Chapter Seven – Hereditary Genodermatoses with Cancer Predisposition

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Synopsis

Hereditary genodermatoses with cancer predisposition are reviewed, including Nevoid Basal Cell Carcinoma Syndrome, Neurofibromatosis Types 1 and 2, Tuberous Sclerosis Complex, Xeroderma Pigmentosum, and Dyskeratosis Congenita. Hereditary melanoma is also included, though it differs from the others in several respects. The underlying genetic aberrations causing these syndromes are largely known, allowing novel treatments to be developed for some of these disorders. Early recognition and diagnosis allows for close follow-up and surveillance for associated malignancies.

Keywords

genodermatoses; Nevoid Basal Cell Carcinoma Syndrome; Neurofibromatosis Type 1; Neurofibromatosis Type 2; Tuberous Sclerosis; melanoma; Xeroderma Pigmentosum; Dyskeratosis Congenita

Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

History/Disease Overview

A relationship between multiple basal cell carcinomas and developmental defects was suggested by Binkley and Johnson in 1951 [1] and Howell and Caro in 1959 [2], but it was Gorlin and Goltz who, in 1960, first described a distinct syndrome consisting of the presence of multiple nevoid basal cell epitheliomas, jaw cysts, and bifid ribs [3]. Nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin syndrome, is a rare condition, with an estimated prevalence of 1 per 40–57,000 [4], though the figure may be higher [5]. Two major features characterize the phenotype of NBCCS: developmental abnormalities and multiple neoplasms. Developmental abnormalities include palmar and plantar pits, coarse facies with

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frontal bossing, cleft palate, strabismus, corpus callosum dysgenesis, falx cerebri calcification, spina bifida occulta, bifid ribs, mesenteric cysts, macrocephaly, and polydactyly. Neoplasms include basal cell carcinomas (BCCs), medulloblastomas, rhabdomyosarcomas, odontogenic keratocysts, fibrosarcomas, meningiomas, and ovarian fibromas among other benign and malignant neoplasms. In a study of 105 individuals with NBCCS, mostly from multiple case families, palmar pits, jaw cysts, basal cell carcinomas, and calcification of the falx cerebri were present in over 50% of cases, and bifid ribs were present in 42% of cases [6]. Clinical studies have led to revisions of the diagnostic criteria over time. Diagnosis of NBCCS may be made by the presence of two major and one minor or one major and three minor criteria. Major criteria include: (1) lamellar calcification of the falx cerebri under age 20, (2) histologically confirmed odontogenic (jaw) keratocyst, (3) two or more palmar/plantar pits, (4) greater than 5 BCCs in a lifetime or a BCC before age 30 years, and (5) a first-degree relative with NBCCS. Minor criteria include: (1) childhood medulloblastoma, (2) lympho-mesenteric or pleural cysts, (3) macrocephaly, (4) cleft lip/ palate, (5) vertebral/rib anomalies including bifid vertebrae/ribs, extra ribs, and/or splayed ribs, (6) polydactyly, (7) ovarian/cardiac fibromas, and (8) ocular abnormalities including cataracts [5,6]. Of note, making the diagnosis may be difficult in African-Americans since those affected with NBCCS have fewer BCCs than their Caucasian counterparts [7].

Genetics

Chromosomal mapping and genetic studies elucidated the role of inactivating mutations in the human homolog of Drosophila Patched gene (*PTCH1*) on chromosome 9q22.3 as the cause of almost all cases of NBCCS. Approximately 70% of germline *PTCH1* mutations are rearrangements leading to formation of a truncated protein, although deletions, insertions, splice site alterations, nonsense and missense mutations of *PTCH1* are also reported [8–11]. About 6% of mutations are whole gene deletions [5]. Mutations in *PTCH1* are inherited in an autosomal dominant manner, and although penetrance is nearly complete, phenotypic expression of the syndrome is widely variable [12]. This phenotypic variation does not appear to be related to the type of *PTCH1* mutation present [8,13]. *PTCH1* inactivation has been proposed to occur in two steps—the first "hit" occurs in the germline and the second, postnatally. Heterozygosity for *PTCH1* due to the inherited germline mutation is likely to give rise to the developmental abnormalities seen in NBCCS. Subsequent postnatal loss of the normal Patched allele by mutation or silencing may lead to multiple BCCs and other neoplasms [14]. Thus, *PTCH1* acts as a tumor suppressor. Reports of segmental cases of NBCCS, hypothesized to be due to post-zygotic mutations, are rare [15]. A few cases of NBCCS are due to mutations in *PTCH2* on chromosome 1p32, which is also a tumor suppressor, and suppressor of fused (*SUFU*) on chromosome 10q24-q25 [16,17].

