X-linked malformations of neuronal migration

W.B. Dobyns, MD; E. Andermann, MD; F. Andermann, MD; D. Czapansky-Beilman, MD; F. Dubeau, MD; O. Dulac, MD; R. Guerrini, MD; B. Hirsch, PhD; D.H. Ledbetter, PhD; N.S. Lee, MD†; J. Motte, MD; J.-M. Pinard, MD; R.A. Radtke, MD; M.E. Ross, MD, PhD; D. Tampieri, MD; C.A. Walsh, MD, PhD; and C.L. Truwit, MD

Article abstract—Malformations of neuronal migration such as lissencephaly (agyria-pachygyria spectrum) are well-known causes of mental retardation and epilepsy that are often genetic. For example, isolated lissencephaly sequence and Miller-Dieker syndrome are caused by deletions involving a lissencephaly gene in chromosome 17p13.3, while many other malformation syndromes have autosomal recessive inheritance. In this paper, we review evidence supporting the existence of two distinct X-linked malformations of neuronal migration. X-linked lissencephaly and subcortical band heterotopia (XLIS) presents with sporadic or familial mental retardation and epilepsy. The brain malformation varies from classical lissencephaly, which is observed in males, to subcortical band heterotopia, which is observed primarily in females. The XLIS gene is located in chromosome Xq22.3 based on the breakpoint of an X-autosomal translocation. Bilateral periventricular nodular heterotopia (BPNH) usually presents with sporadic or familial epilepsy with normal intelligence, primarily in females, although we have evaluated two boys with BPNH and severe mental retardation. The gene for BPNH has been mapped to chromosome Xq28 based on linkage studies in multiplex families and observation of a subtle structural abnormality in one of the boys with BPNH and severe mental retardation.

NEUROLOGY 1996;47:331–339

Malformations of neuronal migration are an important cause of mental retardation and epilepsy that have been more frequently recognized due to the widespread clinical use of MRI. Many of these malformations have proven to be genetic. For example, isolated lissencephaly sequence and Miller-Dieker syndrome are caused by deletion of a lissencephaly gene in chromosome 17p13.3, while many other malformation syndromes are inherited as autosomal recessive traits.[1-3] In all, more than 25 genetic syndromes associated with lissencephaly or other malformations of cortical development have been described.[3]

In this paper, we review data that support the existence of two distinct X-linked malformations of neuronal migration: (1) X-linked lissencephaly and subcortical band heterotopia (XLIS); and (2) bilateral periventricular nodular heterotopia (BPNH).

Embryology of the cerebral cortex. Formation of the cerebral cortex begins soon after closure of the rostral end of the neural tube. It may be divided into three overlapping stages, including: (1) proliferation of neural precursors and their differentiation into young neurons and glia; (2) migration of postmitotic immature neurons from the ventricular zone to the emerging cerebral cortex; and (3) development of a mature cortex by formation of cortical lamination, synaptogenesis, and apoptosis (programmed cell death). In humans, cortical neuronal migration occurs in two major waves that continue for several months.[4-6] Neurons in the first wave are generated in the sixth postconceptual week and migrate to form the preplate in the seventh week. By week 10, the preplate splits into a superficial marginal zone, which later gives rise to cortical layer 1, and the deeper subplate, which is a transient neuronal layer that is crucial for the formation of appropriate cortical synaptic afferent and efferent connections.[5] The second and larger wave of young neurons are generated in the ventricular zone in the 10th week and

† Deceased.

From the Departments of Neurology (Drs. Dobyns, Czapansky-Bielman, Ross, and Truwit), Pediatrics (Dr. Dobyns), Laboratory Medicine and Pathology (Dr. Hirsch) and Radiology (Dr. Truwit), University of Minnesota Medical School, Minneapolis, MN; the Montreal Neurological Institute and Departments of Neurology and Neurosurgery (Drs. E. Andermann, F. Andermann, Dubeau, and Tampieri), Human Genetics (Dr. E. Andermann) and Radiology (Dr. Tampieri), McGill University, Montreal, Quebec, Canada; Département de Neuropédiatrie (Drs. Dulac and Pinard), Hôpital Saint Vincent de Paul, Paris, France; Division of Child Neurology and Psychiatry (Dr. Guerrini), Stella Maris Foundation and University of Pisa, Pisa, Italy; the National Center for Human Genome Research (Dr. Ledbetter), National Institutes of Health, Bethesda, MD; the Department of Neurology (Drs. Lee and Radke), Duke University, Durham, NC; Unité de Neuropédiatrie (Dr. Motte), American Memorial Hospital, Reims, France; and the Department of Neurology (Dr. Walsh), Beth Israel Hospital and Harvard University, Boston, MA.

Received July 8, 1995. Accepted in final form November 13, 1995.

Address correspondence and reprint requests to Dr. W.B. Dobyns, Department of Neurology, Box 486 UMHC, 420 Delaware Street SE, Minneapolis, MN 55455.

