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 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 heterotopias (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.

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. 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. The second and larger wave of young neurons are generated in the ventricular zone in the 10th week and...
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. 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, 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 gyrual 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 wrote: "There is no essential difference between agyria and pachgyria 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."

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. 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, and is not always present.

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-pachgyria, and generalized pachgyria. The cortex is abnormally thick and consists of superficial and deep cellular layers separated by a thin and inconstant cell-sparse layer. Common associated abnormalities include a hypoplastic or absent corpus callosum, persistent cavum septi pellicudi, 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.

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.

semioval 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. 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. 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.

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). 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 inconsistent abnormalities include abnormal T2 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. 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 and more recent MRI studies. Several patients with malformations transitional between band heterotopia and pachygyria have been reported. A woman reported by Matell and widely quoted as the first description of pachygyria possibly also had SBH. The 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.
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 (BP NH) show nodular masses of gray matter, which line the ventricular walls and protrude into the lumen (figure 3). 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 non-contiguous BP NH resemble “pearls on a string.” On MR images, the signal intensity is always that of gray matter. Patients with BP NH may have additional abnormalities such as mild cerebellar hypoplasia or mild hypogenesis of the corpus callosum. Rare patients have areas of overlying cortical dysplasia (C.L. Truwit, W.B. Dobyns, unpublished data).

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. Pathologically, the subependymal nodules of TSC consist primarily of undifferentiated cells or abnormal parallel gray matter, which suggests that they contain neurons as well.

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, 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. 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. 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. The relative thickness of the band correlates with the phenotype as patients with thicker bands have more severe mental retardation and seizures. Similarly, the severity of mental retardation correlates with the severity of epilepsy as patients with Lennox-Gastaut syndrome have more severe mental retardation.

Skew of sex ratio. Since SBH were “rediscovered” on imaging studies, 51 of 54 reported patients with sporadic SBH have been female (table 1). 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

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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 pigmeni, microphthalmia with linear skin defects, oro-facio-digital syndrome type 1, and pyruvate dehydrogenase deficiency due to mutation of the Ela gene.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-
nal grandmother of the proband appeared normal, but imaging studies could not be performed. In the remaining three families, women with documented SBH had sons with lissencephaly. In one of these families, a woman with SBH had two daughters with SBH and a son with lissencephaly, each by a different father.

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. 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. 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. Czapsky-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. 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, choroideremia, Duchenne muscular dystrophy, Hunter syndrome, hypohidrotic ectodermal dysplasia, incontinentia pigmenti, Lowe oculocerebrorenal syndrome, and Menkes disease. Cloning of the translocation break-point has led to cloning of the gene for five of these diseases.

**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 diffusible 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

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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. Several asymptomatic individuals with BPNH have been discovered during family evaluations.

Skew of sex ratio. Considering only sporadic (nonfamilial) BPNH, 19 of 26 individuals with BPNH have been female (table 2). 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.

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). In the largest family, six females from four generations were affected, while no males were affected. 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. 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) D'Mario et al.; (B) Oda et al.; (C) Kamuro and Tenokuchi; (D) Huttonlocher et al.; and (E and F) Dubeau et al.]

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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.\(^2\) These patients are similar to some other male patients reported in the literature.\(^5,6\)

Other male patients from the literature and the MNI series have had more severe abnormalities, including developmental delay or mental retardation.\(^2\) 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. Czapsky-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.\(^5\) 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**


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W. B. Dobyns, E. Andermann, F. Andermann, et al.
Neurology 1996;47:331-339
DOI 10.1212/WNL.47.2.331

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