PTCH1, PTCH2, and *SUFU* are components of the Hedgehog (Hh) signaling pathway, which was first elucidated in Drosophila [4,18,19]. Two transmembrane proteins—Patched and Smoothened—transduce the secreted Hh protein signal. In the absence of Hh, Patched catalytically inhibits Smoothened [20]. Secreted Hh binds to Patched, releasing inhibition of Smoothened and effecting downstream events including cell cycle regulation via the transcription factor Ci and a complex of cytoplasmic proteins including Fused (Fu), Suppressor of Fused (Su(fu)), and Costal-2 (Cos2) [21]. In this model, Patched inactivation or the constitutive activity of Smoothened leads to overactivity of the Hh pathway resulting in neoplasm formation, though the mechanism connecting pathway overactivity and tumor formation is not yet defined. Not surprisingly, *PTCH1*, Smoothened (*SMO*), and *SUFU* mutations have been identified in sporadic BCCs, medulloblastomas, and odontogenic keratocysts, further implicating the role of the Hh signaling pathway in the development of these tumors [19,22–26].

Genetic Testing/Treatment

Molecular genetic testing can confirm the diagnosis in individuals when the diagnosis is clinically considered. Prenatal diagnosis of NBCCS is possible, though knowledge of the disease-causing mutation in a given family is required [5,27].

There are many current treatments for BCCs such as surgical excision and topical immunomodulation. However, the application of these traditional treatments to the BCCs that occur in NBCCS is problematic because of the multiplicity and recurrent nature of the tumors. Photodynamic therapy is emerging as a promising treatment for BCCs in patients with NBCCS [28]. A recent trial with oral non-steroidal anti-inflammatory drugs in patients with NBCCS with less severe disease showed significantly reduced numbers of BCC in the treated versus the placebo group [29]. Since BCCs arise in NBCCS as a result of overactivation of the Hh pathway, novel therapies inhibiting this pathway might be expected to suppress tumor growth. Cyclopamine, a Hh pathway antagonist, inhibited growth of medulloblastomas in a mouse model of NBCCS [30]. In recent clinical trials, the effects of Hh inhibitors were studied in one patient with sporadic metastatic medulloblastoma and 33 patients with locally advanced or metastatic BCC, one of whom had NBCCS [31,32]. Rapid reductions of tumor size and associated symptoms were noted in the patient with metastatic medulloblastoma. 18 of 33 patients with locally advanced or metastatic BCC had a partial or complete response, and 11 had stable disease. These studies are promising; however, further research is needed to guide recommendations for use of these Hh inhibitors in individuals with NBCCS.

Neurofibromatosis Type 1

History/Disease Overview

Neurofibromatosis type 1 (NF1), first described by von Recklingausen in 1882 [33], occurs in approximately 1 in 3,500 individuals [34]. It is characterized by a combination of cutaneous, neurologic, skeletal, and ocular findings, including benign and malignant tumors primarily of the nerve sheath. To date, the NIH diagnostic criteria for NF1 includes at least two of the following features: (1) six or more café-au-lait macules (with largest diameter >0.5cm in prepubertal individuals or >1.5cm in post-pubertal individuals, (2) axillary or inguinal freckling (Crowe sign), (3) two or more neurofibromas of any type or at least one plexiform neurofibroma, (4) two or more iris hamartomas (Lisch nodules), (5) a distinctive bony lesion, such as sphenoid wing dysplasia or long bone cortical thinning with or without pseudoarthrosis, and (6) a first degree relative with NF1 [35]. The majority of individuals can be diagnosed by age 3 [36].

Café-au-lait macules are the most common feature of NF1, occurring in 95% of individuals and typically appearing by age 3 [36]. Other cutaneous manifestations include axillary and/or inguinal freckling, present in the majority of children; xanthogranulomas, observed in early childhood and possibly associated with chronic myeloid leukemia in children; and diffuse hyperpigmentation [34,37]. Neurofibromas, benign nerve sheath tumors arising from Schwann cells, are a hallmark finding of NF1, though their numbers vary across affected patients. Dermal, spinal, and plexiform neurofibromas may occur in NF1. The number of neurofibromas varies among patients with NF1. Spinal neurofibromas may cause nerve compression [38]. Dermal and plexiform neurofibromas can lead to significant cosmetic deformity; additionally, plexiform neurofibromas may develop into malignant peripheral nerve sheath tumors (MPNST), which may metastasize extensively and be fatal [36,39]. The lifetime risk for development of MPNST is 10% [36]. Additional neurologic findings include optic pathway gliomas, cognitive deficits including learning disabilities, and epilepsy. Optic pathway gliomas are low-grade pilocytic astrocytomas capable of involving the optic nerve, chiasm, tract, and/or hypothalamus, which may cause visual loss and/or

endocrine dysregulation [39]. Vascular abnormalities cause significant mortality and include severe hypertension, usually secondary to renal artery stenosis; cerebrovascular disease, possibly leading to cerebral hemorrhage; and pulmonary arterial hypertension [40]. Skeletal abnormalities associated with significant morbidity include scoliosis, pseudoarthroses, sphenoid wing dysplasia, macrocephaly, and short stature. Additional malignancies that may occur in patients with NF1 include pheochromocytoma, pancreatic endocrine tumors, rhabdomyosarcomas, and duodenal somatostatinomas [41,42]. Glomus tumors were also recently associated with NF1 [43].

