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Introduction

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Disease is from of old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible. JEAN MARTIN CHARCOT

Congenital or hereditary conditions with lesions of both the skin and the nervous system, both of which are derived from ectoderm, have been traditionally considered together as *neurocutaneous disorders*. The earlier term *phakomatosis* (derived from the Greek word *phakos*, meaning 'lentil,' 'lens,' or 'mother spot') was devised by van der Hoeve to describe tuberous sclerosis and von Recklinghausen neurofibromatosis, disorders with characteristic cutaneous lesions and the potential for tumor formation. Although the term phakomatosis was widely used for several years, the gradual inclusion of conditions with vascular and other skin lesions and disorders without an increased tumor risk made the broader concept of neurocutaneous syndromes more appropriate.

The broader delineation of neurocutaneous syndromes exploits several types of skin and hair abnormalities in addition to the hyperpigmented and hypopigmented maculae that originally defined the phakomatoses (Tables 1.1 and 1.2). Many of these disorders also have important ophthalmologic signs (Table 1.3), and while tumor formation is no longer a required feature of neurocutaneous syndromes, several of them do carry a substantial risk of benign or malignant neoplasms (Table 1.4). Syndrome diagnosis also facilitates the recognition of cardiac (Table 1.5), gastrointestinal (Table 1.6), or other complications.

Neurocutaneous syndromes, by definition, promote neurological dysfunction, but not all of them directly affect the central nervous system. Several conditions cause peripheral neuropathy, either exclusively or in conjunction with the brain disorder (Table 1.7). Disorders such as hereditary hemorrhagic telangiectasia (Chapter 20), Sturge–Weber syndrome (Chapter 23) and homocystinuria (Chapter 26) indirectly lead to neurological dysfunction via vascular lesions (Table 1.8) within the nervous system.

The original conditions described as phakomatoses, tuberous sclerosis complex (Chapter 6) and neurofibromatosis type 1 (Chapter 4), are both inherited as autosomal dominant traits, but the array of disorders now included among the neurocutaneous disorders also includes autosomal recessive and X-linked traits as well as sporadic conditions (Table 1.9). Several disorders that are not inherited in a classic mendelian pattern, such the epidermal nevus syndrome and hypomelanosis of Ito (Chapters 10 and 14) probably result from mosaicism (Table 1.9). Germ line mosaicism has been shown to explain some instances of multiply affected children of seemingly non-affected parents, and some of the apparently sporadic disorders may yet prove to arise from somatic mosaicism.

As with most other areas of medicine, our understanding of neurocutaneous syndromes has benefited greatly from the application of newer genetic techniques. Some conditions once thought to be distinct, such as Cowden disease and Ruvalcaba–Riley–Smith syndrome, are now known to be dissimilar phenotypes resulting from one mutated gene (Chapter 15). Xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy (Chapter 29) are related by having defective DNA repair mechanisms. In contrast, disorders such as tuberous sclerosis complex (Chapter 6) can arise from mutations of either of two different genes which nevertheless produce nearly identical phenotypes because the two gene products seem to work together on the same cellular process.

While each of the conditions included in this book has a distinct pathophysiology, the clinical utility of using cutaneous signs to help identify unusual genetic or congenital disorders is well recognized. The concept of neurocutaneous disorders unifies a group of rare neurological disorders whose recognition depends predominantly on simple visual diagnosis.

Table 1.1. Types of skin lesions

Decreased skin pigmentation
- Chediak–Higashi syndrome
- Hypomelanosis of Ito
- Tuberous sclerosis complex
- Xeroderma pigmentosum

Increased skin pigmentation
- Basal cell nevus syndrome
- Epidermal nevus syndrome
- Incontinentia pigmenti
- Neurocutaneous melanosis
- Neurofibromatosis type 1
- Xeroderma pigmentosum

Skin tumors/hamartomas
- Encephalocraniocutaneous lipomatosis
- Epidermal nevus syndrome
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Tuberous sclerosis complex
- Fabry disease
- Fucosidosis

Skin vascular lesions
- Ataxia–telangiectasia
- Blue rubber bleb nevus syndrome
- Hemangioma–vascular anomaly syndrome
- Hereditary hemorrhagic telangiectasia
- Homocystinuria
- Neurocutaneous angiomatosis
- Sturge–Weber syndrome
- Xeroderma pigmentosum

Hyperkeratotic/ichthyotic lesions
- Lipoid proteinosis
- Multiple carboxylase deficiency
- Multiple endocrine neoplasia type 2
- Refsum disease
- Rhizomelic chondrodysplasia punctata
- Sjögren–Larsson syndrome