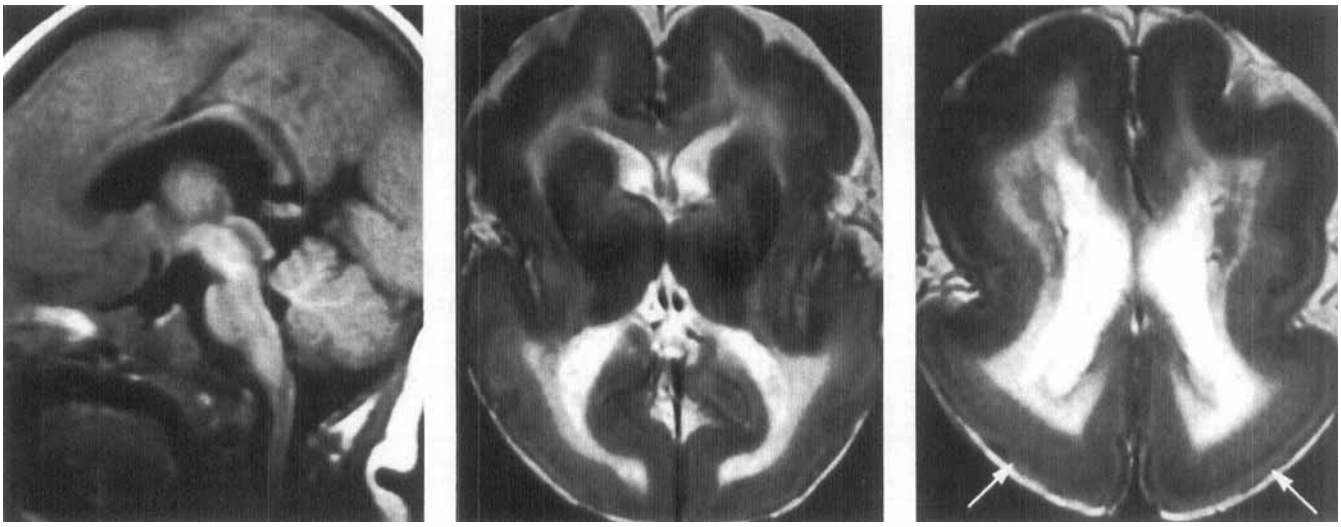

Figure 1. Classical lissencephaly in a 5-month-old boy. Although limited sulcation is seen frontally, the overall pattern is one of agyria/pachygyria or lissencephaly. Note the dramatic thick cortex with hyperintense cell-sparse layer (arrows) just deep to the superficial cellular layer of the cortex. The posterior portions of the lateral ventricles are mildly enlarged.

start to migrate out by the 11th week to fill the region between the preplate and subplate, forming the cortical plate. Migration of immature neurons to the embryonic cortex peaks between the 12th and 14th weeks, and ends by the 16th week when the ventricular zone is largely depleted of cells.[4-6] Thereafter, the majority of cells arising in the ventricular zone (actually the subventricular zone) are young glia.

Classical studies have shown that the cerebral cortex is formed by an "inside-out" migration of ventricular zone cells, so that the early generated neurons migrating to the cortical plate will occupy deeper layers, while later-migrating neurons pass the established cells to occupy more superficial positions. Most neurons are guided to the cortex by climbing radial glia fibers, although recent studies have shown both radial and tangential migration,[7] which suggests that several mechanisms for control of migration must exist.

Description of malformations. *Classical lissencephaly.* Classical lissencephaly (smooth brain) or generalized agyria-pachygyria is a severe brain malformation in which the cerebral surface is largely but not completely smooth. The posterior half is usually agyric with only a few undulations of the surface, while the anterior half is pachygyric with a few scattered abnormal sulci. More normal gyral development may occur in the orbitofrontal and inferior temporal regions and the hippocampi.

The cytoarchitectural changes clearly demonstrate an abnormality of neuronal migration. In his definitive description of the pathologic changes, Crome[8] wrote: "There is no essential difference between agyria and pachygyria other than one of degree, which is reflected in the varying number of imperfectly formed sulci. The gray matter in both conditions is arranged in four layers: (1) marginal, containing a slight excess of nerve fibers, (2) superficial cellular, (3) sparsely cellular, usually containing a large number of tangential and some radial nerve fibers, and (4) deep cellular, formed by nerve cells without definite orientation and a lattice-like network of nerve fibers. The ratio of gray to white matter is abnormal, the gray being greatly increased."[8]

The superficial cellular layer consists of small and medium-sized pyramidal cells and a few round cells with a distinctly radial arrangement, while the deeper layer of heterotopic nerve cells is more pleomorphic with pyramidal, fusiform, and round cells with no distinct cellular organization.[8] The cell-sparse layer consists only of a thin layer of tangential fibers intermixed with a few nerve cells between the superficial and deep layers of gray matter,[9] and is not always present.[6]

Brain imaging studies show absent or decreased surface convolutions and underdeveloped opercula, which result in a figure-eight shape on axial sections (figure 1). A spectrum of malformations is observed that includes generalized agyria, mixed agyria-pachygyria, and generalized pachygyria. The cortex is abnormally thick and consists of superficial and deep cellular layers separated by a thin and inconstant cell-sparse layer.[5,10,11] Common associated abnormalities include a hypoplastic or absent corpus callosum, persistent cavum septi pellucidi, and mildly enlarged lateral ventricles. Classical lissencephaly specifically excludes polymicrogyria, other cortical dysplasias, diffuse or focal heterotopia, calcifications other than the midline calcification sometimes seen in Miller-Dieker syndrome, brainstem hypoplasia, cerebellar hypoplasia, or severe congenital microcephaly with birth occipitofrontal circumference below −4 standard deviations.[2,3,11]

Subcortical band heterotopia. Subcortical band heterotopia (SBH) consists of bilateral and symmetric ribbons of gray matter located in the centrum

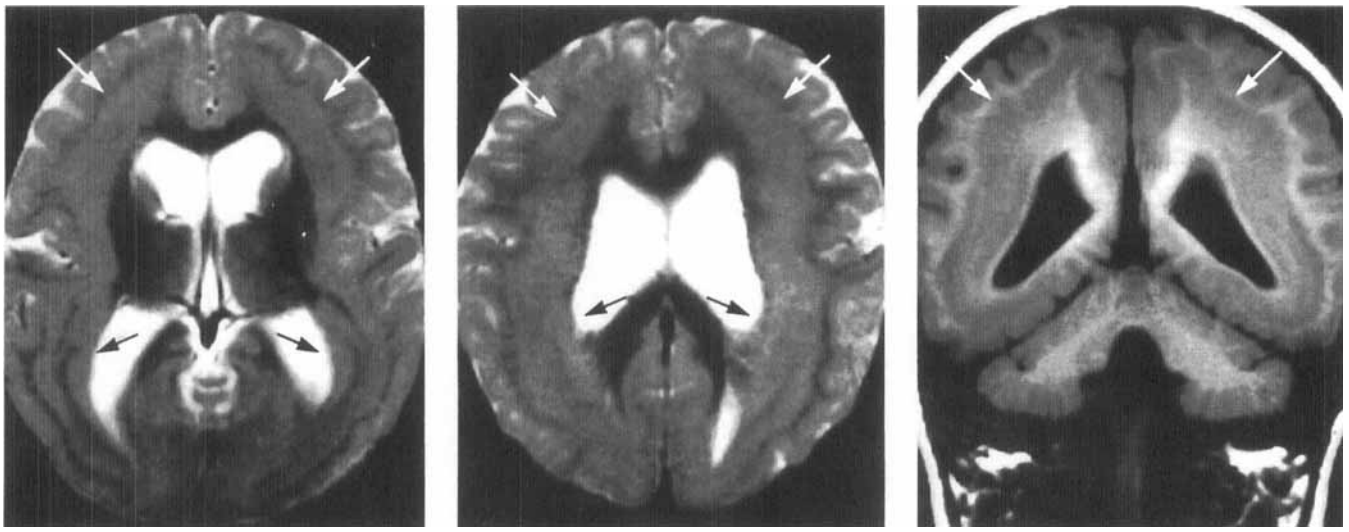

Figure 2. Subcortical band heterotopia in a 3-year-old girl. Note bilateral and symmetric bands with the signal intensity of gray matter (white arrows) diffusely within the substance of the white matter. As is occasionally seen in this disorder, the bands seem to fuse medially with the cingulate. Also note additional heterotopia (black arrows) along the trigones of the lateral ventricles. The overlying cortex appears normal.

