

Subcortical laminar heterotopia and lissencephaly in two families: a single X linked dominant gene

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Abstract

Neuronal migration disorders can now be recognised by MRI. This paper reports two families in which the mothers had subcortical laminar heterotopia and four of their children had either similar heterotopia (two girls) or severe pachygyria or lissencephaly (two boys). Laminar heterotopia was more evident on MRI T2 weighted images. The patients had mild to severe epilepsy and mental retardation depending on the extent of cortical abnormalities. In these families, subcortical laminar heterotopia, pachygyria, and lissencephaly seem to share the same X linked or autosomal dominant gene. No chromosomal abnormalities, especially of chromosome 17, could be identified. For appropriate genetic counselling of the family of a child with lissencephaly or subcortical laminar heterotopia, MRI should be performed in parents or siblings with mental retardation or epilepsy.

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Several types of extensive neuronal migration disorders including lissencephaly, pachygyria, and laminar heterotopia were first reported after neuropathological studies. Computed tomography (CT) and MRI now allow diagnosis of neuronal migration disorders during life. Recently several authors have described MRI images of subcortical laminar heterotopia giving a double cortex appearance.¹⁻⁵ The clinical features of these cerebral malformations are similar and include epileptic seizures, delayed motor development, and mental retardation. Although the origin and mechanisms of such cortical dysplasia are unknown, some have a chromosomal origin—for example, Miller-Dieker syndrome, a form of lissencephaly type I, is associated with chromosome 17 abnormality.⁶ Pachygyria and heterotopia may coexist in the same patient,⁷ and several family members may exhibit the same type of malformation, either pachygyria or lissencephaly.^{8,9} To our knowledge, there are no reports of multiple family members with different types of neuronal migration disorders. We describe two families in which patients with lissencephaly and patients with subcortical laminar heterotopia coexist in the same and different generations, thus confirming a familial link between these disorders.

Patient reports

Family 1 comprised three brothers from non-consanguineous parents (fig 1).

PATIENT 1

The proband (II 3), an 8 year old boy, was born with an uncomplicated delivery after full term pregnancy. The mother received antiepileptic treatment during pregnancy and had two generalised tonic-clonic seizures during the last month of gestation. Birth weight was 3450 g and head circumference was 32 cm. Several malformations were found—namely, microcephaly, hypertelorism, cleft lip and palate, abnormal palmar creases, and bilateral talus valgus. Development was severely retarded. At the age of 1 month, he began to have seizures with clonic eyelid movements. He continued to have seizures of different types including infantile spasms and generalised tonic-clonic convulsions uncontrolled by various antiepileptic drugs. At 8 years, he weighed 15 kg (-4.5 SD of normal), was short (1 m, -4 SD), microcephalic (-4.5 SD), and had no visual contact. He had axial hypotonia, bilateral pyramidal signs, nystagmus, convergent strabismus, and dorsal scoliosis. Spinal radiographs showed dysraphism with dorsolumbar scoliosis, T12 hemivertebra, spina bifida occulta of L5 and S1, and bilateral coxa valga. The karyotype, including high resolution banding (RHG, RTBG) of chromosome 17, was normal. His EEGs were abnormal for age, resembling those of younger children with brain malformation; however, no β -activity was recorded. They showed generalised epileptiform abnormalities including spikes, polyspikes and slow wave complexes and abnormal background activity.

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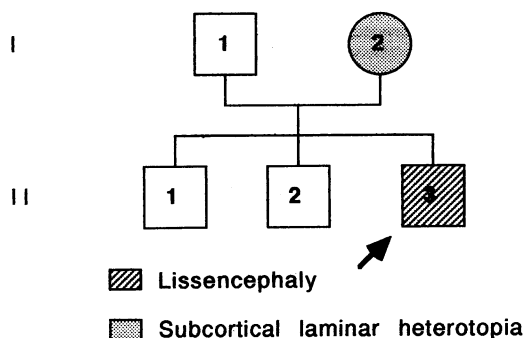


Figure 1 Pedigree of family 1.

Figure 2 Family 1, patient 1 (II 3): T1 weighed MRI (TR: 460, TE: 14), sagittal cut. Lissencephaly with smooth brain surface, thick cortical layer, thin layer of white matter, and enlargement of lateral ventricles.