Rash-like lesions
- Cowden disease
- Epidermal nevus syndrome
- Incontinentia pigmenti
- Lipoid proteinosis
- Multiple carboxylase deficiency
- Xeroderma pigmentosum

Skin laxity/fat loss
- Ehlers–Danlos syndrome
- Progeria
- Pseudoxanthoma elasticum
- Trichothiodystrophy

Table 1.2. Hair abnormalities

Disorder	Hair abnormality
Adrenoleukodystrophy	Friable, thin hair, alopecia
Ataxia–telangiectasia	Hypertricosis, scattered gray hair
Cerebello-trigemino-dermal dysplasia	Localized alopecia
Chediak–Higashi syndrome	Silvery hair tint
Cockayne syndrome	Thin, dry hair
Coffin–Siris syndrome	Scalp hypotricosis with frontal and facial hirsuitism
Encephalocraniocutaneous lipomatosis	Patchy alopecia
Epidermal nevus syndrome	Patchy areas of curly, different textured hair
Giant axonal neuropathy	Curly, kinky hair
Homocystinuria	Hypopigmented, brittle, fine hair
Hypomelanosis of Ito	Alopecia, graying, tricorrhexia
Incontinentia pigmenti	Hypopigmented hair, alopecia
Lipoid proteinosis	Patchy alopecia at pressure points, loss of eyelashes
Menkes kinky hair disease	White/gray color, pili torti, trichorrhexis
Multiple carboxylase deficiency	Alopecia
Progeria	Alopecia
Rhizomelic chondrodysplasia punctata	Alopecia
Trichothiodystrophy	Sparse, lusterless, brittle hair
Tuberous sclerosis complex	Poliosis

Table 1.3. Ophthalmic abnormalities

Disorder	Eye findings
Ataxia–telangiectasia	Conjunctival telangiectasia
Cerebello-trigemino-dermal dysplasia	Hypertelorism, corneal opacity from trauma
Cerebrotendinous xanthomatosis	Cataracts, optic neuropathy
Chediak–Higashi syndrome	Pale iris, photophobia, nystagmus
Cockayne syndrome	Pigmentary retinopathy, optic atrophy
Encephalocraniocutaneous lipomatosis	Ocular choristoma, lens dislocation
Epidermal nevus syndrome	Cataract, coloboma of eyelid or iris, corneoscleral mass, optic nerve hypoplasia, retinal pigmentary abnormality or hamartoma
Fabry disease	Corneal deposits
Familial dysautonomia	Decreased tearing, corneal hypoesthesia
Fucosidosis	Corneal opacities, tortuous conjunctival and retinal vessels, microaneurysms
Hemangioma–vascular anomaly syndrome	Amblyopia
Hereditary hemorrhagic telangiectasia	Conjunctival telangiectasias, bloody tears
Homocystinuria	Lens dislocation, glaucoma, optic atrophy, cataracts, retinal degeneration
Hypomelanosis of Ito	Corneal opacity, optic nerve hypoplasia
Incontinentia pigmenti	Cataracts, ptosis, retinal detachment, pigmentary abnormalities
Lesch–Nyhan disease	Traumatic corneal opacities
Lipoid proteinosis	Moniliform blepharosis
Multiple carboxylase deficiency	Blepharitis, conjunctivitis, corneal ulcers, optic neuropathy
Multiple endocrine neoplasia	Conjunctival neuromas, thickened corneal nerves on slit lamp examination
Neurofibromatosis type 1	Lisch nodules, optic glioma
Neurofibromatosis type 2	Cataracts, optic nerve meningioma
Pseudoxanthoma elasticum	Angioid streaks of retina, retinal hemorrhage, retinal scars
Refsum disease	Retinitis pigmentosum, late cataracts
Rhizomelic chondrodysplasia punctata	Cataracts
Sjögren–Larsson syndrome	Glistening white retinal dots
Sturge–Weber syndrome	Glaucoma, buphthalmos, choroidal hemangioma
Trichothiodystrophy	Cataracts, salt and pepper retinopathy
Tuberous sclerosis complex	Retinal hamartoma
von Hippel–Lindau disease	Retinal angioma
Xeroderma pigmentosum	Photophobia, conjunctival erythema and telangiectasia

