and poorly differentiated cells having frequent mitotic figures and tumor cell necrosis. Homer-Wright (neuroblastic) rosettes are seen in many cases (blue circles).* **B**, *Classic type (molecularly by methylation classifier and Next-generation sequencing is subclass group 4).* **C**, *Desmoplastic/nodular type. Black arrows point to the nodular pattern (molecularly is SHH-B group).*

and return to homeostasis or cell death. There is redundancy and extensive communication of P53 pathway with other cellular pathways and feedback loops. The downstream genes regulated by the wild-type P53 are robust; however, loss-of-function mutation of *TP53* turns off the entire pathway. Interestingly, mutations in *TP53* can function efficiently initializing malignancy rapidly in tissue of ectodermal or mesodermal-derived origin (in case of medulloblastoma and rhabdomyosarcoma), whereas same mutations in endodermal-derived stem cells require other mutations in oncogenes or tumor-suppressor genes, occurring prior to the *TP53* mutations, to develop malignancy (in case of lung and colonic cancer).[40]

Surprisingly, P53-mutant loss of function is accompanied by 3 phenomena. First, P53 mutant can drive P53 wild-type to a mutant conformation in similar mechanism to the prions.[41] Second, P53 mutant has the ability of acquiring novel functions.[42] Last, mutations within *TP53* cause stabilization of P53-mutant and its overexpression that led to its discovery originally.[43] Among the novel functions, P53 mutant significantly upregulates mevalonate pathway via SREBP2 and promotes the synthesis of ubiquinone that supports the synthesis of pyrimidine nucleotide.[44]

PTEN HAMARTOMA TUMOR SYNDROMES

The defining feature of PTEN hamartoma tumor syndrome (PHTS) is the presence of hamartomatous tumors.

COWDEN SYNDROME

Multiple hamartomas arising from all three germ layers happens, of which facial trichilemmomas and adult cerebellar dysplastic gangliocytomas are highly pathognomonic.

Cowden syndrome (CS) is caused by *PTEN* germline mutations; however, somatic mutations are rarely encountered in CNS malignancies. Generally, PTEN levels are frequently downregulated in cancer, even in the absence of genetic aberrations.[45] E3 ubiquitin ligase WWP1 negatively regulates PTEN, and it was suggested to have oncogenic function.[46] PTEN tumor-suppressor activity depends on its lipid phosphatase activity, which antagonizes PI3K-AKT-mTOR signaling at the plasma membrane. Additionally, PTEN has phosphatase independent functions in the nucleus like DNA repair regulation and maintaining chromosomal stability and can be exported extracellularly through exosomal export or secretion to produce tumor-suppressor effects in adjacent cells.[47]

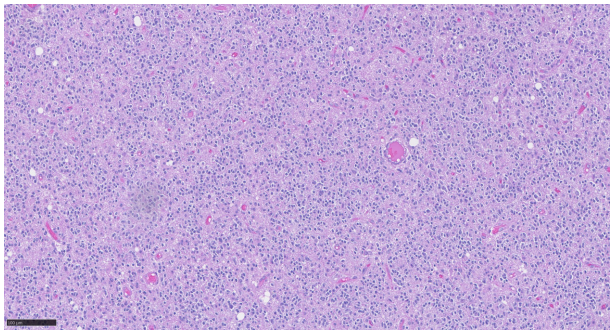

FIGURE 7. *Oligodendroglioma in CMMRD (H&E staining). Tumor is formed of a uniform population of tumor cells with round nuclei, scant cytoplasm, and an artifactual perinuclear halo (so-called fried egg appearance).*

CS and Bannayan-Riley-Ruvalcaba syndrome are considered variable phenotypic presentations of the same disorder.

Dysplastic Cerebellar Gangliocytomas

They are benign cerebellar tumors composed of dysplastic and enlarged ganglionic cells infiltrating and enlarging the internal granular layer of the cerebellar gray matter, causing abnormal thickening of cerebellar folia. Though WHO grade 1 has been assigned, it is not clear whether this is a neoplasm or hamartoma. The tumor may spread locally but not outside the cerebellum. Most cases occur in the adults and all of them display *PTEN* mutations, which are not common in pediatric tumors. It may arise in conjunction with CS or without other PHTS signs.