semiovale between the cortex and ventricular walls, which are separated from both by layers of white matter. The heterotopia may form solid sheets or be split into many elongated islands with axes radiating toward the hemispheric surface.[9] The heterotopic bands range in shape from thin strips to thick wedge-like sheets, and extend throughout most of the hemispheres from frontal to occipital regions, sparing only the striate, cingulate, and fusiform gyri and medial temporal areas. The overlying gyral pattern may be entirely normal, or there may be a slight reduction in the number of gyri consistent with mild pachygyria. The basal ganglia are normal except for the claustrum, which is incorporated into the band.[12] This malformation has also incorrectly been called the "double cortex syndrome."

Histologically, the cortex appears normal with the usual six layers. Beneath it is a zone of well-myelinated white matter of variable width, which includes the U-fibers. The heterotopic band seen beneath this white matter zone consists primarily of small pyramidal cells. The neurons appear randomly arranged in the outer part of the band, while a suggestion of columnar organization is evident in the deepest part, emphasized by thin, radially arranged bundles of myelinated fibers, which course through it. Closer to the ventricle, the heterotopia breaks up into nodules in some areas, separated by thicker bands of white matter. Another broad zone of white matter lies between the heterotopia and the lateral ventricles.[12]

Brain imaging studies, especially MRI, show symmetric and circumferential bands of gray matter located beneath the cortex and separated from it by a thin band of white matter (figure 2).[13-15] The inner margin of the band is smooth. The outer margin may be smooth, especially when the heterotopic band is thick, or may undulate with the interdigitations of the true cortex and white matter, generally when the band is thin. The bands vary in thickness from several millimeters to more than one centimeter in width. The subcortical bands sometimes appear to be contiguous with the cingula (C.L. Truwit, unpublished data). The claustra are generally absent, with the band often coursing through their expected location. Occasionally, a second band heterotopia is seen in the peritrigonal regions, medial to the major subcortical bands.

The cortical sulci overlying the bands often appear abnormally shallow, while some patients have areas of overlying pachygyria in which the cortex is thinner, rather than thicker, than normal. Other inconstant abnormalities include abnormal T_2 prolongation of white matter on MRI, mild atrophy, and ventriculomegaly. The remainder of the brain appears normal. Rarely, a forme fruste of SBH consisting of bilateral and symmetric bands with a regional distribution occurs.[16] The relationship of these partial bands to diffuse SBH is uncertain.

Agyria, pachygyria, and SBH belong to a continuum of malformations of neuronal migration based on both older pathologic[17,18] and more recent MRI[3,19] studies. Several patients with malformations transitional between band heterotopia and pachygyria have been reported.[3,20] A woman reported by Matell[17] and widely quoted as the first description of pachygyria possibly also had SBH.[9]

Subependymal (periventricular) nodular heterotopia. Subependymal or periventricular nodular heterotopia are conglomerate masses of gray matter adjacent to the walls of the lateral ventricles. The heterotopic gray matter forms clusters of rounded, irregular nodules separated from each other by layers of myelinated fibers. Microscopically, both neurons and glial tissue are present with no consistent arrangement, although some rudimentary layering

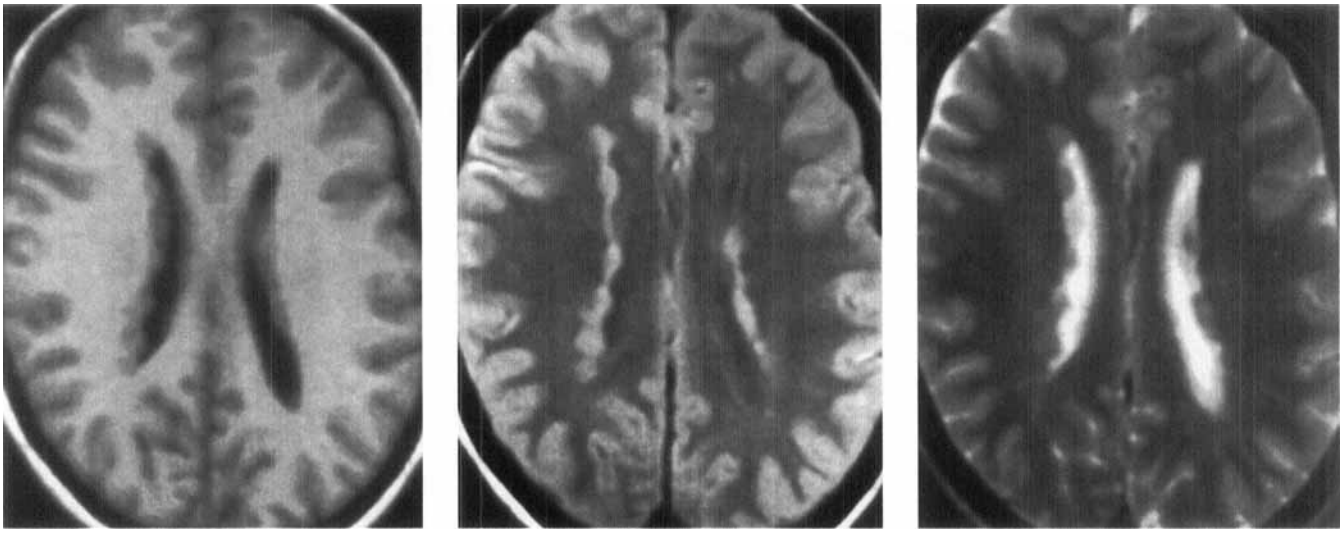

Figure 3. Bilateral periventricular nodular heterotopia in a 36-year-old woman with recent onset of seizures. Note multiple small nodules apparently protruding into lumina of the lateral ventricles. The lesions exhibit gray matter signal intensity on T_1-weighted (left), proton-density (middle), and T_2-weighted (right) images. The overlying white matter and cortex appear normal.

occurs.[9] The subependymal nodules may be unilateral or bilateral, large or small, diffuse or regional, and contiguous or noncontiguous. Some unilateral nodular heterotopia are associated with subcortical heterotopia.