Genetics

NF1 is caused by an approximately equal number of spontaneous and autosomal dominantly-inherited germline mutations in the *NF1* gene, located on chromosome 17q11.2, encoding neurofibromin, a tumor suppressor predominantly expressed in neural crest cells including neurons, Schwann cells, and early melanocytes [44,45]. Similar to basal cell carcinomas in Gorlin syndrome, neurofibromas are thought to arise after a "second-hit" to *NF1*, leading to loss of heterozygosity [46]. Neurofibromin regulates Ras guanosine triphosphatase activity by converting Ras into its inactive form and suppressing cell growth [34,47,48]. In NF1, the Ras/Raf/ERK signaling pathway is unchecked, leading to unregulated cell proliferation. One important protein activated by Ras is the mammalian target of rapamycin (mTOR) protein. Interestingly, another protein in this signaling pathway, SPRED1, inhibits the Raf protein, and mutations in *SPRED1* account for an NF-1-like syndrome consisting of multiple café au lait macules, axillary freckling, and macrocephaly [35,49].

In individuals with NF1, there is complete penetrance by age 20, although there is variable phenotypic expression [34]. Even among individuals from the same family sharing the same mutation, phenotypes can differ substantially. Partial and complete gene deletions, insertions, nonsense, frameshift, and splice mutations as well as amino acid substitutions and chromosomal rearrangements affecting the *NF1* gene may cause NF1 [34,50]. Interestingly, NF1 can be manifested by somatic mosaicism due to mutations in the *NF1* gene that occur postzygotically during development [51,52].

Genetic Testing/Treatment

A comprehensive genetic screening test identified mutations in over 95% of subjects who fulfilled the NIH diagnostic criteria [50]. Genetic testing is indicated for prenatal testing, preimplantation genetic diagnosis, and for confirmation in individuals with suspected NF1 who do not meet the full diagnostic criteria [34]. One caveat of genetic testing, however, is that in most cases the disease phenotype cannot be predicted by the genotype. Exceptions are for patients with complete deletions of the *NF1* gene and a three-base pair inframe deletion in exon 17, which do result in predictable phenotypes. Complete deletions are associated with a severe NF1 phenotype including numerous neurofibromas, significant cognitive deficits, dysmorphic facies, and an elevated risk of MPNST development [53,54]. The three base-pair inframe deletion is associated with a mild phenotype, including even the absence of cutaneous neurofibromas [55].

Affected individuals should be followed annually with physical examinations, including fundoscopy at least until age 7, with assessment and work-up of symptoms that may indicate MPNST development; routine imaging in asymptomatic individuals is not recommended [42]. Thalidomide and a vascular endothelial growth factor receptor (VEGFR) inhibitor, both angiogenesis inhibitors, are being tested to treat MPNSTs and plexiform neurofibromas, since both tumors require intact vascular supplies [35,56]. Novel treatments for NF1 are emerging from advances in understanding the functional consequences of the

genetic mutations, specifically altering the Ras/Raf/ERK signaling pathway. Ras inhibitors, for example, are postulated to inhibit the pathway, and in this manner substitute for neurofibromin. Tipifarnib, a farnesyltransferase inhibitor that targets Ras, is currently being investigated for treatment in NF1 patients with plexiform neurofibromas [57]. Rapamycin, though primarily used for its immunosuppressive properties, is now being considered for use in NF1 patients since it, like neurofibromin, inhibits mTOR signaling and may substitute for NF1 in this way [58,59].