Proteus-like syndrome is associated with *PTEN* pathogenic variants but lack hamartomas.

TURCOT SYNDROME

Turcot syndrome is a historical term for conditions showing brain tumors, intestinal polyps, and cancers caused by *APC* germline mutations. Recently, it was divided subsequently into 2 distinct disorders based on different genetic profiles involving distinct inheritance and cancer spectrum.

Mismatch Repair Cancer Syndrome

This AD disorder is caused by mutations in one of the mismatch repair (MMR) genes *MLH1*, *PMS2*, *MSH2*, and *MSH6*. Individuals carry biallelic homozygous or compound heterozygous deleterious germline mutations in MMR, leading to constitutional MMR deficiency syndrome (CMMRD) in contrast to heterozygous monoallelic germline loss-of-function mutations followed by somatic loss of the remaining wild-type allele, which happens in Lynch syndrome (LS).

Based on the effect of acetylsalicylic acid (ASA) in reducing cancer risk in individuals with LS, ASA is used to reduce the risk of cancer in CMMRD.[48]

Astrocytomas and oligodendrogliomas (Figure 7) occur in the first 2 decades. Presence of giant cells on histology, multiple brain tumors, and developmental brain anomalies are suggested to be characteristic features for CMMRD. In addition, medulloblastomas and primitive neuroectodermal tumors were reported.

Individuals with CMMRD may have NF1-like phenotype, presenting with café-au-lait spots, neurofibromas, Lisch nodules, and axillary freckling. Gastrointestinal polyposis and malignancies are encountered in almost all the patients.

Familial Adenomatous Polyposis

It is caused by heterozygous mutations in the *APC* tumor-suppressor gene. APC inhibits the WNT/β-catenin signaling. Without APC, β-catenin remains undegraded, resulting in uncontrolled proliferation. β-catenin is also involved in cell migration, adhesion, transcriptional activation, and apoptosis inhibition.

Polymerase proofreading-associated polyposis syndrome is AD highly penetrant disorder caused by *POLE* and *POLD1* germline mutations. Affected individuals develop adenomatous polyposis and are at risk for colonic and endometrial cancer at early age.

NEVOID BASAL CELL CARINOMA SYNDROME (GORLIN SYNDROME)

The nevoid basal cell carcinoma syndrome is caused by germline mutations of *PTCH1* and rarely *SUFU* or *PTCH2*.

PTCH1 is a receptor for secreted hedgehog signaling molecules, including sonic hedgehog (SHH).[49] SHH binds to and inhibits PTCH1, which permits the signal transducer Smoothened (SMO) activation.[50] Mutated *PTCH1* does not inhibit SMO, resulting in activation of SUFU-GLI. GLI is a transcription factor that causes cell proliferation.[51] The risk of developing medulloblastomas is substantially higher in individuals with *SUFU* pathogenic variants with a male predominance of 3:1.

Gorlin-Koutlas syndrome is defined by occurring of multiple schwannomas in an extended family who also develop multiple nevocytic nevi and vaginal leiomyomas.

RHABDOID TUMOR PREDISPOSITION SYNDROME

Rhabdoid tumor predisposition syndrome (RTPS) is caused by *SMARCB1* germline mutations. SMARCB1/INI1 is part of the BAF chromatin-remodeling complex (aka SWI/SNF complex). Knock-out of Ini1 in mice embryo results in their demise,[52] but Ini1-heterozygous mice develop aggressive cancer, including rhabdoid-like tumors and T-cell lymphomas.[53] Different mouse models showed that early Ini1 loss causes rhabdoid tumors, whereas Ini1 loss at later stages combined with *Nf2* inactivation causes schwannomas. Atypical teratoid/rhabdoid tumor (AT/RT) (Figure 8) presents in patients aged 3 yr or below. Both supra and infratentorial locations are common.