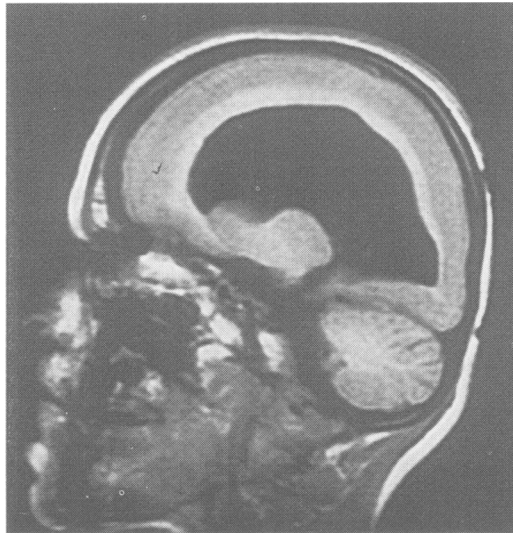
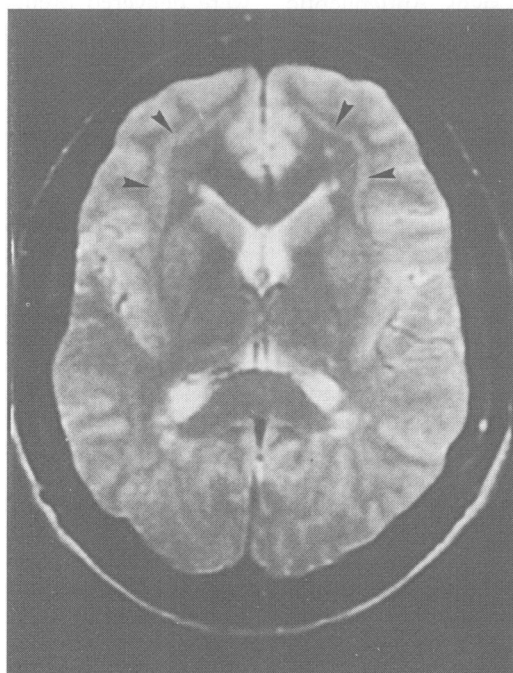


Figure 3 Family 1, patient 2 (I 2): T2 weighted MRI (TR, TE: NA), axial cut. Frontal symmetric thin layer of high signal (arrowheads) forming a subcortical heterotopic grey matter band parallel to a mildly pachygyric cortex.



On MRI, enlarged lateral ventricles associated with abnormalities of the cortex and white matter were seen. The cortical surface exhibited generalised agyria. There was increased thickness of cortical grey matter, loss of cortical white matter interdigitations, and decreased white matter throughout the hemispheres. Temporal lobes and hippocampi were present. No layered organisation of the cortex was visible on coronal or sagittal T1 (fig 2) or axial T2 weighted images.

PATIENT 2

The mother of the proband (I 2), a 40 year old cleaning woman, had epilepsy treated with phenobarbitone and diazepam since the age of 11 years without interruption. Generalised tonic-clonic seizures occurred every other year. Head circumference was 54 cm. On MRI coronal and sagittal T1 and axial T2 weighted images (fig 3), the frontal parenchyma appeared as a four layered structure showing normal interdigitations with a layer of white matter. Below this was a smooth and thin layer of tissue with the appearance of grey matter. There was a thick fourth layer of white matter. The cortex was of normal thickness but slightly pachygyric. The bilateral layered aspect seemed to consist of heterotopic tissue forming a band parallel to the cortex in the white matter, along the grey matter of the frontal gyri, thus giving a double cortex image. No EEG or karyotype was performed.

The father of the proband (I 1), a 43 year old labourer, was epileptic since the age of 12. Generalised tonic-clonic seizures were well controlled by phenytoin and phenobarbitone. Neurological examination was normal; head circumference was 57 cm; and MRI showed no abnormality. No EEG or karyotype were performed.