Neurofibromatosis Type 2

History/Disease Overview

Neurofibromatosis type 2 (NF2), like NF1, is a neurocutaneous disorder. Though NF2 shares some features with NF1, they are distinct syndromes with many differences firmly distinguished in 1987 with the discovery that the gene causing NF1 mapped to chromosome 17q whereas tumor DNA from individuals with NF2 showed loss of heterozygosity for markers on chromosome 22q [60–62]. First described in 1822, NF2 is rare, affecting 1 in 25,000 individuals [63,64]. Bilateral vestibular schwannomas are the most frequent clinical feature, present in up to 95% of cases. According to the most commonly used Manchester diagnostic criteria, NF2 can be diagnosed on the basis of this feature alone [63,64]. NF2, however, is a multiple neoplasia syndrome, and other tumors affecting the nervous system, skin, and eyes also occur. Diagnostic criteria, in addition to bilateral vestibular schwannomas, include: (1) a family history of NF2 and a unilateral vestibular schwannoma or two NF2-associated nervous system tumors or cataracts, (2) a unilateral vestibular schwannoma and two NF2-associated nervous system tumors or cataracts, or (3) multiple meningiomas and a unilateral vestibular schwannoma or two other NF2-associated nervous system tumors or cataracts [64]. Nervous system tumors include schwannomas developing in cranial nerves other than 8, spinal nerves, and peripheral nerves, meningiomas, ependymomas, pilocytic astrocytomas, and occasionally neurofibromas as in NF1 [64,65]. Bilateral hearing loss, secondary to vestibular schwannomas, is common. Peripheral neuropathy, though not one of the diagnostic criteria for NF2, can develop in affected individuals, both in association with and independent of nerve-compressing tumors [64]. The most common ocular finding is early cataracts, which may lead to loss of vision [66]. Other ocular manifestations include epiretinal membranes and retinal hamartomas [67]. Cutaneous findings include rough, slightly hyperpigmented plaques with overlying hypertrichosis as well as subcutaneous and intradermal tumors, typically schwannomas, although, as previously mentioned, neurofibromas may occur [68,69]. Café au lait macules, typical of NF1, may be seen in NF2 as well, though in one series, no patient had more than six [68–72].

Genetics

NF2 is caused by mutations in the tumor suppressor *NF2* gene on chromosome 22q12. The NF2 protein (named merlin or alternatively schwannomin) normally regulates mitogenic intracellular pathways including the phosphoinositide-3-kinase (PI3K) signaling pathway, which includes Akt and mTOR, and the mitogen-activated protein kinase (MAPK) signaling pathway, which includes Ras/Raf/MEK/ERK. Inherited in an autosomal dominant fashion, NF2 has nearly complete penetrance by age 60 [63,73]. Age of onset is typically around 18 years [74]. Affected individuals in the same family usually share similar phenotypic features, but there is variable expressivity among families, which can largely be attributed to the type of *NF2* mutations segregating in each family. Severe disease and a higher mortality are associated with constitutional nonsense or frameshift mutations, which result in a truncated protein, as well as splice-site mutations within exons 1–5 [75]. Mild disease and a lower mortality are associated with missense mutations and inframe or large deletions as

well as splice-site mutations within exons 11–15 [76–78]. Fifty percent of NF2 patients have a *de novo* mutation [74], and mosaic forms of NF2 occur with high frequency in these patients [79]. Most patients with mosaic forms of NF2 have mild disease or limited involvement; there is also a lower risk of transmission to offspring from individuals with mosaic forms of NF2 since it is likely that less than 50% of germ cells carry the mutation [64].

Genetic Testing/Treatment

Genetic testing of individuals without symptoms from affected families is recommended and allows for early diagnosis which can improve clinical care. For asymptomatic individuals with an affected parent, screening guidelines recommend: annual follow-up by an ophthalmologist, neurologist, and audiologist from infancy; head and spinal MRIs starting at around age 10 repeated every 2–3 years for spinal MRI; and presymptomatic genetic testing at around age 10 if not performed earlier by request of the parents. For asymptomatic individuals from families with severe disease, MRIs and genetic testing are recommended at an earlier age, and MRIs may be performed annually [64,80].

Treatment for NF2 is directed at early and complete removal of bilateral vestibular schwannomas in order to preserve hearing. In patients with an intact cochlear nerve following vestibular schwannoma surgery, cochlear implants may improve hearing. Meningiomas are typically managed by neurosurgical intervention. These tumors may or may not be fully resectable, depending on their location in the nervous system; furthermore, resection of meningiomas in some locations, such as the skull base or optic nerve sheath, carries greater risks than other locations, such as the cerebral hemisphere or spinal canal [81,82]. With close ophthalmologic follow-up, cataracts may be found early and those associated with significant loss of visual acuity extracted [66]. Skin tumors, when symptomatic, may be excised. The use of mTOR inhibitors is currently being investigated for individuals with NF2 [83].