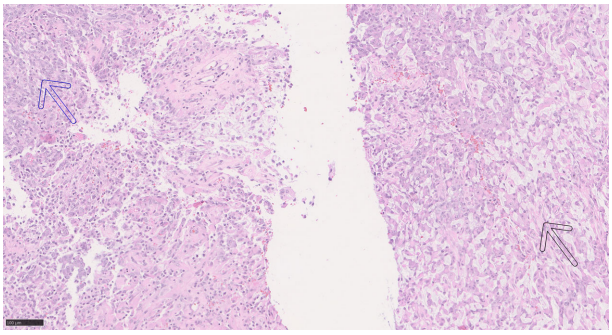

FIGURE 8. *AT/RT (H&E staining). This is a poorly differentiated WHO grade 4 embryonal tumor that usually presents in patients aged 3 yr or below. Both supra and infratentorial locations are common. The characteristic feature of the tumor is presence of large number of cells having copious eosinophilic cytoplasm and eccentrically located nuclei, so-called rhabdoid cells (black arrow on the right). Apart from this the neoplastic cells can display epithelial, mesodermal (blue arrow on the left), and neuroectodermal differentiation.*

HEREDITARY RETINOBLASTOMA

Hereditary retinoblastoma is caused by *RB1* germline mutations and 90% of cases present before 3 yr of age. Trilateral retinoblastoma presents as midline intracranial neuroblastoma (in the pineal gland or in the supra/parasellar region) with bilateral intraocular retinoblastomas (Figure 9). Noninheritable cases of retinoblastoma are always unilateral.

Retinoblastoma (RB) inhibits cell growth through interaction with E2F transcription factors.[54] The CDK–RB–E2F axis forms the core transcriptional machinery driving cell cycle progression and alterations in the components of this axis occur in virtually all cancers. Interestingly, mice with single copy of *Rb* develop multiple neuroendocrine neoplasia.[55] Moreover, most sporadic cancers inactivate RB by phosphorylation rather than losing it entirely – possibly to take advantage of RB antiapoptotic role under stress.[56]

Inactivation of *RB1* is usually caused by mutations affecting the coding region. Silencing by methylation of *RB1* promoter is observed in retinoblastoma as second event and is classified

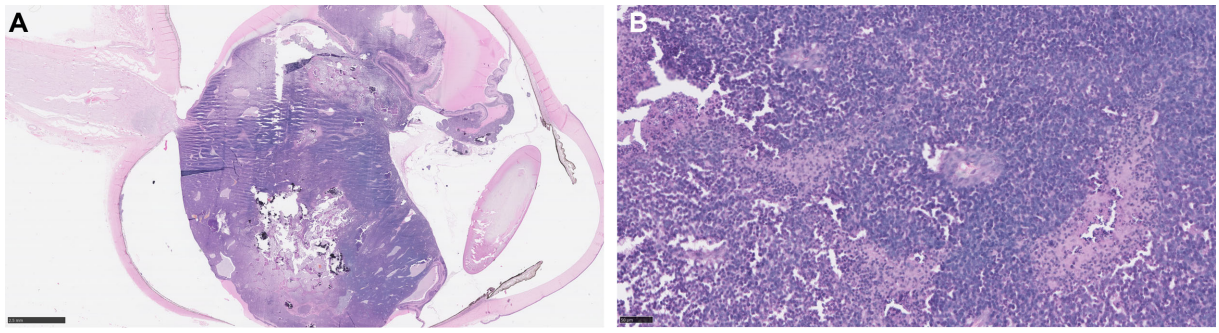

FIGURE 9. *Retinoblastoma.* **A**, *Tumor shows endophytic growth inward toward vitreous cavity and fill it.* **B**, *Tumor consists of small round blue cells.*