The proband (II 2) had a 9 year old brother. Pregnancy and delivery were normal. Birth weight was 4000 g and there were no neonatal problems. The parents noted slightly retarded development. He walked at 2 years. Neurological examination at 1 year of age showed a left hemiplegia and slight strabismus. He had no seizures. Parents refused further examinations. A 15 year old brother of the proband (II 1) was clinically normal. No MRI could be performed.

Family 2 comprised five children from the same mother and three different fathers (fig 4).

PATIENT 3

The proband (III 3) was born at 37 weeks gestation to unrelated parents. His weight was 2600 g and head circumference was 31 cm. He was hypotonic. At the age of 6 months, he developed infantile spasms treated with valproate. He continued to have seizures, failed to thrive, and developed severe mental retardation. At 7 years of age he weighted 17 kg (-3 SD) and did not walk. He was microcephalic with head circumference 45.5 cm

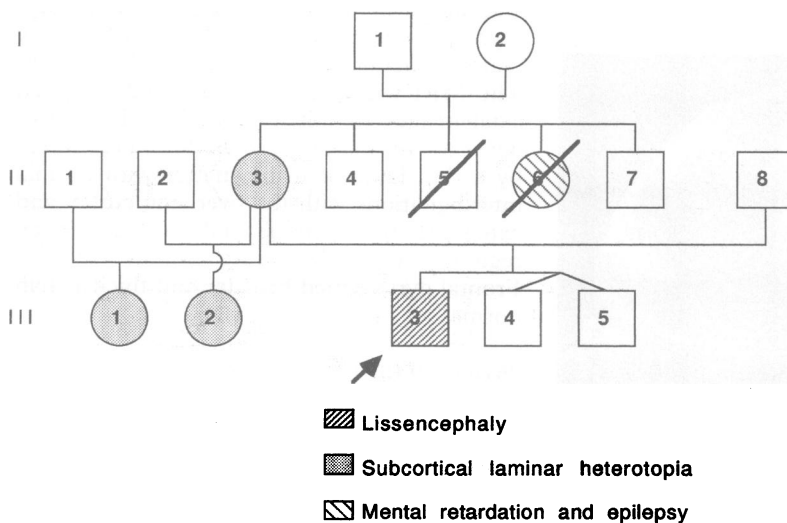
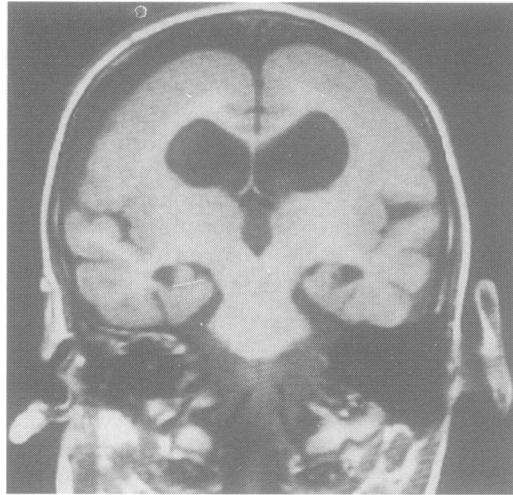


Figure 4 Pedigree of family 2.

Figure 5 Family 2, patient 3 (III 3): T1 weighted MRI (TR: 600, TE: 20), coronal cut. The agyric and thick frontal cortex is separated from a thin layer of white matter by a straight line. Temporal lobes are pachygyric.