Tuberous Sclerosis Complex

History/Disease Overview

Similar to NF1 and NF2, tuberous sclerosis complex (TSC) is a neurocutaneous disorder affecting multiple systems. First reported by Bourneville in 1880, TSC was named after the cerebral cortical lesions resembling tubers and the peri-ventricular calcification characteristic of the disorder [84]. Multiple hamartomas, or tumors, can develop in multiple organs, such as the brain, skin, kidney, eye, lung, and liver in TSC patients. The incidence is estimated to be 1 per 6,000 live births [85]. Diagnostic criteria for TSC endorsed by the Tuberous Sclerosis Alliance organization include both major and minor categories. The diagnosis is made with two major features (excluding lymphangioleiomyomatosis and renal angiomyolipoma alone) or one major and two minor features. Major diagnostic criteria include: (1) facial angiofibromas ('adenoma sebaceum') or forehead plaque, (2) nontraumatic ungual or periungual fibroma ('Koenen tumor'), (3) 3 or more hypomelanotic macules ('ash leaf spots' or 'Fitzpatrick patches'), (4) connective tissue nevus ('Shagreen patch'), (5) multiple retinal nodular hamartomas, (6) cortical tuber, (7) subependymal nodule, (8) subependymal giant cell astrocytoma, (9) single or multiple cardiac rhabdomyoma, (10) lymphangioleiomyomatosis, and (11) renal angiomyolipoma [86]. Minor criteria include: (1) multiple dental enamel pits, (2) hamartomatous rectal polyps, (3) bone cysts, (4) cerebral white matter radial migration lines, (5) gingival fibromas, (6) nonrenal hamartomas, (7) retinal achromic patch, (8) cutaneous symmetric hypopigmented macules ('confetti' macules), and (9) multiple renal cysts [86].

Neurologic manifestations are present in approximately 85% of children and adolescents with TSC and include epilepsy, cognitive impairment, behavioral problems, and autism. These neurologic problems are the primary cause of morbidity and mortality in affected individuals and are likely due to the presence of brain lesions including cortical tubers, subependymal nodules, subependymal giant cell tumors, and white matter abnormalities [87–90]. In familial cases of TSC, nodules have a high likelihood of transforming into an ependymal giant cell tumor, with a prevalence of about 11% in affected individuals [91]. Epilepsy, caused by diminished GABA (gamma-aminobutyric acid) neuronal inhibition, typically starts in the first few months of life and affects 90% to 96% of TSC patients [92]. Control of seizures is necessary to reduce the risk of cognitive impairment. Mental retardation (MR) is seen in up to 50% of affected individuals, almost all of whom have seizures; however, not all patients with seizures have MR [93,94].

After neurologic complications, those from renal involvement are the major contributors to mortality in TSC [95]. Angiomyolipomas, the most common renal abnormality, affect about 80% of individuals with TSC, increase in incidence with age, and are usually treated with embolization or renal sparing surgery if necessary [95–98]. They are typically bilateral, and may be symptomatic especially in women [95,98]. Renal cysts and renal cell carcinoma can also occur. Cardiac rhabdomyomas are often the first manifestation of TSC; they are benign, largely asymptomatic tumors that regress with age and rarely require surgery. Magnetic resonance imaging can diagnose cardiac rhabdomyomas in utero; most of these cases are affected with TSC [99,100]. Pulmonary involvement is rare in TSC; the most common lesion is lymphangioleimyomatosis, typically affecting premenopausal adult women [101,102]. Ocular findings include retinal astrocytic hamartomas (also called 'mulberry lesions'), which occur in 40%–50% of TSC patients and increase with age [103]. Oral involvement includes pitting of dental enamel, occurring in about 50% to 100% of cases and gingival fibromas, noted mostly on the anterior upper jaw [86,101,104,105]. Surgery may be needed for large gingival lesions.

TSC patients typically have a variety of dermatologic manifestations. Small, confetti-like hypopigmented macules and medium to large hypopigmented patches with an ash leaf, round, or polygonal shape may be observed. The 'ash leaf spot' is typically present at birth, and so can help to confirm the diagnosis [101,106]. Facial angiofibromas, small pink papules, are typically found around the central face, particularly the nasolabial folds, and can be removed with carbon dioxide (CO_2) or other destructive lasers [101]. Fibrous plaques, resembling angiofibromas histologically, are large plaques typically found on the forehead or scalp. Whereas angiofibromas typically appear around age 5, fibrous plaques may be present in affected individuals under age 2 or even at birth [86,92,107]. Many consider angiofibromas and fibrous plaques the same in terms of diagnostic criteria for TSC. Ungual or periungual fibromas, pink papulonodules arising from the nail bed and also resembling angiofibromas histologically, become apparent at puberty and increase in number with age; they affect toenails more commonly than fingernails and may be symptomatic, requiring surgery. Connective tissue nevi, or Shagreen patches, can be found on the trunk, especially the lumbosacral region and may also increase in size with age [101]. Café-au-lait macules may also occur in up to 30% of TSC patients, although their frequency in TSC patients compared to unaffected individuals is the same [108,109]. Molluscum fibrosum pendulum, pedunculated skin-colored papules, may also develop [101].