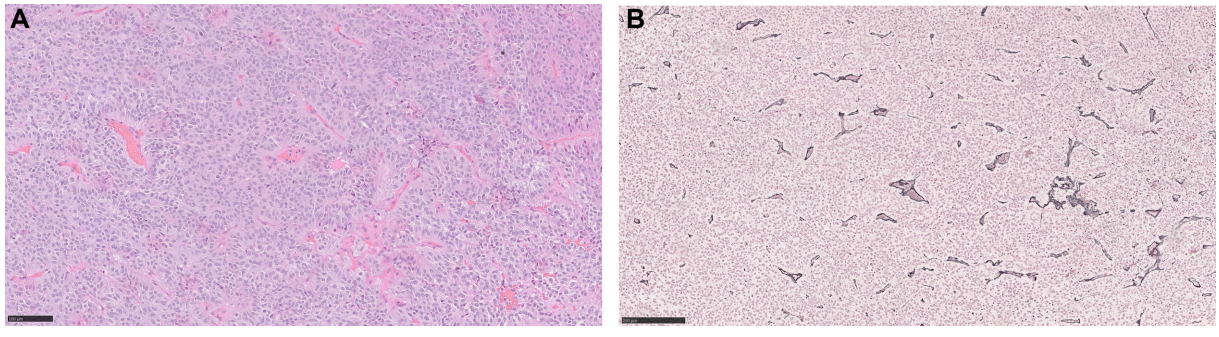

FIGURE 10. *Pituitary adenoma in MEN1 (H&E staining). The adenomas display proliferation of monomorphic epithelioid cells having copious cytoplasm. The cells are arranged in sheets and cords* **A**, *destroying the typical acinar (nested) architecture of the normal adenohypophysis. The effacement of the normal acinar network of the gland can be confirmed by a reticulin stain* **B** *that is diagnostic of an adenoma. No acinar outlines could be appreciated on reticulin staining.*