Table 1.4. Tumors with neurocutaneous disorders

Disorder	Tumor type
Ataxia–telangiectasia	Lymphoma, leukemia, basal cell carcinoma
Basal cell nevus syndrome	Basal cell carcinoma, melanoma, medulloblastoma, ovarian fibroma and fibrosarcoma, neurofibroma, adrenal cortical adenoma
Cowden disease	Dysplastic cerebellar gangliocytoma, ovarian, breast, uterine, and thyroid cancers
Encephalocraniocutaneous lipomatosis	Subcutaneous lipomas
Epidermal nevus syndrome	Basal cell and squamous carcinoma, apocrine carcinoma, various others
Hemangioma–vascular anomaly syndrome	Hemangioma of skin or viscera
Hypomelanosis of Ito	Cystic teratoma, choroid plexus papilloma
Macrodactyly–fibrolipoma syndrome	Nerve fibrolipoma
Multiple endocrine neoplasia type 2	Medullary thyroid carcinoma, pheochromocytoma, mucosal neuroma
Neurocutaneous melanosis	Melanoma of skin or leptomeninges
Neurofibromatosis type 1	Neurofibromas, optic glioma, pheochromocytoma, others
Neurofibromatosis type 2	Vestibular schwannomas, meningioma, glioma
Tuberous sclerosis complex	Renal angiomyolipoma, renal carcinoma, cardiac rhabdomyoma, facial angiofibromas, giant cell astrocytoma
von Hippel–Lindau disease	Renal carcinoma, pancreatic cystadenoma, hemangioblastoma, endolymphatic sac tumor, pheochromocytoma
Xeroderma pigmentosum	Squamous cell and basal cell carcinoma, melanoma, keratoacanthoma fibrosarcoma

Table 1.5. Cardiac disease with neurocutaneous disorders

Disorder	Dysfunction
Coffin–Siris syndrome	Congenital heart lesions
Fabry disease (variant type)	Hypertrophic cardiomyopathy, angina, arrhythmia
Familial dysautonomia	Postural hypotension, tachycardia
Homocystinuria	Myocardial infarction
Progeria	Myocardial infarction
Pseudoxanthoma elasticum	Cardiomyopathy, mitral valve prolapse
Refsum disease	Variable arrhythmia
Rhizomelic chondrodysplasia punctata	Congenital heart lesions
Tuberous sclerosis complex	Cardiac rhabdomyoma, arrhythmia

Table 1.6. Gastrointestinal abnormalities with neurocutaneous disorders

Disorder	Comment
Blue rubber bleb nevus syndrome	Bleeding with anemia
Cerebrotendinous xanthomatosis	Chronic diarrhea
Cowden disease	Intestinal polyps; adenocarcinoma
Ehlers–Danlos type 4	Bowel perforation
Fabry disease	Abdominal pain and diarrhea
Hereditary hemorrhagic telangiectasia	Intestinal bleeding
Multiple endocrine neoplasia type 2	Intestinal ganglioneuromatosis; constipation, diarrhea, or obstruction
Pseudoxanthoma elasticum	Gastrointestinal hemorrhage
Tuberous sclerosis complex	Sigmoid polyps (usually asymptomatic)

Table 1.7. Neurocutaneous disorders with peripheral neuropathy

Disorder	Comment
Ataxia–telangiectasia	Axonal neuropathy with neurogenic amyotrophy
Cerebello-trigemino-dermal dysplasia	Trigeminal sensory loss in all patients
Cerebrotendinous xanthomatosis	Axonal neuropathy
Chediak–Higashi syndrome	Predominantly sensory neuropathy, cranial nerve palsies
Cockayne syndrome	Disordered myelin production, sensorineural deafness
Fabry disease	Small unmyelinated nerve fibers affected; painful paresthesias are major symptom
Familial dysautonomia	Autonomic and sensory neuropathy
Fucosidosis	Nerve biopsy shows nonspecific abnormalities; some patients have carpal tunnel syndrome
Giant axonal neuropathy	Distal weakness and atrophy, decreased proprioception
Macrodactyly–fibrolipoma	Fibrolipoma of nerve proximal to enlarged digit
Neurofibromatosis type 1	Peripheral nerve tumors
Neurofibromatosis type 2	Increased risk of mononeuropathy
Refsum disease	Remitting course, palpable nerves

Table 1.8. Cerebrovascular lesions with neurocutaneous disorders

Disorder	Lesion type
Blue rubber bleb nevus syndrome	Venous malformation
Cerebrotendinous xanthomatosis	Premature atherosclerosis
Encephalocraniocutaneous lipomatosis	Progressive vasculopathy
Ehlers–Danlos type 4	Aneurysm, arterial dissection, stroke
Fabry disease	Cerebral infarction and hemorrhage
Hemangioma–vascular anomaly syndrome	Intracranial vasculopathy, arterial anomalies
Hereditary hemorrhagic telangiectasia	Arteriovenous malformation, angiomas, paradoxical embolism
Homocystinuria	Arterial and venous thrombosis
Menkes kinky hair disease	Vasculopathy with hemorrhage
Neurocutaneous angiomatosis	Arteriovenous malformation, anomalous veins
Neurofibromatosis type 1	Moyamoya syndrome, arterial dysplasia
Progeria	Vasculopathy, cerebral infarction
Pseudoxanthoma elasticum	Aneurysm, cerebral infarction
Sturge–Weber syndrome	Leptomeningeal and brain venous angioma