MRI studies of bilateral periventricular nodular heterotopia (BPNH) show nodular masses of gray matter, which line the ventricular walls and protrude into the lumen (figure 3).[21] They may be diffuse and contiguous, or regional and noncontiguous. When contiguous, they are usually thick and involve most of the lateral subependymal plate, while noncontiguous BPNH resemble "pearls on a string." On MR images, the signal intensity is always that of gray matter. Patients with BPNH may have additional abnormalities such as mild cerebellar hypoplasia[21,22] or mild hypogenesis of the corpus callosum. Rare patients have areas of overlying cortical dysplasia (C.L. Truwit, W.B. Dobyns, unpublished data).[23]

The nodules differ from the subependymal nodules of tuberous sclerosis (TSC), which are smaller, less extensive, often calcified, inhomogeneous, and usually have signal intensities that parallel white matter.[21] Pathologically, the subependymal nodules of TSC consist primarily of undifferentiated cells or abnormal parallel gray matter, which suggests that they contain neurons as well.[24]

X-linked lissencephaly and subcortical band heterotopia. XLIS is an intriguing malformation syndrome that causes classical lissencephaly in hemizygous males and SBH in heterozygous (carrier) females. While lissencephaly and SBH were first described and their relationship proposed 50 to 100 years ago,[17,18] the observation received little attention until the advent of MRI. XLIS was delineated as a distinct genetic syndrome only recently based on four related observations: (1) consistent clinical manifestations in males with lissencephaly and in females with SBH; (2) a striking skew of the sex ratio toward females among patients with sporadic SBH; (3) several multiplex families with X-linked inheritance of classical lissencephaly in males and SBH in females; and (4) a girl with classical lissencephaly and a de novo X-autosomal translocation.

Clinical manifestations. Children with classical lissencephaly have profound mental retardation, mixed hypotonia and spasticity, epilepsy with multiple seizure types including infantile spasms, feeding problems, and shortened lifespan.[7] The clinical manifestations in boys with X-linked lissencephaly are similar to those with classical lissencephaly due to other causes such as deletion of the chromosome 17 lissencephaly gene.[2,3,11]

Most patients with SBH have mental retardation, behavior problems, and epilepsy. Seizures usually begin in childhood, but may not begin until the twenties. Seizure types include partial and generalized tonic or tonic-clonic, partial complex, atonic (drop), and atypical absence seizures. Some have infantile spasms or Lennox-Gastaut syndrome. Most patients have mild or moderate mental retardation, while some have either normal intelligence or severe mental retardation (table 1). Cognitive development may slow after onset of the seizures.[15] The relative thickness of the band correlates with the phenotype as patients with thicker bands have more severe mental retardation and seizures.[14] Similarly, the severity of mental retardation correlates with the severity of epilepsy as patients with Lennox-Gastaut syndrome have more severe mental retardation.[15]

Skew of sex ratio. Since SBH were "rediscovered" on imaging studies,[13,25] 51 of 54 reported patients with sporadic SBH have been female (table 1).[14-16,26-35] We have evaluated three other males as part of an ongoing research project. The phenotype appears to

Table 1 *Sex ratio and manifestations in patients with sporadic subcortical band heterotopia*

	References															
	15	26	27	28	29	30	31	32	33	14	34	16	35	12	Total	%
Number	10	1	2	1	1	1	1	1	1	27	1	1	3	3	54	
Gender																
Male	0	0	0	0	0	0	0	0	0	1	1	1	0	0	3	6
Female	10	1	2	1	1	1	1	1	1	26	0	0	3	3	51	94
Mental development																
Severe mental retardation	2	0	1	0	0	0	0	0	0	5	0	0	2	1	11	20
Moderate mental retardation	4	0	1	0	0	0	0	1	0	7	0	0	0	0	13	24
Mild mental retardation	3	0	0	1	1	0	1	0	1	8	1	0	0	1	17	32
Borderline mental retardation	0	0	0	0	0	0	0	0	0	4	0	0	1	0	5	9
Normal intellect	1	1	0	0	0	1	0	0	0	3	0	1	0	1	8	15
Seizures																
Any type	10	1	2	1	1	1	1	1	1	25	1	1	3	2	51	94
Infantile spasms	0	0	0	0	0	0	0	0	0	4	0	0	0	0	4	7
Brain abnormalities																
Subcortical band	10	1	2	1	1	1	1	1	1	27	1	1	3	3	54	100
Pachygyria	9	1	0	0	1	0	1	0	0	27	0	0	2	0	41	76
White matter abnormality	0	0	0	1	0	0	0	0	0	11	0	0	0	0	12	22
Ventriculomegaly	0	0	1	1	0	0	1	0	1	21	1	0	2	0	28	52
Vermis hypoplasia	0	0	0	0	0	0	0	0	0	2	0	0	0	0	2	4

be the same in affected males and females. A similar deviation of the sex ratio has been observed in several other genetic syndromes including Aicardi syndrome, focal dermal hypoplasia or Goltz syndrome, incontinentia pigmenti, microphthalmia with linear skin defects, oro-facio-digital syndrome type 1, and pyruvate dehydrogenase deficiency due to mutation of the E1α subunit.[36-38] For all of these syndromes, the skew toward females suggests the effects of an X-linked gene that causes prenatal lethality or more severe symptoms with early death in affected males.[38] The critical region for microphthalmia with linear skin defects has been mapped to chromosome Xp22, which further supports involvement of genes on the X chromosome in this group of disorders.[37]

X-linked inheritance. X-linked inheritance of lissencephaly, or lissencephaly and SBH, has so far been reported in five families (figure 4). In the first, three brothers had classical lissencephaly.[39] Evaluation of their mother was not possible. In the second, a boy and four maternal uncles had lissencephaly and absent corpus callosum. The mother and mater-