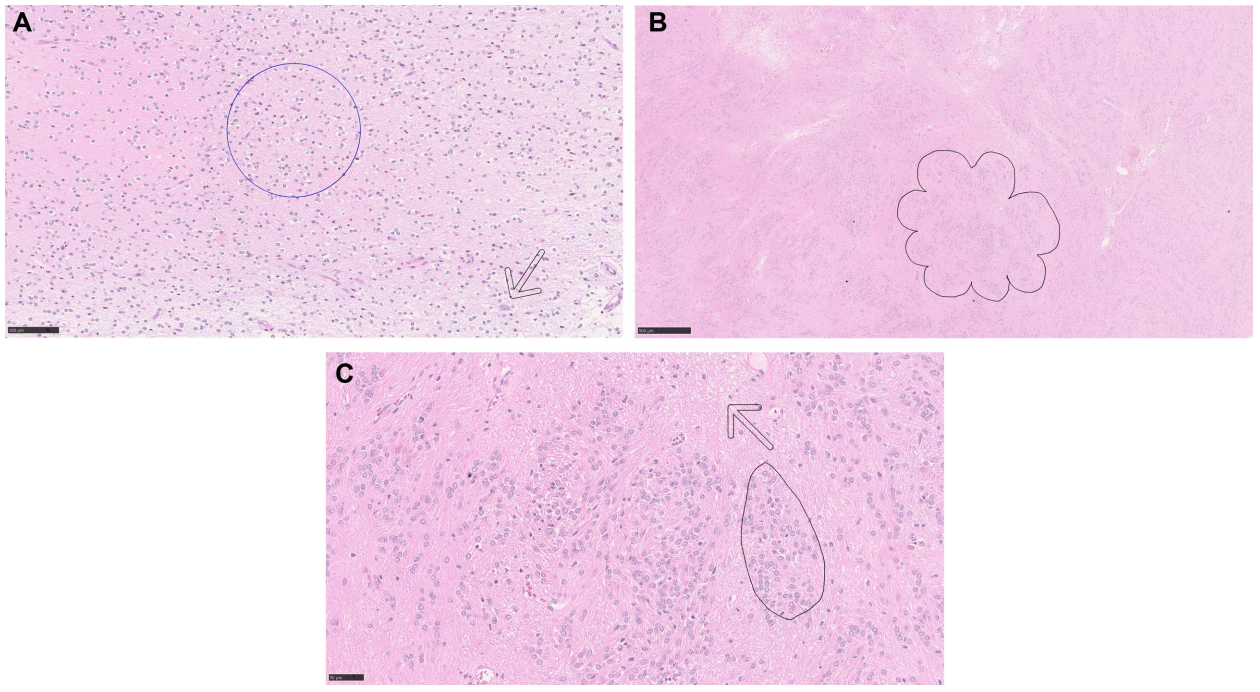

FIGURE 11. *Tumors of Noonan syndrome.* **A**, *DNT: tumor is formed of round uniform cells resembling those found in oligodendrogliomas (blue circle) and floating mature neurons (black arrow).* **B** *and* **C**, *Subependymoma: tumor shows lobulated architecture* **B** *with variably size clusters of tumor cells embedded in the fibrillary matrix (C, circle) separated by a loose matrix (C, arrow).*

as somatic epimutation. However, monoallelic germline *RB1* promoter methylation has also been described.[57] RB1 itself is known epigenetic regulator interacting with SWI/SNF complexes, histone deacetylase, and DNA methyltransferase DNMT1.[58]

ATAXIA-TELANGIECTASIA

A total of 85% of patients develop lymphomas and acute leukemias, but brain tumors may happen. Ataxia-telangiectasia (AT) is caused by AT mutated (*ATM*) germline mutations. ATM kinase regulates the cellular response to DNA double-strands breaks by activating P53 and inhibiting MDM2 (P53-specific inactivator), leading to P53 accumulation.[59] It also activates other DNA repair proteins (eg, BRCA1 and NBS1), CHK2 (control cell cycle), eIF-4E (protein translation), and PP2A (AKT phosphatase).[60-62] The presence of neurological symptoms likely develops because of PP2A inhibition.[63] In the absence of ATM, cells build up somatic mutations, leading to malignancies.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

It is characterized by parathyroid, pancreatic islet cell/gastrointestinal, and anterior pituitary tumors. Multiple endocrine neoplasia type 1 (MEN1) results from *MEN1* germline mutations. Menin is a component of MLL1/MLL2-containing histone methyltransferase complexes that trimethylate H3K4.[64] However, it interacts with myelocytomatosis oncogene (MYC) and enhances the transcription of MYC target genes independent from H3K4me3 inhibitory activity.[65] Menin inhibits SHH[66] and HOX signaling via PRMT5. It interacts with CHES1 in S-phase checkpoint pathway related to DNA damage response.[67] It has essential role in WNT/β-catenin signaling.[68] Additionally, it binds transcription factor JUND, inhibiting its transcriptional activity.[69] It remains unclear why tumors arise only in neuroendocrine organs.

Pituitary adenomas (PA) (Figure 10) are broadly categorized into macro- or micro-adenomas (1-cm cutoff), functional (hormone-secreting), or nonfunctioning. Functional adenomas secrete 1 hormone (commonly GH or ACTH), though some may secrete 2 hormones. These functional adenomas are microadenomas and are detected early because of early hyperpituitarism symptoms. Nonfunctioning adenomas are usually macroadenomas, causing hypopituitarism by compressing the adjacent normal parenchyma.

MEN4

MEN4 is caused by CDKN1B germline mutations and characterized by parathyroid and anterior pituitary tumors in association with tumors of the adrenals, kidneys, and reproductive organs.[70]

