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Genetic Aspects of Neurocutaneous Disorders

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Among the conditions that are included under the heading of "neurocutaneous disorders" are neurofibromatosis 1, tuberous sclerosis complex, von Hippel-Lindau, incontinentia pigmenti, Sturge-Weber syndrome, hypomelanosis of Ito, and linear nevus sebaceous syndromes. The clinical features, pathogenesis, and neurobiological basis of some of these disorders are discussed in other articles in this issue. We will focus on genetic aspects of a selected subgroup of these conditions, concentrating on the genetic defect, mutation spectrum, clinical genetic testing, and issues pertinent to counseling.
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In this article, we review what is known of the genetics of selected neurocutaneous disorders including incontinentia pigmenti (IP), von Hippel Lindau (VHL) syndrome, tuberous sclerosis complex (TSC), and neurofibromatosis 1 (NF1). For each condition, we will summarize the pattern of inheritance, discovery of the genetic basis, the structure of the causative gene(s), the spectrum of mutations, genotype-phenotype correlations, current methods of genetic testing and their clinical use, and genetic implications for the patient/their families.

IP (Bloch-Sulzberger syndrome, OMIM #308300)

IP is an X-linked dominant condition that is lethal in most (but not all) males. The primary clinical features are abnormalities of the skin, but the disorder also affects teeth, hair, nails, eyes, and the nervous system. The typical skin lesions progress through 4 stages.

1. Erythematous and vesicular lesions, usually in a linear distribution, appear at birth or shortly thereafter. Lesions may appear in crops and last a few weeks to months.
2. Verrucous stage, with crusted, hyperpigmented pustules, mostly on the extremities. This lasts for several months.
3. Hyperpigmented stage consisting of swirling whorls of macular hyperpigmented lesions, fading during adolescence.
4. Atrophic stage: the patient has pale and hairless patches or streaks on the skin.

Other features include abnormalities of the teeth, hair (alopecia), nails, and retina (neovascularization). Neurologic problems (seizures and developmental delay) occur in a small minority of patients (perhaps less than 10%).[1] The diagnosis is based on clinical features and family history.

IP is inherited in an X-linked dominant fashion, with lethality in males. A few male cases of IP have Klinefelter syndrome (47, XXY), somatic mosaicism, or hypomorphic alleles. Linkage analysis in families with IP mapped the gene to Xq28 (linked to DXS52). In the year 2000, IP was shown to be caused by mutations in the *IKBKG/NEMO* gene located at Xq28.[2] IKBKG stands for "inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma," and NEMO stands for "NF-kappa-B essential modulator." *NEMO* is a 23-kbp gene containing 10 exons with 3 alternative noncoding first exons (1a, 1b, and 1c). In addition, there is a truncated copy of *NEMO* containing only exons 3 to 10 (*delta-NEMO*) located distal to the *NEMO* gene.

The most common mutation of *NEMO* in IP is a genomic rearrangement that deletes the segment between a repetitive sequence that occurs both in intron 3 and distal to exon 10. This genomic rearrangement deletes exons 4 to 10 of the *NEMO* gene (Fig 1). This particular deletion (called NEMOΔ4-10) accounts for the majority (70%-80%) of new

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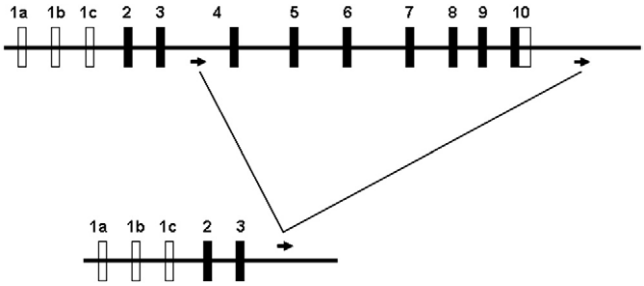

Figure 1 Common NEMOΔ4-10 delection in IP. The diagram shows the exon-intron structure of the *NEMO* gene (not to scale), with the most common mutation that results in loss of exons 4 to 10 indicated in the bottom line. This is a result of intrachromosomal rearrangement that occurs between repetitive elements (arrows) in intron 3 and downstream of exon 10.

mutations in *NEMO*, and occurs (in the majority of cases) during paternal gametogenesis by intrachromosomal interchange.[3] In the remaining cases, a variety of other mutations in the *NEMO* gene have been discovered, including small duplications, substitutions, and deletions, in most cases resulting in premature truncation of the protein and loss of *NEMO* function. Included here is the duplication of a 7-cytosine tract within exon 10, which is consistent with survival in males.[3]