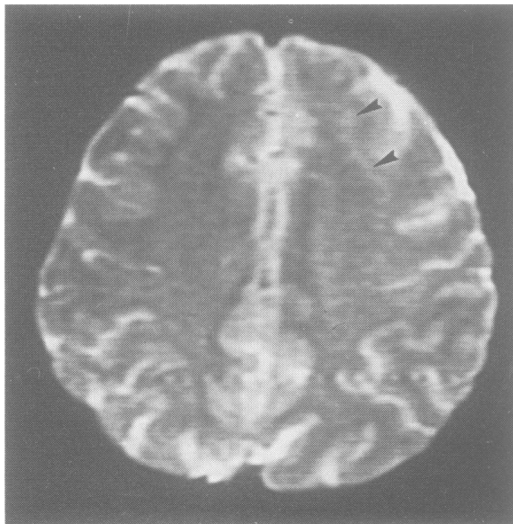


(-5 SD), had no visual contact, pronounced hypotonia, and pyramidal signs. Antiepileptic drugs did not control partial seizures consisting of eye and head rotation to the right. Generalised slow waves with bursts of β rapid rhythms on the anterior regions as described in lissencephaly were seen on EEGs and CT showed smooth cortex with bilateral frontal agyria or pachygyria and dilated lateral ventricles. Axial and coronal T1 weighted MRI (fig 5) showed agyria and pachygyria of the frontal lobes, and pachygyria of the parieto-occipital and temporal lobes. There was increased thickness of cortical grey matter, loss of cortical white matter interdigitation in the frontal lobes, and decreased white matter throughout the hemispheres. The karyotype was normal, including high resolution banding (RHG, GTG, RTBG).

PATIENT 4

The mother of the proband (II 3) walked at the age of 2 to 3 years. Her school performance was poor. She had sudden falls without clonic movements or loss of consciousness, accompanied by a sensation of fear. No EEG could be performed. She was not on antiepileptic drugs. At the age of 40, MRI axial T2 weighted images (fig 6) in the ante-

Figure 6 Family 2, patient 4 (II 3): T2 weighted MRI (TR: 2000, TE: 80 2/2), axial cut. Thin layer of heterotopic grey matter in frontal lobe (arrowheads).



rior and dorsal frontal lobes showed normal periventricular white matter surrounded by a thickened cortex with broad gyri, and an abnormally smooth white-grey matter junction. The cortex consisted of two layers of grey matter separated by a thin and discontinuous layer of white matter. On T2 weighted images, the white matter exhibited a slightly enhanced signal in the frontal region. The karyotype was normal, including with high resolution (RHG, GTG, RTBG).

One of her sisters (II 6) had mental retardation of unknown origin and epilepsy. She died aged 22 during a seizure, without any neuro-radiological investigations.

The 40 year old father of the proband (II 8) was clinically normal, and MRI showed no abnormality. No EEG or karyotype were performed.

The brothers of patient 3 (III 4 and III 5) were twins. Pregnancy was normal and they were delivered prematurely at seven months without complications. Speech development was slightly delayed. At three years, neurological examination, EEG, and MRI were normal in both.

PATIENT 5 (III 2)

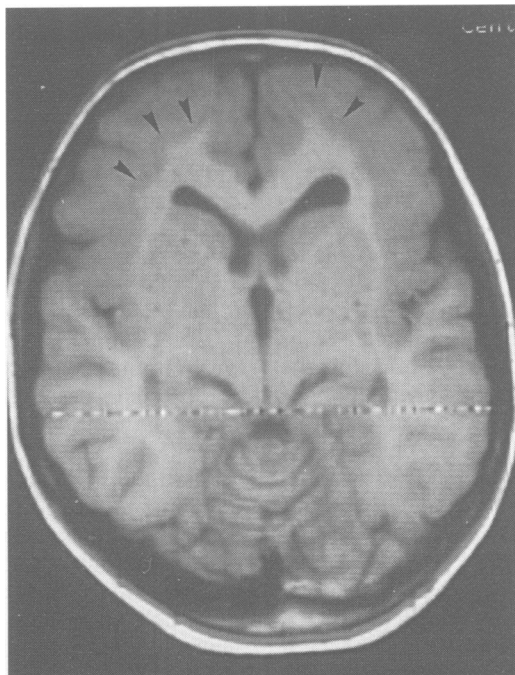
Patient 5 was the daughter of patient 4 and of an unknown father. She was born after a full term uncomplicated pregnancy and delivery. Birth weight was 3200 g, head circumference 33.5 cm. Her early growth and development were normal, but at 10 months of age, slight psychomotor retardation was noted. She walked at 2 years, was hyperkinetic, and did not speak well at 5 years. At the age of 6, occasional generalised tonic-clonic and atypical absence seizures appeared. She failed in regular school and attended an institution for children with mild mental retardation. She had one seizure a month.