Genetics

TSC is caused by autosomal-dominantly inherited and sporadic mutations in two genes: *TSC1*, located on chromosome 9q34, encoding tuberin and *TSC2*, located on chromosome 16p13.3, encoding hamartin. Tuberin and hamartin proteins bind tightly to form a heterodimer with tumor suppressor properties including regulation of cell growth by

inhibiting mTOR via the Rheb (Ras homologue enriched in brain) protein [110–113]. Studies in Drosophila have exposed the role of the tuberin and hamartin genes downstream of the insulin receptor in regulation of cell size [114–116].

TSC exhibits complete penetrance with wide phenotypic variability, even within families sharing the same mutation [101,117]. In TSC, germline mosaicism is possible. In large, multi-generation TSC families, *TSC1* and *TSC2* gene mutations occur in a 1:1 ratio; however, *TSC2* mutations account for the majority of sporadic cases, apparently due to an increased rate of second hit events [118–120]. *TSC1* mutations are generally small deletions and insertions as well as nonsense mutations, whereas *TSC2* mutations can include these as well as large deletions and rearrangements. Phenotype severity generally cannot be predicted by the type and location of the mutation, although some missense mutations in *TSC2* are associated with a mild phenotype [117,121–123]. Of note, large deletions of *TSC2* can also result in deletions of the nearby gene responsible for polycystic kidney disease, *PDK1*, resulting in individuals with TSC and multiple renal cysts in infancy [124,125]. Disease phenotype has been found to differ among TSC patients with *TSC1* versus *TSC2* mutations; individuals with *TSC2* mutations have a similar but more severe phenotype, including more severe mental retardation and increased numbers of cortical tubers, retinal hamartomas, and facial angiofibromas, than those with *TSC1* mutations [118–120,126].

Genetic Testing/Treatment

DNA testing can be performed to confirm a diagnosis as well as for prenatal diagnosis [92]. Identification of affected individuals before or at birth, or during infancy allows for prompt diagnostic evaluation with neuroimaging studies, cardiac evaluation, and renal ultrasonography as well as early intervention with seizure-controlling medications, reducing the potential for intellectual impairment [127]. When TSC-associated seizures are intractable despite standard anti-epileptic medication, vigabatrin (gamma-vinyl-gamma aminobutyric acid), a selective GABA-transaminase inhibitor, may be used to reduce infantile spasms; however, this medication is not available in the U.S [128,129]. TSC patients should be managed by a team of physicians, including neurologists, dermatologists, urologists, pediatricians, and geneticists.

Since mTOR is unregulated in TSC as in NF1, rapamycin may play a role in the treatment of TSC-related tumors [130]. Studies in animal models demonstrate that rapamycin and other mTOR inhibitors are effective treatments for renal tumors, liver hemangiomas, epilepsy, and cutaneous tumors [131–133]. In human studies, rapamycin decreases the volume of renal angiomyolipomas and subependymal giant cell astrocytomas; further studies are needed to evaluate this promising therapy for individuals affected with TSC [134–136].

Xeroderma Pigmentosum

History/Disease Overview

Xeroderma pigmentosum (XP) is characterized by severe ultraviolet (UV) light photosensitivity and a greater than 1,000-fold increase in frequency of squamous cell carcinoma, basal cell carcinoma, and melanoma. Sun sensitivity and freckling are typically seen by 2 years of age [137]. Skin cancers can develop in the first decade of life, with the majority occurring on the head, neck, or face [138]. In addition to cutaneous findings, patients often have ocular abnormalities including ectropion, corneal opacities, and neoplasms; these may cause blindness [137]. Neurologic abnormalities may also occur, depending on the underlying genetic abnormality. XP patients also have increased risks of other cancers, especially oral cancer, most commonly affecting the anterior tongue [139].

Genetics

XP is an autosomal recessive disorder caused by mutations in nucleotide excision repair complementation groups, of which there are seven, A-G; there is also an XP-variant type caused by mutations in the DNA polymerase eta gene. XP variant type is characterized by photosensitivity, skin cancers, and absence of neurologic abnormalities. The complementation groups and DNA polymerase function in DNA repair, particularly after UV damage. Mutations in *XPA* and *XPC* account for approximately 50% of cases of XP [139]. The relationship between defects in these complementation groups and the clinical disease phenotype is complex; while mutations in several genes can cause the same phenotype, different mutations in the same gene can cause different phenotypes [139,140]. For example, some forms of XP are associated with neurologic problems including mental retardation, sensorineural deafness, spasticity, and hyporeflexia due to progressive neuronal degeneration [140]. Furthermore, Cockayne syndrome (CS) and trichothiodystrophy (TTD), other autosomal recessive disorders, are also caused by defects in nucleotide excision repair genes. Although individuals with CS and TTD are photosensitive like XP individuals, they do not have an increased frequency of skin cancers [139,140]. XP and CS can occur together in the same individual as the XP/CS complex; these individuals often have skin and eye findings of XP with the short stature, immature sexual development, retinopathy, and progressive neurologic degeneration of CS [139]. Interestingly, polymorphisms in the *XPD* gene are related to early onset of sporadic basal cell carcinoma, suggesting the importance of the NER pathway in BCC development [141–143].