NEMO appears to be essential for activation of the NF-kappa-B transcription factor and thus is involved in inflammation and apoptotic pathways. In females who carry a mutant *NEMO* gene, cells that express the mutant gene are eliminated by apoptosis. This explains the extremely skewed X-inactivation pattern in which the mutant allele is preferentially inactivated.[4]

Genetic testing in individual cases and families is available on a clinical basis (see www.genetests.org or http://www.bcm.edu/geneticlabs/tests/alltests.html). Methods currently used include Southern blotting and direct sequencing of exons. Consultation with a clinical geneticist is important before genetic testing. This should include clinical examination of the child, parents, and siblings and will help to distinguish between familial and sporadic cases. This information is critical for appropriate genetic counseling.

VHL (OMIM #193300)

VHL is an autosomal dominant disorder that is characterized by tumors of the brain and spinal cord and of other viscera. Cerebellar and spinal hemangioblastomas are the typical central nervous system tumors, whereas hemangioblastomas of the retina are a common clinical finding. Visceral tumors include pheochromocytoma, renal cell carcinoma, renal cysts, and pancreatic cystadenoma.[5]

Linkage studies allowed for mapping of the *VHL* gene to chromosome 3p25,[6] and positional cloning led to the identification of the *VHL* gene in 1993.[7] The gene is relatively small (3 exons distributed over 10 kbp of genomic DNA) and encodes a 30-kDa protein (pVHL) that functions as a tumor suppressor. Virtually all patients with VHL syndrome harbor a germline mutation in the *VHL* gene, and lesions (cysts or tumors) contain an additional somatic mutation (consistent with Knudson's 2-hit model). Studies of the biological function of pVHL have led to the discovery of a novel oxygen-sensing cellular-signaling pathway that regulates the expression of hypoxia-inducible genes such as vascular endothelial growth factor, platelet-derived growth factor B, and transforming growth factor α.[8,9] pVHL assembles a protein complex that, in the presence of oxygen, binds to hypoxia inducible factor (HIF) and results in polyubiquitination and proteosomal degradation of HIF.[10] Loss-of-function mutations of the *VHL* gene result in defects of HIF polyubiquitination, and overproduction of growth factors (vascular endothelial growth factor, platelet-derived growth factor B, and transforming growth factor α), which lead to hemangioblastoma and renal cell carcinoma.

Over 300 distinct mutations, scattered over all 3 exons, have been identified in VHL patients, including partial or complete gene deletions, nonsense, missense, frameshift, and splicing mutations.[11] Missense mutations are likely to be associated with the subtype of VHL that is associated with pheochromocytoma, whereas mutations that result in a loss of pVHL function are associated with a reduced risk of pheochromocytoma.[12] Molecular genetic testing is essential for confirmation of diagnosis in index cases and is important for surveillance of asymptomatic carriers. Patients and family members should receive genetic counseling before and after genetic testing. Current methods include Southern blotting or fluorescent in situ hybridization to detect large deletions and sequence analysis of the exons to detect small mutations. It is estimated that 80% of the cases are familial (will have an affected parent), whereas 20% are sporadic and are the result of novel germline mutations.

TSC (OMIM #191100)

TSC is also inherited in an autosomal dominant fashion, although about two thirds of the cases are sporadic. It is characterized by hamartomatous lesions in the brain (cortical tubers and subependymal nodules), kidneys (angiomyolipomas), skin, heart, and lungs. Neurologic symptoms predominate in this disorder and include mental retardation, autistic features, behavioral abnormalities, and intractable epilepsy.

Genetic linkage analysis in familial cases led to the mapping of a *TSC* gene (designated *TSC1*) to chromosome 9q34[13] and a second locus at chromosome 16p13.3 (designated *TSC2*).[14] The identity of the *TSC1* gene was determined in 1997, whereas the *TSC2* gene was discovered in 1993.[15,16] Among the familial cases, about half are linked to the *TSC1* locus and half to the *TSC2* locus, but among the sporadic cases, most (over 70%) are caused by defects in *TSC2*.

The *TSC1* gene contains 23 exons and encodes a 130-kDa protein, hamartin. The *TSC2* gene contains 41 exons and encodes a 200-kDa protein, tuberin. Hamartin and tuberin function together as a protein complex and participate in the mammalian target of rapamycin (mTOR) signaling pathway that is involved in regulating cell growth.[17] This explains the

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