At 10 years of age, neurological examination showed a fine intention tremor, mild pyramidal syndrome, and drooling. Head circumference was 49.5 cm (-2.5 SD). Neuropsychological evaluation showed mental delay, mainly for speech; she could not read or write. An EEG showed sharp waves and spikes in the frontal regions. The karyotype was normal. On CT the white-grey matter junction seemed abnormally smooth. The MRI with T1 (fig 7) and T2 weighted axial images exhibited a band of tissue, isodense to grey matter, separated from the cortex by a thin layer of white matter with normal interdigitations with the overlying cortex and extending from the frontal to the parietal regions. Ventricles were mildly dilated. Frontal gyri seemed broader and thicker than normal.

PATIENT 6 (III 1)

Patient 6 was the daughter of patient 4 and of another unknown father by artificial insemination. Pregnancy and delivery were normal. Birth weight was 2700 g. She started walking alone at 30 months of age, and her speech developed slowly during the first four years of life. She was retarded and required special

Figure 7 Family 2, patient 5 (III 2): T1 weighted MRI (TR: 600, TE: 20), axial cut. Thick frontal cortex separated from the white matter by a straight line. On T1 images heterotopic band is not well visualised (arrowheads).



schooling. Her first generalised tonic-clonic seizures occurred at 10 years. Her global IQ was 66.

At 13 years of age, neurological examination and head circumference were normal. She attended a trade school. Generalised epileptiform abnormalities with 3–5 Hz spike-wave discharges and bifrontal δ activity were found on EEGs. Karyotype was normal, including high resolution banding (RHG, GTG, RTBG). CT was considered normal. Axial T1 and T2 weighted MRI views (fig 8) showed abnormal thickness of the cortex in frontal and sylvian regions. The white matter was scanty and there were few white matter interdigitations. The lateral ventricles were slightly enlarged. The thick cortex consisted of internal and external layers of grey matter

Figure 8 Family 2, patient 6 (III 1): T2 weighted MRI (TR: 2000, TE: 80 2/2), axial cut. Thick frontal cortex separated into two bands of grey matter by a thin band of white matter seen better on T2 images (arrowheads).



separated by a thin white matter layer. The cerebral tissue therefore appeared as a four layered structure.

Discussion

Neuronal migration disorders, including laminar and nodular (subcortical or periventricular) heterotopia, have been recognised by neuropathologists for many years.

The first anatomical description of laminar heterotopia was reported at necropsy¹⁰ and it is now possible to recognise this abnormality with MRI. Barkovich and coworkers reported five unrelated patients, four girls and one boy, with seizures and mental retardation whose MRI scans showed generalised “band heterotopia” associated with a normal gyral pattern or pachygyria.² A similar MRI pattern, termed “generalised cortical dysplasia”, was described by Marchal and coworkers in two young females, with histological confirmation of their heterotopic nature.³ The two girls with “double cortex” reported by Livingston and Aicardi⁴ also had MRI images similar to those of the four female patients we report. Palmini and coworkers reviewed 10 female patients, including the ones reported by Marchal *et al*³ and by Livingston and Aicardi,⁴ and added six new patients, with “double cortex syndrome”.¹¹ Two girls presenting similar MRI images, mental retardation, and Lennox-Gastaut syndrome were recently reported.¹² Furthermore, two sisters exhibiting developmental delay, ataxia, and subcortical heterotopia on MRI have been reported recently.¹³ The MRI images of these patients are reminiscent of the neuropathologically demonstrated subcortical laminar heterotopia encountered in mildly retarded adults with epilepsy.^{14 15}

Laminar heterotopia was first described by Matell¹⁰ in a 25 year old mildly retarded epileptic woman. It was defined as heterotopic grey matter separated from the cortex by a layer of white matter.¹⁵ Laminar heterotopia may be surrounded by normal cortex.^{14 (patient 2) 16 17} There is another type of laminar heterotopia in which heterotopic grey matter is separated from the cortex by a thin layer of white fibres and associated with abnormalities of the cortical architecture, including modifications in cortical layers 4 to 6, which are in continuity with the heterotopic tissue.^{3 (patient 1) 10 14 (patient 1)} In these cases, the cortex has a pachygyric aspect. Transitional cases have been described, characterised by gyri wider than normal but with well defined major fissures and laminar heterotopia.¹⁶