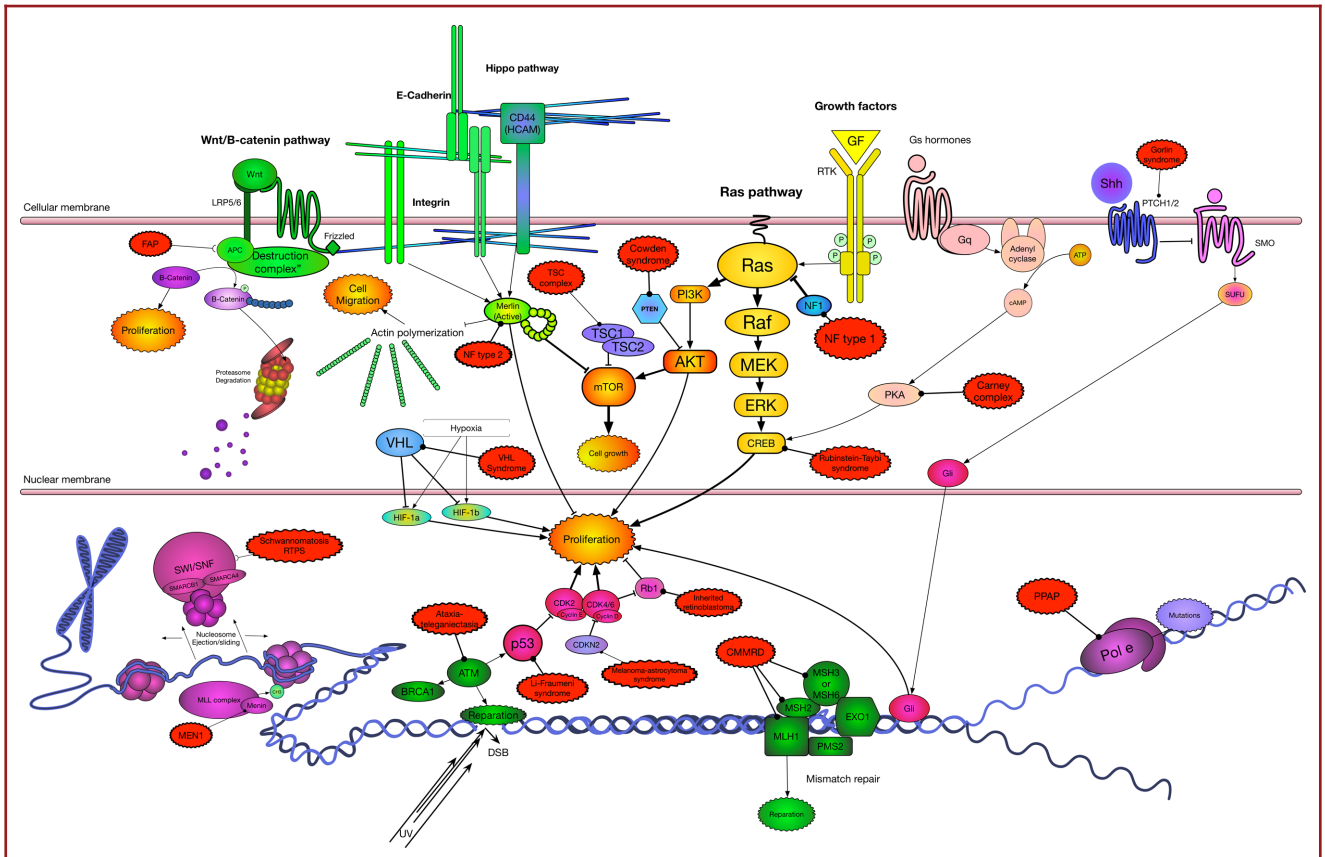

FIGURE 12. *Diagram illustrates signaling pathways involved in hereditary predisposition cancer syndromes pathogenesis. Many HCS genetic alterations affect cell cycling proteins (LFS, RB, and MAS), DNA repair (ATM, CMMRD, and PPAP), mTOR pathway (NF1, NF2, TSC, VHL, and Cowden), or epigenetic modifications (RTS, RTPS, Schwannomatosis, and MEN1). "→," stimulation; and "⊣" inhibition. Color code: "warm" colors (yellow, orange, and peach) represent proto-oncogenic proteins, whereas "cold" colors (blue, magenta, violet, and green) represent tumor suppressors. Red patches – names of the diseases linked with the associated abnormal proteins. Golden yellow – Ras-Raf-MEK-ERK (also known as MAPK/ERK) pathway, one of the main growth signaling pathways. Yellow-green – hypoxia-inducible factors sustain growth and development in an oxygen-deprived environment. Orange – PI3K-AKT (also known as protein kinase B) pathway, the second major cellular growth, and proliferation signaling cascade. AKT phosphorylates more than a hundred of other proteins and is highly conservative throughout all eukaryotic organisms. The RAS pathway also activates it. Peach – protein kinase A/cAMP pathway; regulated by G proteins (Gs activates, Gi inhibits); involved in glucose metabolism, cellular growth, and proliferation (via CREB). Lime – proteins involved in cytoskeleton regulation and intercellular contacts (WNT/B-catenin pathway, Merlin). WNT pathway is a key regulator of cellular polarity, migration, and body axial orientation; it also controls regeneration in adult bone marrow, skin, and intestine. Merlin is a membrane-cytoskeleton scaffolding protein, normally promotes contact-mediated growth and proliferation inhibition through the Hippo pathway (not shown in a diagram). Green – DNA reparation proteins; includes single- and double-strand breaks repair systems and mismatched base repair system. Mismatch errors occur when DNA in the synthetic (S) phase, whereas others can occur throughout the cell cycle. Double-stranded breaks, as shown, mostly happen because of ultraviolet radiation, which explains sunlight sensitivity in AT. Blue – inhibitory proteins (VHL, NF1, and TSC1/TSC2). These are major negative regulators of growth