Table 1.9. Hereditary patterns of neurocutaneous disorders

Autosomal dominant disorders
- Basal cell nevus syndrome
- Cowden disease
- Ehlers–Danlos type 4
- Hereditary hemorrhagic telangiectasia
- Multiple endocrine neoplasia type 2
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Tuberous sclerosis
- von Hippel–Lindau disease

Autosomal recessive disorders
- Ataxia–telangiectasia
- Chediak–Higashi syndrome
- Cockayne syndrome
- Cerebrotendinous xanthomatosis
- Familial dysautonomia
- Fucosidosis
- Homocystinuria
- Lipoid proteinosis
- Multiple carboxylase deficiency
- Pseudoxanthoma elasticum
- Refsum disease
- Rhizomelic chondrodysplasia punctata
- Sjögren–Larsson syndrome
- Trichothiodystrophy
- Xeroderma pigmentosum

X-linked disorders
- Adrenoleukodystrophy
- Fabry disease
- Incontinentia pigmenti[a]
- Lesch–Nyhan disease
- Menkes kinky hair disease

Mosaic disorders
- Encephalocraniocutaneous lipomatosis
- Epidermal nevus syndrome
- Hypomelanosis of Ito

Undetermined/sporadic disorders
- Blue rubber bleb nevus syndrome
- Cerebello-trigemino-dermal dysplasia
- Coffin–Siris syndrome
- Giant axonal neuropathy
- Hemangioma–vascular anomaly syndrome
- Macrodactyly–fibrolipoma syndrome
- Neurocutaneous angiomatosis
- Neurocutaneous melanosis
- Progeria
- Sturge–Weber syndrome

[a] X-linked dominant.

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Genetics of neurocutaneous disorders

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Introduction

Neurocutaneous disorders in humans affect both the nervous system and the skin. Developmentally, both the skin and nervous system arise from embryonic ectoderm. There are more than 40 such disorders described in this text, with the majority displaying Mendelian inheritance. Mendelian inheritance refers to so-called 'single gene' conditions; conditions that have a specific clinical picture (phenotype) based on mutation of one gene. All the many facets of a disease and the multitude of differences between one affected person and another cannot be attributed entirely to the action of a single gene. There are modifier genes that influence phenotype as well as environmental conditions. 'Single gene' conditions are sometimes genetically heterogeneous; mutations in different genes can result in similar (often indistinguishable) phenotypes. Many of the neurocutaneous diseases exhibit variable phenotypes due to different mutations in a single gene (e.g. the proto-oncogene RET in multiple endocrine neoplasia type 2B (MEN2B), or the ATP-binding cassette C6 gene (ABCC6) in *Pseudoxanthoma elasticum*) while others have very similar phenotypes that result from mutations at different genetic loci (e.g. the Osler–Rendu–Weber syndromes and tuberous sclerosis complex). Disease-causing mutations in the causative genes have been identified for many of the neurocutaneous disorders during the past 15 years as a result of the rapid technologic advances in gene hunting. This chapter is devoted to discussing the hereditary patterns and causative genes.

Inheritance patterns

The hereditary influence on the traits of living organisms mainly resides in the chemical information of the nucleic acids (genes) of the organism. Groups of genes are packaged together to form chromosomes within the nucleus of the cell. The chromosomes replicate and divide for passage into daughter cells, allowing the exact chemical information to be inherited by the next generation. There are two copies of each gene (and therefore, two copies of every chromosome) present in the somatic cells of eukaryotic organisms. Only one of the two genes (chromosomes) will be passed on in a germ cell. When two germ cells come together to create the new organism, the number is restored. A gene resides in a specific location (locus; plural loci) on a chromosome with specific neighboring genes and markers. Each of the two copies of a gene is termed an allele. The mutated copy of a gene is termed the abnormal allele, while the normal copy is termed the wild type allele. Genotype refers to the genes themselves with the terms homozygous and heterozygous, respectively, referring to whether an individual has two copies that are the same (normal or mutated) or different (one normal copy and one mutated copy). An individual with two normal alleles has a normal homozygous genotype while an individual with two abnormal alleles has an abnormal homozygous genotype. In a heterozygous genotype the individual has one normal and one abnormal allele on each of the two matched chromosomes. An individual exhibiting symptoms of a disorder has an abnormal 'phenotype'. Phenotype refers to the traits presenting as a consequence of the genotype. When an abnormal phenotype manifests in a patient with a heterozygous genotype, the disorder is dominant (only one abnormal or mutated copy of the gene is required to produce the disease phenotype). In a recessively inherited disorder, the disease phenotype is only produced in the presence of a homozygous abnormal genotype.