On the other hand, lissencephaly, sometimes called agyria, is defined by the absence of sulci and gyri. Lissencephalic cortex is always disorganised, four layered, and can be associated with aberrant neurons in the white matter, especially islands of heterotopic grey matter bordering the lateral ventricles.^{18 19} Pachygyria and agyria may occur in the same brain.^{7 20 (patient 1)} There are several case reports of agyria, pachygyria, and subcortical laminar heterotopia in the same brain.^{7 20 (patient 2)}

Therefore, according to the histological features, laminar heterotopia, pachygyria, and lissencephaly may represent different degrees of the same abnormality of neuronal migration.^{11 15}

The causes of neural migration disorders remain unknown. Vascular and toxic causes have been suspected.⁷ However, only the Miller-Dieker syndrome, characterised by a typical craniofacial appearance and lissencephaly,^{19 21} is now aetiologically well defined and related to a microscopical^{6 22} or submicroscopical^{23 24} deletion of chromosome 17. Other syndromes with lissencephaly have been described and classified by Dobyns *et al.*²⁵ Most patients with lissencephaly, however, are sporadic and described as an "isolated lissencephaly sequence"⁷ without features of the Miller-Dieker syndrome or chromosomal abnormalities.^{25 26} Van Tuinen *et al* found no submicroscopical deletion of 17p13 in two patients with isolated lissencephaly sequence, but they could not exclude a very small deletion.²³ Schwartz *et al* also reported a negative result with a patient with isolated lissencephaly sequence.²⁴ More recently, Ledbetter²⁷ found among 25 patients with Miller-Dieker syndrome either cytogenetically detectable (56%) or submicroscopical (32%) microdeletions; and among 45 patients with isolated lissencephaly sequence only 13% exhibited submicroscopical deletions. Among 60 patients with isolated lissencephaly sequence, Dobyns and Ledbetter²⁸ found a normal karyotype in 52 patients, a de novo X;2 translocation in one, and small submicroscopical deletions in the 17p13-3 region in five of 30 patients studied in this manner. Thus isolated lissencephaly sequence is probably heterogeneous²⁹; and the de novo X;2 translocation might suggest X linked inheritance of some cases of isolated lissencephaly sequence. In a recent review of 76 patients with lissencephaly type I, including 21 new cases, Dekijk-Van Andel *et al* showed that 25% had Miller-Dieker syndrome with chromosome 17 abnormality, 25% showed clinical features of Miller-Dieker syndrome with chromosomal abnormality, and 50% had isolated lissencephaly sequence consisting of agyria, pachygyria, or both.³⁰ Unfortunately, the sex ratio was not mentioned in this series. In our two families, karyotypes performed in five patients with high resolution banding did not show any abnormalities.

The two families we report are unusual for several reasons. Firstly, the cerebral malformations were familial with variable expressivity. There were four and possibly five female patients who had laminar heterotopia, and two male patients with lissencephaly. These patients exhibited different severity of epilepsy and mental retardation, which seemed to correlate with the extent of the cortical malformation. Both mothers were socially integrated and had the mildest abnormalities on MRI. By contrast, the two affected sons had agyria associated with severe epilepsy and mental retardation. The two mothers, and the two

affected daughters had a four layered cortex with laminar heterotopia, whereas the sons had a more severe neural migration disorder with lissencephaly. Thus the clinical features and cortical dysplasia in our families were more severe in males than in females. To our knowledge, a familial association of lissencephaly and laminar heterotopia has never been reported, and this supports the idea that lissencephaly and laminar heterotopia are developmentally related.

Among the 23 patients recently reported with laminar heterotopia on MRI^{2-4 11-13} (and the present cases) 22 were female and only one was a male.² Most often the family history was not documented. In one case of Ricci *et al*¹² and in our observations, the mothers were epileptic or showed laminar heterotopia. Similar findings are suggested in the relatively rare anatomical studies of laminar heterotopia. Mattel reported a female patient whose maternal aunt was epileptic.¹⁰ Weist and Hallervorden's second patient was a 44 year old woman without neuropsychiatric family history; for patient 1, clinical data were poor and sex was not reported but the mother was epileptic.¹⁴