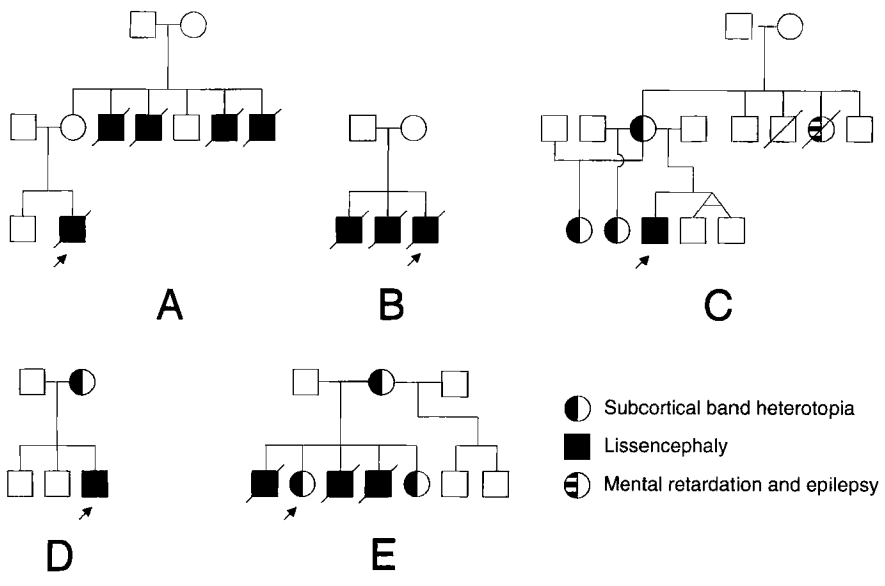

Figure 4. Pedigrees of five families showing X-linked inheritance of either lissencephaly (A, B) or both lissencephaly and subcortical band heterotopia (C to E). Modified from (A) Berry-Kravis and Israel[40]; (B) Pavone et al.[39]; (C and D) Pinard et al.[41]; and (E) Scheffer et al.[42]

nal grandmother of the proband appeared normal, but imaging studies could not be performed.[40] In the remaining three families, women with documented SBH had sons with lissencephaly.[41,42] In one of these families, a woman with SBH had two daughters with SBH and a son with lissencephaly, each by a different father.[41]

X-linked lissencephaly associated with congenital microcephaly, characteristic facial changes, and genital anomalies was reported in another family with three affected males and one affected female.[43] The clinical manifestations appear similar to XLIS, except that one apparently affected male did not have lissencephaly. If this boy was misclassified, the phenotype would be consistent with XLIS.

XLIS maps to Xq22.3. We evaluated a girl with isolated classical lissencephaly in whom chromosome analysis detected an apparently balanced, de novo X-autosomal translocation: 46,XX,t(X;2)(q22.3;p25) de novo.[11] A somatic cell hybrid retaining the derivative 2 (complete karyotype 2qter-2p25::Xq22.3-Xqter) as the only human chromosome was constructed (D.H. Ledbetter, unpublished data). Preliminary molecular studies show that the breakpoint is distal to marker DXS87, which places the gene in the telomeric half of band Xq22 (W.B. Dobyns and D. Czapansky-Bielman, unpublished data). The only known genes in this region at present are *COL4A5* and *COL4A6*. These results both support the existence of XLIS and localize the gene to Xq22.3, based on experience with X-autosomal translocations in other X-linked genetic diseases.

X-autosomal translocations. In females with balanced X-autosomal translocations, the normal random pattern of inactivation is altered so that the normal X becomes inactive in a large majority of cells.[44] The explanation for this phenomenon is complex. The translocated X is broken into two derivative chromosomes, each of which is attached to part of an autosome. In cells in which the derivative X is inactivated, the inactivation spreads from the inactivation center in proximal Xq to involve a portion of the attached autosome. This results in functional deletion of the autosomal segment. Further, the X chromosomal material on the other derivative chromosome will escape inactivation, resulting in functional duplication. These cells are at a disadvantage compared with cells with the normal X inactivated due to the functional aneuploidy.

Thus, cells with the translocated X active have a significant competitive advantage and predominate over those with the normal X active. If the breakpoint disrupts a gene, no functioning gene product is produced and the female may have an X-linked disorder usually observed in males. This mechanism has been observed in many X-linked disorders including Aarskog syndrome,[45] choroideremia,[46] Duchenne muscular dystrophy,[47] Hunter syndrome,[48] hypohidrotic ectodermal dysplasia,[49] incontinentia pigmenti,[50] Lowe oculocerebrorenal syndrome,[51] and Menkes disease.[52] Cloning of the translocation breakpoint has led to cloning of the gene for five of these diseases.[53-57]

Pathogenesis. While the nature of the product of the XLIS gene is not known, it must be expressed at a critical time throughout the brain as all major pathways of neuronal migration are affected. Because of the similarity of the phenotypes, we speculate that the products of the XLIS and chromosome 17 lissencephaly genes are functionally related, either as members of the same gene family, interacting receptor and ligand, or protein subunits. The two gene products could function as (1) receptors for a diffusable directional signal, (2) cell adhesion molecules, (3) an extracellular matrix protein, or (4) a transcription factor regulating a group of genes required for migration.

Due to the striking difference in phenotype between males and females, we hypothesize that lissencephaly in males results from complete absence of the XLIS gene product, while SBH in females results from functional mosaicism due to the effects of Lyonization. In this hypothesis, neurons that reach the cortex contain a functioning XLIS gene on the active X chromosome, while neurons in the heterotopia have a mutation of the XLIS gene on the active X leaving them with no functioning XLIS genes and thus no gene product. Similarly, we propose that SBH in rare males is caused by somatic mosaicism for mutations of the XLIS gene, or possibly the chromosome 17 lissencephaly gene.

Bilateral periventricular nodular heterotopia. Subependymal nodular heterotopia appear to be heterogeneous based on striking differences in location of the heterotopia and severity of symptoms. In general, focal and unilateral subependymal heterotopia vary greatly in severity and have not been observed in multiple members of the same family. In contrast, bilateral and symmetric subependymal (periventricular) heterotopia or BPNH usually present with a similar relatively mild phenotype, and have been observed in multiple individuals from several unrelated families. As for XLIS, it usually results in a more severe phenotype in males than in females. Specifically, this syndrome causes typical mild BPNH in females and some males, and either prenatal lethality or a more severe phenotype in other males.

BPNH was delineated based on four related observations: (1) consistent clinical manifestations in individuals with typical BPNH; (2) skew of the sex ratio toward females among sporadic patients with BPNH; (3) observation of several multiplex families in which only females were affected; and (4) observation of two boys with a more severe phenotype consisting of BPNH, cerebellar hypoplasia, severe mental retardation, and syndactyly. Preliminary linkage data and a subtle structural abnormality in one of the two severely affected boys combine to map this disorder to chromosome Xq28.