In human there are 23 pairs of chromosomes with 22 of the pairs referred to as autosomes. Autosomes are numbered by size from largest (chromosome pair 1) to smallest

(chromosome pair 22). The autosomes are the same in men and women. Genes residing on the autosomes are inherited the same in men and women. The 23rd pair of chromosomes is composed of the sex chromosomes, X and Y. Females have two copies of the X chromosome and males have one X chromosome and one Y chromosome. Genes carried on the X and Y chromosomes display different inheritance patterns than the genes on the autosomes because of the difference in copy number between males and females. A number of neurocutaneous diseases are due to mutations of genes residing on the X chromosome.

Types of mutations

The genes of living organisms contain variable lengths of chemical codes made up by combinations of four deoxyribonucleotides (guanine denoted G, adenine A, thymine T, and cytosine C). A specific combination of three nucleotides together forms a codon. Each codon encodes for a specific protein building block called an amino acid. A total of 20 amino acids are represented by 61 codons. With the exception of the code for methionine (ATG), the other 19 amino acids are coded for by more than one combination of three nucleotides with most of the variation occurring at the third and final nucleotide of the codon. Thus some variations in nucleotides do not change the amino acid sequence of the encoded protein allowing organisms to survive despite mutational pressures from the environment. A difference between the DNA of two individuals at a specific site can represent either harmless variation (a polymorphism) or a mutation resulting in production of a disease phenotype. When the change of a nucleotide in a codon results in the change of one amino acid to another, the change is called a 'missense' mutation. The consequence from missense mutations cannot be definitively concluded until the changes are proven to alter the normal function of the gene product. If abnormal function of the gene product cannot be detected, the missense mutation will be referred as missense polymorphic variant.

Three specific codons (TGA, TAG, and TAA) encode the signal that a protein is complete. These three are called termination or STOP codons. Mutations of amino acid codons into any one of these three termination codons will terminate the gene product prematurely and produce a nonfunctional protein. These mutations are termed 'nonsense' mutations.

Since nucleotides are read in groups of three (the reading frame), the only meaningful way for the nucleotides to code for a protein is by reading sequentially from the first coding frame starting at the initiation codon ATG. Within a gene, codons are assigned numbers that represent their location. The ATG (START) codon is always 1, with all subsequent codons sequentially numbered. The system works well in describing the location of a particular disease-causing mutation. Mutational events causing insertion or deletion of nucleotides other than in a multiple of three will ruin the reading frame, consequently changing every codon after the site of interruption. In most cases, changing the reading frame results in formation of a premature STOP codon, producing a premature gene product. A premature gene product is nonfunctional most of the time. Insertion or deletion sometimes involves large fragments of the genetic code. The results of a large insertion or deletion are similar to those of small insertion or deletion events causing the gene to no longer produce normal functional protein. In some neurocutaneous genetic diseases, like tuberous sclerosis complex, deletion can involve the whole gene depriving the individual of one of their normal copies of gene. In summary, nonsense mutations and insertion or deletion mutations (both large and small) that disrupt the reading frame fall in the category of 'protein truncation' mutations in contrast to missense mutations and in-frame insertions or deletions. These two broad categories sometimes produce different phenotypes even when the same gene is mutated.

The genetic codes for eukaryotic organisms are packed in discrete domains called exons with intervening sequences in between called introns. This phenomenon is believed to be of evolutionary advantage because those domains with either structural or enzymatic functions can be shuffled into different combinations for survival and adaptation to changing environments. The mechanism termed 'splicing' allows the nonessential intronic sequences to be removed and ensures production of a functional protein sequence. The splicing events are regulated by the nucleotide sequences immediately flanking the exon called splice donor or acceptor sites. Mutations altering these immediate flanking sequences of an exon will affect the accuracy or efficiency of the splicing process. As a result, the exon with the mutated splice sites will either be skipped or a nearby cryptic splice site will be used. Either event results in a nonfunctional gene product.

