

Development of the Cerebral Cortex: II. Lissencephaly

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Lissencephaly refers to disorders of brain formation in which the surface of the cerebral cortex appears smooth. In affected individuals the layers of cells in the cerebral cortex are abnormal. Scientists believe that this is due to disruption of the early migration pattern of neurons. The two most common forms of lissencephaly are isolated lissencephaly and Miller-Dieker syndrome (MDS). Patients with MDS have congenital abnormalities affecting the heart, kidneys, and other organ systems in addition to the abnormalities that are seen within the CNS in both variants.

As was discussed in the last Development and Neurobiology column (see January issue of the *Journal*), the normal cerebral cortex is divided into six distinct cellular layers (Fig. 1). The brains of patients with lissencephaly have only four.

As might be expected with such disturbances of brain maturation, these patients are profoundly retarded from birth and often develop seizure disorders.

In 1993, a gene on chromosome 17 was isolated and was named LIS1. Unrelated patients with lissencephaly were found to be missing one copy of this gene because of a microdeletion, a mutation that results in the loss of stretches of DNA on a chromosome. Depending on the size of the deletion, the protein that is encoded by that gene will be either truncated or entirely missing. In patients with isolated lissencephaly, the deletions are small and are contained within the boundaries of the LIS1 gene. In patients with the more severe MDS, the deletions are larger and they extend beyond the boundaries of the LIS1 gene. These results suggested that in MDS, the dele-

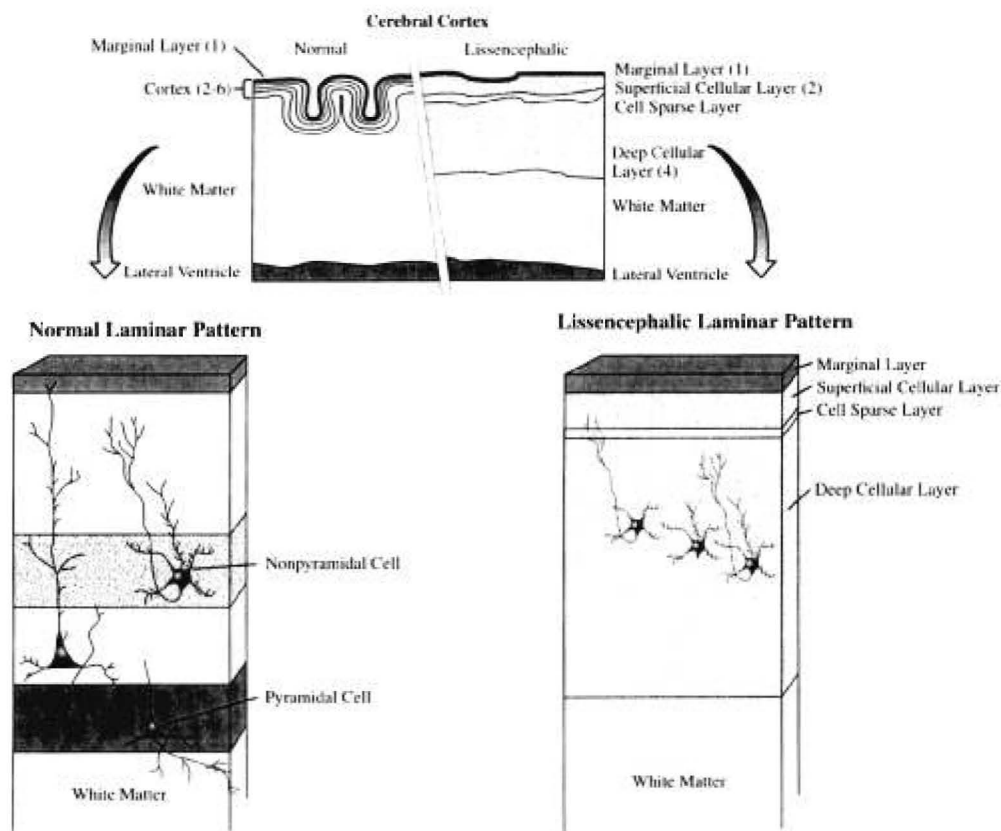


Fig. 1 The normal cerebral cortex is a highly organized structure, and its six layers are shown on the left (1–6). In contrast, the lissencephalic brain is composed of only four layers. Adapted from Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH (1993), Lissencephaly: a human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13. *JAMA* 270:2838–2842; copyright ©1993, American Medical Association.

tion affects not only a gene that is important for brain development, but also additional nearby genes required for normal development of other organ systems. Disorders in which multiple adjacent genes are deleted are termed contiguous gene syndromes and, as might be expected, often produce more severe disorders than mutations within single genes.

Several groups isolated the LIS1 gene and began to study the function of the protein that it produces. It is currently believed that LIS1 encodes a regulatory subunit of an enzyme, termed platelet-activating factor (PAF)-acetylhydrolase. This enzyme leads to the release of potent phospholipids that act as signaling proteins within neurons. Thus, the function of the LIS1 protein appears to be to translate a signal arriving at the surface of the neuron to the inside of the cell. The highest levels of LIS1 within the body are detected in the developing cortex, a finding that is consistent with the protein's putative role in neuronal migration.

The next question was: How does a mutation of LIS1 lead to disturbances in neuronal migration? The LIS1 gene product is believed to regulate the activity of PAF. The mutation thus leads to the unregulated activity of PAF and the production of abnormal amounts of signaling proteins within the developing neuron. One result of the mutation is a change in the structure of neurons. The cytoskeleton of the cell is made up of proteins that give cells their distinctive shapes. Normal cellular movement requires continuous rearrangement of the cytoskeleton. Disruptions of the cytoskeleton and its flexibility affect the ability of neurons to migrate normally and are thought to lead to the disrupted cortical pattern seen in children with lissencephaly.

Although scientists have made impressive strides in understanding the molecular basis for lissencephaly, additional

research is required to understand the details of the disruption to normal development. It is unclear whether LIS1 is required for the initiation of migration, for the successful migration of neurons through the cortical layers, or for some other step in the process by which neurons find their ultimate destination. It is likely that over the next several years, additional genes will be discovered that disrupt these early events in brain development. And it is possible that some of these genes are responsible for the pathophysiology of various developmental disorders that we see in our offices.

WEB SITES OF INTEREST

<http://www.lissencephaly.org>

http://bioinfo.weizmann.ac.il/_ls/orly_reiner/orly_reiner.html

ADDITIONAL READINGS

- Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K (1994), Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor. *Nature* 370:216-218
- Rakic P, Komuro H (1995), The role of receptor/channel activity in neuronal cell migration. *J Neurobiol* 26:299-315
- Reiner O, Albrecht U, Gordon M et al. (1995), Lissencephaly gene expression in the CNS suggests a role in neuronal migration. *J Neurosci* 15:3730-3738

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