Genetic Testing/Treatment

Clinical molecular testing is available for *XPA* and *XPC* genes only [139]. Treatment of XP involves early recognition, strict avoidance of UV exposure of the skin and eyes, routine skin examinations for detection followed by complete excision of skin cancers, and neurologic follow-up if needed. High-dose oral isotretinoin has been shown to decrease numbers of skin cancers in individuals with multiple skin cancers, though toxicity limits its use [139].

Dyskeratosis Congenita

History/Disease Overview

Dyskeratosis Congenita (DC) is a rare syndrome with an unknown true prevalence but thought to affect about 1 in 1 million individuals in North America [144]. DC is characterized by abnormal skin pigmentation, nail dystrophy, oral premalignant leukoplakia, bone marrow failure, and a predisposition to cancer, particularly myelodysplasia, acute myeloid leukemia, and cutaneous squamous cell carcinoma of the head and neck. Other findings include ocular abnormalities such as epiphora, blepharitis, and abnormal eyelashes; hair findings including alopecia and premature graying; dental findings such as periodontal disease, decreased tooth root/crown ratio, and enlarged tooth pulp chambers; microcephaly; short stature; and esophageal stenosis among others [144,145]. Approximately 90% of affected individuals develop bone marrow failure by age 30, which accounts for the majority of mortality [146]. Age of onset and disease severity can vary among affected individuals, unpredictably, even within the same family.

Genetics

Mutations in six genes, *TERC* (RNA subunit of telomerase), *TERT* (telomerase reverse transcriptase), *DKC1* (dyskerin), *NHP2* (nucleolar protein family A, member 2, or NOLA2), *NOP10* (nucleolar protein family A, member 3, or NOLA3), and *TINF2* (TRF1-interacting nuclear factor 2), encoding telomerase complex components, cause about 50% of cases of DC [146,147]. The mode of inheritance varies by gene, and X-linked, autosomal recessive,

and autosomal dominant inheritance patterns have been described. These mutations uniformly result in short telomeres, which accumulate as cells divide and recruit DNA damage proteins that lead to apoptosis or cellular senescence that can lead to organ failure [147]. Three main types of DC can occur: classical DC, and cryptic and severe variants [146]. Cryptic variants include aplastic anemia, myelodysplasia, paroxysmal nocturnal hemoglobinuria, essential thrombocythemia, and pulmonary fibrosis. Severe variants include Hoyeraal-Hreidarsson syndrome and Revesz syndrome. Since there is marked clinical and genetic heterogeneity of DC, most of these variants were only recognized as being associated with classical DC after their underlying mutations were identified [146]. The link between short telomeres, cellular senescence, and malignancy may be present in sporadic cancers as well as in DC [148–150].

Genetic Testing/Treatment

Leukocyte telomere length testing by automated multicolor flow cytometry fluorescence in situ hybridization (flow-FISH) should be used in individuals with suspected DC; findings of DC include telomeres less than the first percentile for age in three to four of six cell types examined [144,151]. In these individuals, genetic testing should be considered [144]. Management of DC includes routine screening for malignancies by gynecologists, otolaryngologists, dermatologists, and dentists, and annual pulmonary function testing [144]. Treatment of bone marrow failure and/or leukemia may include hematopoietic stem cell transplant, but there is a higher mortality associated with use in DC than in other bone marrow failure syndromes [146]. Other treatments include androgen therapy [144,152].

Hereditary Melanoma

History/Disease Overview

The incidence of cutaneous malignant melanoma (CMM), which occurs in a familial setting and sporadically, continues to increase and is the fifth and sixth most common cancer in the U.S in men and women, respectively [153,154]. Unlike the other inherited genodermatoses discussed, there is no distinctive, prodromic, or diagnostic phenotype of familial melanoma. Melanoma is heterogeneous and etiologically complex. The interaction of genetic, host, and environmental factors contributes to the development of CMM in melanoma-prone families and in sporadic cases. Ultraviolet radiation (UVR) is the main environmental risk factor for CMM, and data suggest that intense intermittent sun exposure at any age impacts risk more than total lifetime exposure [155]. Phenotypic host factors, such as the presence and number of benign and dysplastic nevi, blond or red hair color, light eye color, freckling, and skin sensitivity to the sun, are also associated with increased risk of CMM. Within melanoma-prone families, these environmental and host factors are often shared. Norris, Clark, and Lynch were among the first to describe the occurrence of high rates of melanoma in certain families [156–158]. Approximately 5%–12% of CMM cases occur in individuals with one or more affected first-degree relatives [159]. Within melanoma-prone families, CMM lesions are typically thinner, are diagnosed at a younger age, and there is a higher frequency of multiple primary melanomas (MPMs), compared to nonfamilial melanoma cases; however, lesion histology, prognosis, and survival are similar [159,160].