Penetrance, expressivity, mosaicism, and genetic heterogeneity

Penetrance, expressivity, and mosaicism are descriptive terms that apply in most cases to dominantly inherited disorders. Penetrance is the percentage of individuals with an abnormal phenotype among the total number

of individuals who have an abnormal genotype. The stringency and accuracy of diagnostic criteria, therefore, affect the determination of the penetrance of a disorder. Nonpenetrance occurs when an individual has an abnormal genotype but no phenotypic findings are associated with the disorder at any point during the individual's lifetime. Huntington's chorea, a degenerative neurological disease, has 100% penetrance by age 70 years. Expressivity is the variable phenotypes observed among individuals who have an abnormal genotype. Individuals affected by neurofibromatosis type 1 have a wide spectrum of disease phenotypes varying from mild to severe forms. Other factors such as modifier genes and environmental factors also affect the role of the abnormal gene, thereby modifying the phenotypes. Mosaicism describes different genotypes in different cells within the body of an individual. In a mosaic state, only some of the cells within an individual's body have an abnormal disease genotype. Mosaicism affects somatic tissues as well as germ cells. However, mosaicism involving germ cells but not somatic tissues will be missed with genetic testing of DNA extracted from peripheral blood lymphocytes, the most common source of DNA for testing. Mosaicism leads to problems in genetic counseling because individuals who have germline mosaicism for a disease-causing mutation cannot be identified until after the birth of a second affected child. Genetic heterogeneity refers to defects in different genes resulting in the same phenotype (disease). Genetic heterogeneity results in some diseases having multiple inheritance patterns. For example, retinitis pigmentosa (RP), the most common inherited form of blindness, is inherited in autosomal dominant, autosomal recessive and X-linked patterns.

For convenience of discussion, we have grouped the neurocutaneous disorders into four categories based on inheritance (autosomal dominant (AD), autosomal recessive (AR), X-linked, multiple types of inheritance) and a fifth category describing conditions that result from mosaicism.

Autosomal dominantly inherited neurocutaneous disorders

Autosomal dominant disorders are characterized by their vertical transmission pattern through successive generations. There is no gender bias regarding frequency or severity of disease. The risk for an affected parent to have an affected child is 50%. Half-sibs or full-sibs will have the same risk of inheriting a disease gene from the affected parent. The phenotype is observed in individuals with a heterozygous genotype. Table 2.1 lists examples of AD neurocutaneous disorders along with the catalog number of the Online Mendelian Inheritance in Man (OMIM #), chromosomal location and gene designation (when known). For diseases with known underlying genetic etiologies the name and chromosomal location of the gene are indicated. All of the neurocutaneous disorders listed show complete penetrance. Mosaicism has been described in some of the diseases (i.e. the Marfan syndrome, von Hippel–Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis complex).

Autosomal dominant genetic disorders caused by mutations at one genetic locus

Many of the autosomal dominant neurocutaneous disorders are caused by mutation in a single gene. These include the Marfan syndrome, von Hippel–Lindau syndrome, multiple endocrine neoplasia 2B, Cowden syndrome, Ruvalcaba–Myhre–Smith syndrome (also called Bannayan–Zonana syndrome), neurofibromatosis type 1 and neurofibromatosis type 2.

Prevalence of the Marfan syndrome is reported as between 1 and 2 in 10 000. It is estimated that approximately 25% of the patients have the disease as a result of a new mutation. The Marfan syndrome was shown by Dietz et al. (1991) to be caused by mutations of the fibrillin-1 gene (FBN1). Fibrillin-1 together with other proteins including elastin, thrombospondin, microfibril-associated glycoprotein, emilin, and fibrillin-2 form the microfibrils in the extracellular matrix for cell–cell adhesion. Fibrillin-1 mutations in Marfan syndrome patients disrupt the assembly of normal microfibrils. Somatic as well as germline mosaicism has been observed, suggesting that not all of the sporadic Marfan syndrome cases are secondary to new mutations (Rantamaki et al., 1999).

Von Hippel–Lindau (VHL) syndrome occurs in approximately 1 per 40 000 in the population and is described as displaying complete penetrance by the age of 65. As in the Marfan syndrome, new mutational events are estimated to account for around 25% of cases. Latif et al. identified the disease-causing gene (VHL) in 1993. The VHL gene consists of three exons encoding a cDNA of 852 nucleotides. The VHL protein is a component of a complex consisting of elongin B, elongin C, and cullin-2 associated with transcriptional elongation and ubiquitination. The VHL protein was shown to regulate expression of vascular endothelial growth factor (VEGF) via inhibition of the DNA transcription factor Sp1 binding to the VEGF promoter (Mukhopadhyay et al., 1997). VHL can be divided into two categories: Type 1 (those without pheochromocytoma) and Type 2 (those with pheochromocytoma). Differences in the