signaling pathways. This group is heterogeneous by the mechanism of action. Magenta – cell cycle regulatory proteins; includes P53 and RB1 (G1-S checkpoint control). Purple – DNA binding proteins, which include SWI/SNF complexes and RNA polymerases. SWI/SNF complexes, as shown, responsible for proper chromatin packing and nucleosome sliding. Abbreviations: GF – growth factors (such factors as insulin and insulin-like growth factors, epidermal growth factor, nerve growth factor, platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor); UV – ultraviolet light; DSB – double-strand breaks); RTK – receptor tyrosine kinase; MAPK – mitogen-activated protein kinases; MEK – MAPK/ERK kinase; ERK – extracellular signal-regulated kinases; NF1– neurofibromin 1 protein; NF type 1 – neurofibromatosis type 1; Ras – rat sarcoma proteins; RAF – rapidly accelerated fibrosarcoma kinase; cAMP – cyclic adenosine monophosphate; PKA – protein kinase A; CREB – cyclic AMP response element-binding protein; PI3K – phosphoinositide 3-kinase; PTEN – phosphatase and tensin homolog; TSC1/TSC2 – tuberous sclerosis complex proteins 1 and 2; mTOR – mammalian target of rapamycin complex; CD44 (HCAM) – homing cell adhesion molecule; NF type 2 – neurofibromatosis type 2; VHL – von Hippel-Lindau; HIF 1a/1b – hypoxia-inducible factors 1a/1b; LRP5/6 – low-density lipoprotein receptor-related protein 5/6; APC – adenomatous polyposis coli; SWI/SNF – SWItch/sucrose nonfermentable chromatin-remodeling complexes; MLL – mixed lineage leukemia complexes; MEN1 – multiple endocrine neoplasia type 1; ATM – ataxia-telangiectasia mutated; CMMRD – constitutional mismatch repair disorder; EXO1 – exodeoxyribonuclease 1; Shh – sonic hedgehog protein; PTCH1 – protein patched homolog 1; SMO – smoothened; SUFU – suppressor of fused homolog; Gli – glioma associated oncogene; PPAP – polymerase proofreading-associated polyposis; Pole – DNA polymerase epsilon.*

FAMILIAL ISOLATED PITUITARY ADENOMA

It is a familial PA with no other associated tumors like in MEN1, MEN4, and CNC. It is caused by *AIP* germline mutations with incomplete penetrance.[71] AIP is associated normally with GH and prolactin secretory vesicles, but not in thyrotrophs, corticotrophs, gonadotrophs, or follicular cells.