Genetics: CDKN2A/CDK4

Two high-risk melanoma susceptibility genes have been identified: *CDKN2A* (cyclin-dependent kinase inhibitor 2A) and *CDK4* (cyclin-dependent kinase 4) [161–164]. The inheritance pattern for both genes is autosomal dominant. *CDKN2A*, located on chromosome 9p21, is a tumor suppressor gene encoding two proteins p16 and p14ARF involved in cell cycle control maintenance. The p16 protein inhibits CDK4-mediated phosphorylation of the retinoblastoma protein (Rb), thus regulating G1-phase exit, and the p14ARF protein

mediates cell cycle arrest through the p53 pathway [165]. *CDK4*, on chromosome 12q14, functions as an oncogene in the retinoblastoma pathway. Comparison of families with *CDKN2A* and *CDK4* mutations demonstrated similar age at diagnosis, number of CMMs, and number of nevi [166]. However, germline mutations in CDK4 are rare and, to date, reported in only about 10 families [167–169]. Germline mutations in *CDKN2A* account for about 20%–50% of families with three or more members affected with CMM [170,171]. The frequency of detectable mutations increases as the number of CMM cases in a family increases; in families with only 2 affected members, the frequency of detectable *CDKN2A* mutations is less than 5%, whereas in families with greater than 6 affected members, the frequency of detectable *CDKN2A* mutations is more than 50% [159,172]. Similarly, in individuals with MPM, the percentage of detectable *CDKN2A* mutations increases from 10% in those with no family history of CMM to greater than 30% in those with three or more relatives with CMM [159,172].

Studies suggest an association between *CDKN2A* and cancers other than melanoma, contributing to mortality within melanoma-prone families. In melanoma-prone families with *CDKN2A* mutations, there is an increased risk of pancreatic cancer, though accurate prediction of who will develop pancreatic cancer among *CDKN2A* mutation-positive individuals is currently impossible [173,174]. Neural system tumors may be associated with *CDKN2A* mutations affecting p14ARF protein [174]. Breast cancer is associated with *CDKN2A* mutations in a subset of families, mostly from Sweden [175].

Since only about 20%–40% of familial melanoma cases are accounted for by *CDKN2A* and *CDK4* mutations, other genetic factors increase CMM risk within families. There is evidence of other high-penetrance loci on chromosomes 1p22 and 1p36, but the causal genes have not yet been identified [176,177].

Variations in Penetrance

Although *CDKN2A* mutations confer a high risk of melanoma, not all individuals with *CDKN2A* mutations within melanoma-prone families develop melanoma, suggesting incomplete penetrance. A large family-based study of *CKDN2A* mutation carriers from Europe, Australia, and the United States demonstrated that penetrance estimates varied with age as well as geographic location and reflected local incidence rates of CMM in each population [178]. Penetrance estimates in population-based studies in several geographical regions are lower than those from family-based studies [179–181]. Other characteristics also differ among mutation carriers even within one family, including age at CMM diagnosis, the presence/number of dysplastic nevi, the number of CMMs, and cosegregation of pancreatic cancer.

Other Melanoma Susceptibility Genes and Modifier Genes

Low-penetrance melanoma susceptibility genes are also associated with sporadic and familial melanoma; several of these were identified by candidate gene approaches and/or genome wide association studies. These include the melanocortin-1 receptor (*MC1R*) gene, tyrosinase (*TYR*), agouti signaling protein (*ASIP*), tyrosinase-related protein 1 (*TYRP1*), solute-carrier family 45, member 2 (*SLC45A2*), all of which are associated with pigmentation factors and melanoma, and methylthioadenosine phosphorylase (*MTAP*), near *CDKN2A*, and phospholipase A2, group VI (*PLA2G6*), which are associated with nevi and melanoma [182–188]. *MC1R* variants were found to modify the penetrance of *CDKN2A* mutations in melanoma-prone families, suggesting that gene-gene interactions may also contribute to increased CMM risk in melanoma-prone families [189–192].

Genetic Testing

Commercial genetic testing is available to identify *CDKN2A* and *CDK4* mutations, and referral for genetic evaluation may be considered for individuals with three or more primary melanomas or families with at least one melanoma and two or more melanoma or pancreatic cancer cases among first or second degree relatives [193]. However, the frequency of detecting mutations is low even among high-risk individuals [194]. It is important to identify individuals at high risk, including those from melanoma-prone families, who would benefit from routine skin examinations to detect melanomas early, when they are easily cured.

Acknowledgments

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