Table 2.1. Autosomal dominant neurocutaneous disorders

OMIM #	Inheritance	Neurocutaneous disease	Chromosome	Gene designation*
One gene				
154700	AD	Marfan syndrome	15q21.1	FBN1
193300	AD	Von-Hippel–Lindau syndrome	3p26–p25	VHL
162300	AD	Multiple endocrine neoplasia 2b	10q11.2	RET
158350	AD	Cowden syndrome	10q23.3	PTEN
153480	AD	Ruvalcaba–Myhre–Smith syndrome (Bannayan–Zonana syndrome)	10q23.3	PTEN
162200	AD	Neurofibromatosis type 1	17q11.2	NF1
101000	AD	Neurofibromatosis type 2	22q12.2	NF2
Multiple genes				
109400	AD	Basal cell nevus syndrome	9q22.3–31	PTCH
109400	AD	Basal cell nevus syndrome	1p32.2–p32.1	PTCH2
187300	AD	Rendu–Osler–Weber syndrome I (hereditary hemorrhagic telangiectasia I)	9q33–q34.1	ENG
600376	AD	Rendu–Osler–Weber Syndrome II (hereditary hemorrhagic telangiectasia II)	12q11–q14	ACVRLK1
191100	AD	Tuberous sclerosis complex	9q34.3	TSC1
191092	AD	Tuberous sclerosis complex	16p13.3	TSC2
Gene(s) not identified				
135900	AD	Coffin–Siris syndrome	7q32–34	?
106070	AD	Hereditary neurocutaneous angioma	?	?
112200	AD	Blue rubber bleb nevus	9p	MST1?

Notes: *Gene designations are as in the Online Mendelian Inheritance in Man/National Center for Biotechnology Information (OMIM/NCBI).

underlying mutation type (protein truncation vs. missense) lead to the phenotypic differences. Mutational testing by Chen et al. (1995) determined that about half of the VHL type 1 patients carried microdeletions/insertions, nonsense mutations, or deletions in the VHL gene while almost all of the patients with VHL type 2 have missense mutations in one copy of the VHL gene. Both germline and somatic mosaicism have been observed in VHL patients (Sgambati et al., 2000).

It has been discovered for some genes that different mutations within the same gene can cause strikingly different phenotypes. An example would be the gene that is mutated in MEN2B, the RET oncogene. Different mutations in the RET oncogene have been found to cause multiple endocrine neoplasia type 2A (MEN2A), Hirschsprung disease (HSCR), and familial medullary thyroid carcinoma (FMTC). The prevalence for the MEN2 disorders is estimated to be 1 in 30 000 with MEN2B accounting for only 5% of all the MEN2 patients. The RET gene protein is a cell-surface membrane receptor, tyrosine kinase, capable of transducing signals for cell proliferation and differentiation. In MEN2B patients, over 95% of the mutations found in the RET gene involve a specific missense mutation (methionine to threonine at codon 918; abbreviated Met918Thr) in the tyrosine kinase domain that is postulated to permanently activate the RET activity (Hofstra et al., 1994; Bongarzone et al., 1998). Approximately 50% of the MEN2B cases are observed in patients without a family history of the disorder. Neither germline nor somatic mosaicism has been reported in parents of patients with the MEN2B disorder.

Cowden syndrome is a somewhat more rare condition estimated to occur in 1 per 200 000. A strong prevalence is observed in female patients with complete penetrance expected by the age of 20. Nelen et al. in 1996 mapped the Cowden syndrome gene to D10S573, a polymorphic DNA marker in the10q22–23 chromosome region. This region was known to contain the phosphatase and tensin homolog gene (PTEN tumor suppressor gene) that is mutated in some sporadic brain, breast, and prostate cancer tissues. Cowden syndrome (CS) and Lhermitte–Duclos disease (LDD) were long suspected to represent allelic disorders (disorders resulting from mutations within the same gene at different locations within the gene). The study of Liaw et al. (1997) found PTEN mutations in DNA from LDD patients and speculated LDD to be the result of a larger N-terminal truncation of the PTEN gene. They also found mutations in DNA from four of five CS families in their study, thus providing evidence that the earlier speculation

was correct. These authors suggested that PTEN plays an organizer role in the relationship of different cell types within an organ during development.

Two benign familial macrocephaly syndromes (Ruvalcaba–Myhre–Smith syndrome and Bannayan–Zonana syndrome) were thought to represent phenotypic variability resulting from mutation at a single genetic locus. Patients with these syndromes were also found to have mutations in their PTEN gene confirming the two disorders to be allelic (DiLiberti, 1992). PTEN functions as a tumor suppressor to modulate G1 cell cycle progression through negatively regulating the phosphoinositide 3 kinase (PI3-kinase)/Akt1 signalling pathway. A critical target of the PTEN signaling process is the cyclin-dependent kinase inhibitor protein p27 Kip1.