Table 2 *Sex ratio and manifestations in patients with sporadic bilateral periventricular nodular heterotopia*

	References									
	54	55	56	16	52	15	53	19	Total	%
Number	1	2	1	6	1	1	7	7	26	
Gender										
Male	0	1	0	1	1	0	0	4	7	27
Female	1	1	1	5	0	1	7	3	19	73
Mental development										
Borderline MR			1	2	0	1	1	0	5	22
Normal intellect			0	4	1	0	6	7	18	78
Seizures										
All types	1	2	1	5	1	1	7	7	25	96
No seizures	0	0	0	1	0	0	0	0	1	4
Brain abnormalities										
BPNH	1	2	1	6	1	1	7	7	26	100
Cerebellar hypoplasia	?	?	?	?	?	?	?	2	?	?

MR = mental retardation; BPNH = bilateral periventricular nodular heterotopia.

Clinical manifestations. Most probands with typical BPNH have normal intelligence and epilepsy with multiple seizure types that may or may not prove difficult to control.[58,59] Several asymptomatic individuals with BPNH have been discovered during family evaluations.[58]

Skew of sex ratio. Considering only sporadic (nonfamilial) BPNH, 19 of 26 individuals with BPNH have been female (table 2).[19,21,23,58-62] With one possible exception (C.A. Walsh, unpublished data), all affected individuals in multiplex families have also been female. As for XLIS and similar syndromes, this suggests the effects of a gene on the X chromosome with more severe manifestations in males.[38]

X-linked inheritance. BPNH has been reported in four multiplex families in which 14 of 14 affected individuals were female and the incidence of pregnancy loss was increased (figure 5).[22,58,63,64] In the largest family, six females from four generations were affected, while no males were affected.[58] The rate of pregnancy loss was more than 50%, while about 20% is normal. The ratio of liveborn sons to daughters was skewed strongly toward daughters, which suggests that most of the miscarriages were males. None of the affected individuals in the four families had pachygyria or other gyral malformations, mental retardation, or a son with BPNH.

We have evaluated five more patients from two more multiplex families in a recent series from the Montreal Neurological Institute (MNI) and Duke University.[23] In the first family, a mother and daughter had the characteristic lesions, but only the

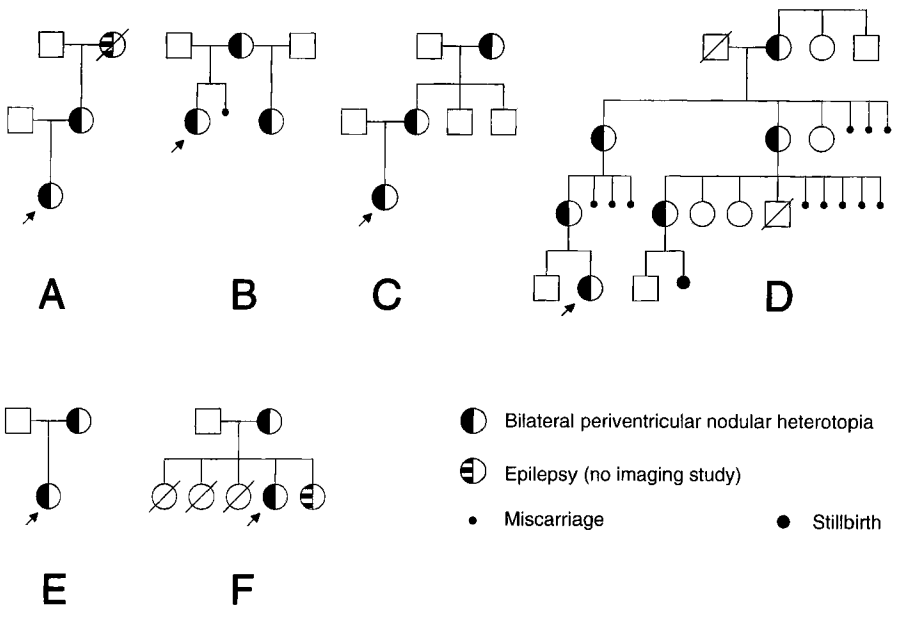

Figure 5. Pedigrees of six families showing X-linked inheritance of bilateral periventricular nodular heterotopia. In the largest family (D), affected women had more daughters than sons and more miscarriages than expected, suggesting prenatal lethality of males. Modified from (A) DiMario et al.[63]; (B) Oda et al.[22]; (C) Kamuro and Tenokuchi[64]; (D) Huttenlocher et al.[58]; and (E and F) Dubeau et al.[23]

mother had epilepsy. In the second, BPNH occurred in a mother and her epileptic daughter. Another daughter had epilepsy, but no imaging study was obtained. Three other daughters were stillborn or died shortly after birth, but it is not known whether they had the same malformation. None of these families had an affected male. These observations further support prenatal death of hemizygous affected males.

BPNH in males. Several affected males have been reported. Some have typical BPNH with normal intelligence and epilepsy, while others have a more complex syndrome associated with severe mental retardation. In the MNI series, there were two sporadic cases of males with contiguous BPNH. Both had normal intelligence and epilepsy; one also had hypoplasia of the corpus callosum and a small cerebellar hemisphere with an adjacent arachnoid cyst.[23] These patients are similar to some other male patients reported in the literature.[58,62]

Other male patients from the literature and the MNI series have had more severe abnormalities, including developmental delay or mental retardation.[23] We recently evaluated two boys with a recognizable syndrome consisting of BPNH, cerebellar hypoplasia, severe mental retardation, and partial syndactyly of the hands and feet. One of the two had areas of overlying cortical dysplasia (probably polymicrogyria) in both central regions (W.B. Dobyns, D. Czapansky-Beilman, C.L. Truwit, unpublished data).

BPNH maps to Xq28. Preliminary linkage analysis in several of the multiplex families showed positive lod scores. Multipoint linkage analysis gave a maximum lod score of 3.65 for markers in distal Xq28.[65] In one of the two boys with BPNH and mental retardation, high-resolution chromosome analysis showed a subtle structural abnormality of Xq28 (B. Hirsch, unpublished data). These two independent observations strongly support localization of the gene for BPNH to distal Xq28.

Pathogenesis. In this disorder, a relatively normal number of neurons successfully migrate to the cortex. The heterotopia are often large, and are located in the area of the embryonic ventricular zone. The neurons in the heterotopia thus failed even to begin migration. We therefore hypothesize that the BPNH gene is expressed earlier than the XLIS or chromosome 17 lissencephaly genes and is involved in control of mitosis. For example, the BPNH gene product could be required to signal neuroblasts to stop dividing and mature into neurons, or it could be a more general regulator of mitosis, mutations of which cause ectopic mitoses. In these models, the subependymal heterotopia are derived from neuroblasts that continue to divide long after they should have stopped.