McCune-Albright syndrome and SDHx mutations are also HCS that predispose to pituitary tumorigenesis.[72,73]

RUBINSTEIN-TAYBI SYNDROME

Rubinstein-Taybi syndrome (RTS) is associated with medulloblastomas, meningiomas, and oligodendrogliomas.

RTS is associated with mutations in the *CREBBP* or its homolog *EP300*. CBP has HAT activity and regulates expression of multiple proteins, such as P53 and MYC. CREBBP mutations results in tumorigenesis and immuno-evasion.[74-76]

OLLIER DISEASE AND MAFFUCCI SYNDROME

Individuals with these disorders develop multiple enchondromas with no causative gene identified to date. However, there is increased incidence of gliomas that harbor *IDH1* and rarely *IDH2* mutations.[77] Notably, *IDH1* and *IDH2* mutations are reported in enchondromas and chondrosarcoma.[78]

WERNER SYNDROME

Werner syndrome (WS) is premature aging syndrome that develops features of aging in the second decade of life. It is caused by *WRN* RecQ helicase mutations, which is not enough alone to develop tumors.[79] Lacking *WRN* results in deletion of telomeres from single sister chromatids that are replicated by lagging strand synthesis.[80] Cancer predisposition is due to cellular senescence and not mtDNA mutagenesis.[81]

NIJMEGEN BREAKAGE SYNDROME

Most malignancies in Nijmegen breakage syndrome (NBS) are lymphoid with reported medulloblastomas. NBS is due to *NBS1* mutations that result in genomic instability. Nbs1-deficient neuroprogenitors show proliferation defects and contain more chromosomal breaks, which are accompanied by ATM-mediated P53 activation.[82]

SIMPSON-GOLABI-BEHMEL SYNDROME

Simpson-Golabi-Behmel syndrome (SGBS) is an overgrowth syndrome caused by *GPC3* germline mutations. Glypican-3 forms a complex with insulin-like growth factor 2.[83] A sellar-suprasellar cyst, dysmorphic pituitary gland, and a cyst of the septum pellucidum are reported.

Beckwith-Wiedemann, Sotos, and Weaver syndromes are also overgrowth disorders that are not connected with GH overproduction.

DICER1 SYNDROME

DICER1 germline mutations cause variety of tumors. Loss of DICER1 in developing lung results in pleuropulmonary blastoma.[84] CNS manifestations of DICER1 syndrome include pituitary blastoma, pineoblastoma, ciliary body medulloepithelioma, primary DICER1-associated CNS sarcomas, and ETMR-like infantile cerebellar embryonal tumor.[85]

NOONAN SYNDROME

Noonan syndrome is a RASopathy disorder due to *PTPN11* germline mutations. Brain tumors such as dysembryoplastic neuroepithelial tumor (DNT) (Figure 11A), subependymoma (Figure 11B and 11C), glioneural tumor, and gliomas were reported.[86]

CONCLUSION

Although most HCS are rare or extremely rare (1:40 000-1:100 000), NF1 and TSC are quite common (1:3000-1:10 000) with high penetrance. For comparison, the incidence of glioblastoma is 1:33 000 to 1:50 000.

Family history of early-onset brain cancer gives a modest increase (2-3-fold) in the cumulative risk of brain cancer: 0.24% in general population vs 0.75% for offspring and 0.53% for siblings. Similar results were obtained in the Norwegian nationwide register-based cohort 1960 to 2001 study (2.6 million children, 2477 primary solid tumors).[87] Interestingly, after excluding hereditary cancer syndromes, a family history of cancer still increased the risk of childhood CNS tumors and neuroblastomas 2.3-fold and retinoblastoma 6.1-fold. This suggests that other unknown genetic mechanisms are involved.

Our review presented the pathological and molecular features (Figure 12) of tumors associated with HCS. Using DNA methylation classifier empowers the pathologists with more objective way of diagnosing the tumors; however, stratification of the tumors in syndrome-associated group vs the sporadic group has not been achieved yet. Further studies are needed to identify features that define syndrome-associated tumors to help diagnosing them and developing targeted therapy for them.

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