Dominant inheritance of brain malformations is rare in comparison with recessive inheritance. Reznik and Alberca-Serrano reported two pedigrees showing familial association of lissencephaly with other brain malformations.^{8 9 31} In the first family,^{8 31} the mother had seizures and hypertelorism; two boys had hypertelorism, early epilepsy, progressive spastic paraplegia, and mental retardation. Their necropsy studies, at ages 19 and 9 years respectively, showed frontoparietal pachygyria and occipital agyria. Within the white matter, there was laminar heterotopia, consisting of a thin band in the prefrontal area that increased in thickness from frontal to occipital regions. The cortical lamination surrounding laminar heterotopia was subnormal in the prefrontal cortex and completely disorganised in the posterior part of the hemispheres. This family have a dominant inheritance for epilepsy, more serious in males than in females, and a dominant or X linked dominant inheritance mode could be suggested. In the second family,⁹ most members (males or females), in three generations, showed hereditary turricephaly with a dermal cleft. Moreover, the four affected girls of the third generation were offspring of consanguineous parents: father was normal, mother had turricephaly, dermal cleft, cyphoscoliosis, and right facial hypoplasia. The four daughters showed microcephaly with turricephaly and craniovertebral dysraphism (fusion of vertebral bodies, spina bifida, club feet and/or dermal cleft). Neuropathological examination of two of these girls disclosed lissencephaly and discontinuous subcortical band heterotopia. The abnormalities were most pronounced in posterior brain regions. These two families seem to show a dominant mode of inheritance, with variable expression of brain malformations and dysraphism.

Our two families illustrate the relation

between subcortical laminar heterotopia, pachygyria, and lissencephaly type I, and the likelihood that these have the same genetic origin.³² Their pedigrees are compatible with the hypothesis of dominant inheritance and more presumably X linked dominant inheritance.

Miller-Dieker syndrome can probably be excluded as the clinical features were different and no chromosome 17 abnormalities were found despite high resolution banding techniques.

A possibility of X linked dominant inheritance is suggested in both our families as the mothers were affected and females were less severely affected than males. The fact that the mother in family 2 and possibly her sister, but none of her three brothers, were affected also suggests this mode of inheritance. Such transmission has been proposed for some diseases including vitamin D resistant rickets,³³ orofacio-digital syndrome type I,³⁴ and more recently in familial aplasia of the cerebellar vermis.³⁵ It has been clearly shown for incontinentia pigmenti,³⁶ Alport syndrome,³⁷ and X linked mental retardation syndrome.³⁸ Moreover, Huttenlocher *et al* recently reported familial periventricular heterotopia and seizures in four generations of a family with an inheritance pattern suggestive of X linked dominant transmission.³⁹ Kamuro and Tenokuchi described the same phenomenon in three generations of another family.⁴⁰ In Rett syndrome⁴¹ and Aicardi syndrome,^{42,43} both of which are found almost exclusively in females, X linked dominant inheritance with lethality in hemizygous males has been postulated. This hypothesis may account for the pronounced female predominance in the "sporadic cases" of subcortical laminar heterotopia reported to date.

One of the main features of this mode of inheritance is relatively mild expression in heterozygous females and more severe expression in hemizygous males. This resembles the findings in our families. As the boys in our two families were severely affected and unlikely to reproduce, however, male to male transmission could not be ruled out. Therefore, the alternative hypothesis of autosomal dominant transmission cannot be entirely excluded. Only genetic linkage analysis can discriminate between these two modes of inheritance in the future.

The gene for this disorder might code for a protein involved in the adhesion of neurons to glial guide cells during their migration from the ventricular wall to the cortical surface. Different glycoproteins representing cell adhesion molecules have been described.^{44,45} Other mechanisms can be proposed. Recently, G protein β -subunit-like repeats have been found in the gene (LIS-1) of Miller-Dieker syndrome on chromosome 17p13.3. The deduced protein, closely related to β -subunits of G proteins, could possibly be involved as G proteins, in signal transduction in neurons, or in neuronal growth cone collapse, affect crucial processes for cerebral development.⁴⁶

The implications for genetic counselling are of great interest, and we propose that in patients with isolated lissencephaly or subcortical laminar heterotopia, MRI studies should be performed in relatives particularly when mental retardation or epilepsy is present.

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