We hypothesize that complete absence of the BPNH gene product causes prenatal death in affected males, and that the few liveborn males with a severe phenotype have less severe mutations of the BPNH gene (or possibly mutations of other genes not yet recognized). We also propose that classical BPNH in males with normal intelligence results from mosaic mutations of the BPNH gene. In this model, neurons that reach the cortex contain a functioning BPNH gene, while neurons in the periventricular nodules do not. As for XLIS, this may result from the effects of X inactivation or Lyonization in females, and from somatic mosaicism in rare males.

References

1. Barth PG. Disorders of neuronal migration. Can J Neurol Sci 1987;14:1–16.
2. Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH. Lissencephaly: a human brain malformation associated with deletion of the *LIS1* gene located at chromosome 17p13. JAMA 1993;270: 2838–2842.
3. Dobyns WB, Truwit CL. Lissencephaly and other genetic disorders of neuronal migration: 1995 update. Neuropediatrics 1995;26:132–147.
4. Sidman RL, Rakic P. Development of the human central nervous system. In: Haymaker W, Adams RD, eds. Histology and histopathology of the nervous system. Springfield, IL: Thomas, 1982;3–145.
5. Barkovich AJ, Gressens P, Evrard P. Formation, maturation, and disorders of brain neocortex. AJNR Am J Neuroradiol 1992;13:423–446.
6. Norman MG, McGillivray BC, Kalousek DK, Hill A, Poskitt KJ. Congenital malformations of the brain: pathological, embryological, clinical, radiological and genetic aspects. New York: Oxford University Press, 1995;223–277.
7. O'Rourke NA, Sullivan DP, Kaznowski CE, Jacobs AA, McConnell SK. Tangential migration of neurons in the developing cerebral cortex. Development 1995;121:2165–2176.
8. Crome L. Pachygyria. J Pathol Bacteriol 1956;71:335–352.
9. Friede RL. Developmental neuropathology. 2nd ed. Berlin: Springer-Verlag, 1989;330–334.
10. Barkovich AJ, Koch T, Carrol C. The spectrum of lissencephaly: report of ten cases analyzed by magnetic resonance imaging. Ann Neurol 1991;30:139–146.
11. Dobyns WB, Elias ER, Newlin AC, Pagon RA, Ledbetter DH. Causal heterogeneity in isolated lissencephaly. Neurology 1992;42:1375–1388.
12. Harding B. Gray matter heterotopia. In: Guerrini R, Canapicchi R, Zifkin BG, et al. Dysplasias of cerebral cortex and epilepsy. Philadelphia: Lippincott-Raven, 1996;81–89.
13. Barkovich AJ, Jackson DE, Boyer RS. Band heterotopias: a newly recognized neuronal migration anomaly. Radiology 1989;171:455–458.
14. Barkovich AJ, Guerrini R, Battaglia G, et al. Band heterotopia: correlation of outcome with magnetic resonance imaging parameters. Ann Neurol 1994;36:609–617.
15. Palmini A, Andermann F, Aicardi J, et al. Diffuse cortical dysplasia, or the 'double cortex' syndrome: the clinical and epileptic spectrum in 10 patients. Neurology 1991;41:1656–1662.
16. Franzoni E, Bernardi B, Marchiani V, Crisanti AF, Marchi R, Fonda C. Band brain heterotopia. Case report and literature review. Neuropediatrics 1995;26:37–40.
17. Matell M. Ein Fall von heterotopie der frauen substanz in den beiden Hemispheren des Grosshirns. Arch Psychiatr Nervenkr 1893;25:124–136.
18. Jakob H. Genetisch verschiedene Gruppen entwicklungsgestörter Gehirne. Z Neurol Psychiatr (Originalien) 1938;160: 615–648.
19. Palmini A, Andermann F, deGrissac H, et al. Stages and patterns of centrifugal arrest of diffuse neuronal migration disorders. Dev Med Child Neurol 1993;35:331–339.
20. Jacob H. Faktoren bei der Entstehung der normalen und entwicklungsgestörten Hirnrinde. Z Neurol Psychiatr (Originalien) 1936;155:1–39.
21. Barkovich AJ, Kjos BO. Gray matter heterotopias: MR characteristics and correlation with developmental and neurologic manifestations. Radiology 1992;182:493–499.
22. Oda T, Nagai Y, Fujimoto S, et al. Hereditary nodular hetero-