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant neurocutaneous disorders occurring in 1 per 3000–4000. The prevalence is much higher among individuals of North African and Asian descent than Caucasians. Approximately 30 to 50% of NF1 cases are estimated to occur secondary to new mutation and complete penetrance is expected to occur by the age of 20 years. Neurofibromatosis type 1 is caused by mutation of the NF1 gene. The NF1 protein, neurofibromin, is a tumor suppressor that negatively regulates proto-oncogene p21 (Ras) via its GAP (GTPase activating protein)-related domain (Weiming et al., 1992). Germline mosaicism in the sperm of a clinically unaffected father of a patient was first reported in 1994 showing a deletion of 12 Kb in one copy of his NF1 gene (Lazaro et al., 1994). Other cases of mosaic microdeletions involving the NF1 gene have also been reported; however, the incidence of mosaicism (somatic and germline) in NF1 has not been determined.

Neurofibromatosis type 2 (NF2) is observed with a much lower incidence rate than NF1, reported at 1 in 33 000. Half of the NF2 patients are new cases without family history of the disease. NF2 is 100% penetrant, while expressivity of the phenotype varies widely. Mutations of the NF2 gene, located on chromosome 22q12.2, were first reported in 1993 (Rouleau et al., 1993). The NF2 protein, schwannomin/merlin, is closely related to the ERM (ezrin–radixin–moesin) family of proteins that serve to link cytoskeleton to membrane proteins. Mosaicism is suspected to be fairly common in NF2 patients (Kluwe & Mautner, 1998).

Autosomal dominant neurocutaneous disorders with genetic heterogeneity

There are several genetically heterogeneous AD neurocutaneous disorders including: basal cell nevus syndrome (BCNS) also called Gorlin syndrome, Rendu–Osler–Weber syndrome (ROWS) also called hereditary hemorrhagic telangiectasia (HHT) and tuberous sclerosis complex (TSC).

Basal cell nevus syndrome (BCNS) results from a mutation in either the PTCH gene or the PTCH2 gene (Johnson et al., 1996b; Smyth et al., 1999). BCNS has a prevalence of 1 in 50 000–60 000. Forty per cent of the BCNS patients have the condition secondary to a new mutation, while 60% have a positive family history. The PTCH gene is the human homolog of a gene found in *Drosophila*, Ptc. Ptc was shown to code for the receptor for hedgehog (Hh) proteins. The Hh proteins bind to Ptc or to a Ptc-Smo (smoothened gene, also found in *Drosophila*) complex to induce Smo activity. Hh proteins will induce Ptc expression to downregulate the Hh signal for regulating cell growth and tissue patterning. The PTCH2 gene was identified after a second mouse Patched gene was identified.

Mutations in either the endoglin gene (ENG) or the activin receptor-like kinase 1 gene (ACVRLK1/ALK1) are causative in hereditary hemorrhagic telangiectasia types 1 and 2 respectively (also called Rendu–Osler–Weber syndrome 1 and 2) (McAllister et al., 1994; Johnson et al., 1996a). The prevalence rate for HHT1 in the United States is roughly 1 in 10 000 and the prevalence for HHT2 is 1 in 3 000 000. In France and some regions of Denmark there is a two to four times higher incidence reported. New mutations are rarely thought to be causative in HHT. To diagnose HHT, four criteria (epistaxis, telangiectasia, visceral lesions and a positive family history) are assessed. A patient is definitively diagnosed if three of the criteria are present. Both ENG protein (endoglin) and the activin receptor- like kinase 1 (ACVRLK1) are components of the transforming growth factor β (TGFβ) receptor complex found primarily on the cell surface membrane of vascular endothelium. The TGFβ receptor complex functions to downregulate growth signaling upon binding TGFβ. Endoglin expression is induced by TGFβ1 and binds TGFβ1 with high affinity. The ACVRLK1 protein has a serine–threonine kinase domain that binds TGFβ and activin.

Tuberous sclerosis complex is caused by a mutation in either the TSC1 or TSC2 gene, with indistinguishable phenotypes observed (van Slegtenhorst et al., 1997; European Chromosome 16 Tuberous Sclerosis Consortium, 1993). TSC exhibits complete penetrance in families linked to either of the TSC-causing genes. Sporadic (new mutation) TSC cases account for 70% of patients. Mutational studies report around 15% of TSC patients have TSC1 gene mutations while 65% of TSC patients have TSC2 gene mutations. Only about 25% of the patients with TSC1 mutations represent sporadic cases. All mutations found within the TSC1 gene are predicted to cause protein truncation while approximately 25% of the TSC2 gene mutations reported are missense mutations. As many as 20% of the TSC2 mutations