topia accompanied by mega cisterna magna. Am J Med Genet 1993;47:268–271.
23. Dubeau F, Tampieri D, Lee N, et al. Periventricular and subcortical nodular heterotopia: a study of 33 patients. Brain 1995;118:1273–1287.
24. Huttenlocher PR, Wollman RL. Cellular neuropathology of tuberous sclerosis. Ann NY Acad Sci 1991;615:140–148.
25. Marchal G, Andermann F, Tampieri D, et al. Generalized cortical dysplasia manifested by diffusely thick cerebral cortex. Arch Neurol 1989;46:430–434.
26. Gallucci M, Bozzao A, Curatolo P, Splendiani A, Cifani A, Passariello R. MR imaging of incomplete band heterotopia. AJNR Am J Neuroradiol 1991;12:701–702.
27. Ricci S, Cusmai R, Fariello G, Fusco L, Vigevano F. Double cortex: a neuronal migration anomaly as a possible cause of Lennox-Gastaut syndrome. Arch Neurol 1992;49:61–64.
28. Landy HJ, Curless RG, Ramsay RE, Slater J, Ajmone-Marsan C, Quencer RM. Corpus callosotomy for seizures associated with band heterotopia. Epilepsia 1993;34:79–83.
29. Soucek D, Birbamer G, Luef G, Felber S, Kristmann E, Bauer G. Laminar heterotopic grey matter (double cortex) in a patient with late onset Lennox-Gastaut syndrome. Wien Klin Wochenschr 1992;104/19:607–608.
30. Iannetti P, Raucci U, Basile LA, et al. Neuronal migrational disorders: diffuse cortical dysplasia or the "double cortex" syndrome. Acta Paediatr 1993;82:501–503.
31. Hashimoto R, Seki T, Takuma Y, Suzuki N. The 'double cortex' syndrome on MRI. Brain Dev 1993;15:57–60.
32. Tohyama J, Kato M, Koeda T, Inagaki M, Ohno K. The 'double cortex' syndrome. Brain Dev 1993;15:83–84.
33. Miura K, Watanabe K, Maeda N, et al. Magnetic resonance imaging and positron emission tomography of band heterotopia. Brain Dev 1993;15:288–290.
34. Ketonen L, Roddy S, Lannan M. Band heterotopia. J Child Neurol 1994;9:384–385.
35. Granata T, Battaglia G, D'Incerti L, et al. Double cortex syndrome: electroclinical study of three cases. Ital J Neurol Sci 1994;15:15–23.
36. Donnenfeld AE, Packer RJ, Zackai EH, Chee CM, Sellinger B, Emanuel BS. Clinical, cytogenetic, and pedigree findings in 18 cases of Aicardi syndrome. Am J Med Genet 1989;32:461–467.
37. Lindsay EA, Grillo A, Ferrero GB, et al. Microphthalmia with linear skin defects (MLS) syndrome: clinical, cytogenetic, and molecular characterization. Am J Med Genet 1994;49:229–234.
38. Wettke-Schäfer R, Kantner G. X-linked dominant inherited diseases with lethality in hemizygous males. Hum Genet 1983;64:1–23.
39. Pavone L, Gullotta F, Incorpora G, Grasso S, Dobyns WB. Isolated lissencephaly: report of four patients from two unrelated families. J Child Neurol 1990;5:52–59.
40. Berry-Kravis E, Israel J. X-linked pachygyria and agenesis of the corpus callosum: evidence for an X chromosome lissencephaly locus. Ann Neurol 1994;36:229–233.
41. Pinard J-M, Motte J, Chiron C, Brian R, Andermann E, Dulac O. Subcortical laminar heterotopia and lissencephaly in two families: a single X linked dominant gene. J Neurol Neurosurg Psychiatry 1994;57:914–920.
42. Scheffer IE, Mitchell LA, Howell RA, et al. Familial band heterotopias: an X-linked dominant disorder with variable severity [abstract]. Ann Neurol 1994;36:511.
43. Zollino M, Mastroiacovo P, Zampino G, Mariotti P, Neri G. New XLMR syndrome with characteristic face, hypogenitalism, congenital hypotonia and pachygyria. Am J Med Genet 1992;43:452–457.
44. Schmidt M, Du Sart D. Functional disomies of the X chromosome influence the cell selection and hence the X inactivation pattern in females with balanced X-autosome translocations: a review of 122 cases. Am J Med Genet 1992;42:161–169.
45. Porteous MEM, Curtis A, Lindsay S, et al. The gene for Aarskog syndrome is located between DXS255 and DXS566 (Xp11.2–Xq13). Genomics 1992;14:298–301.
46. Kaplan J, Gilgenkrantz S, Dufier JL, Frézal J. Choroideremia and ovarian dysgenesis associated with an X;7 de novo balanced translocation. Cytogenet Cell Genet 1989;51:1022.
47. Boyd Y. Females with Duchenne muscular dystrophy. In: Rose FC, ed. Molecular genetics and neurology. London: Smith-Gordon, 1992;49–56.
48. Roberts SH, Upadhyaya M, Sarfarazi M, Harper PS. Further evidence localising the gene for Hunter's syndrome to the distal region of the X chromosome long arm. J Med Genet 1989;26:309–313.
49. Kere J, Grzeschik K-H, Limon J, Gremaud M, Schlessinger D, de la Chapelle A. Anhidrotic ectodermal dysplasia gene region cloned in yeast artificial chromosomes. Genomics 1993;16:305–310.
50. Gorski JL, Burright EN, Reyner EL, Goodfellow PN, Burgess DL. Isolation of DNA markers from a region between incontinentia pigmenti 1 (IP1) X-chromosomal translocation breakpoints by a comparative PCR analysis of a radiation hybrid subclone mapping panel. Genomics 1992;14:649–656.
51. Mueller OT, Hartsfield JK, Gallardo LA, et al. Lowe oculocerebrorenal syndrome in a female with a balanced X;20 translocation: mapping of the X chromosome breakpoint. Am J Hum Genet 1991;49:804–810.
52. Consalez GG, Gecz J, Stayton CL, et al. Fine mapping and cloning of the breakpoint associated with Menkes syndrome in a female patient. Genomics 1992;14:557–561.
53. Attree O, Olivos IM, Okabe I, et al. The Lowe's oculocerebrorenal syndrome gene encodes a protein highly homologous to inositol polyphosphate-5-phosphatase. Nature 1992;358:239–242.
54. Cremers FPM, van de Pol DJR, van Kerkhoff LPM, Wieringa B, Ropers H-H. Cloning of a gene that is rearranged in patients with choroideraemia. Nature 1990;347:674–677.
55. Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell 1987;50:509–517.
56. Pasteris NG, Cadle A, Logie LJ, et al. Isolation and characterization of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: a putative Rho/Rac guanine nucleotide exchange factor. Cell 1994;79:669–678.
57. Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. Nat Genet 1993;3:7–13.
58. Huttenlocher PR, Taravath S, Mojtahedi S. Periventricular heterotopia and epilepsy. Neurology 1994;44:51–55.
59. Raymond AA, Fish DR, Stevens JM, Sisodiya SM, Alsanjari N, Shorvon SD. Subependymal heterotopia: a distinct neuronal migration disorder associated with epilepsy. J Neurol Neurosurg Psychiatry 1994;57:1195–1202.
60. Zimmerman RA, Bilaniuk LT, Grossman RI. Computed tomography in migratory disorders of human brain development. Neuroradiology 1983;25:257–263.
61. Smith AS, Weinstein MA, Quencer RM, et al. Association of heterotopic gray matter with seizures: MR imaging. Radiology 1988;168:195–198.
62. Falconer J, Wada JA, Martin W, Li D. PET, CT and MRI imaging of neuronal migration anomalies in epileptic patients. Can J Neurol Sci 1990;17:35–39.
63. DiMario FJ, Cobb RJ, Ramsby GR, Leicher C. Familial band heterotopia simulating tuberous sclerosis. Neurology 1993;43:1424–1426.
64. Kamuro K, Tenokuchi Y. Familial periventricular nodular heterotopia. Brain Dev 1993;15:237–241.
65. Eksioglu YZ, Scheffer IE, Cardenas P, et al. Periventricular heterotopia: an X-linked dominant epilepsy locus causing aberrant cerebral cortex development. Neuron 1996;16:77–87.

X-linked malformations of neuronal migration

W. B. Dobyns, E. Andermann, F. Andermann, et al.

Neurology 1996;47;331-339
DOI 10.1212/WNL.47.2.331