

extrastriate cortex can be identified by analysis of voxel-based morphometry of MRI scans.

CONGENITAL MALFORMATIONS

X-LINKED LISSENCEPHALY WITH ARX MUTATIONS, ABNORMAL GENITALIA, AND CORPUS CALLOSUM AGENESIS

The clinical and genetic findings of two X-linked lissencephaly with abnormal genitalia (XLAG) pedigrees with ARX mutations are reported from the University of Regensburg, Germany. Case 1 index patient had multifocal clonic seizures at birth and later developed generalized tonic-clonic seizures refractory to treatment. The head circumference at birth was in the 25th percentile and at 9 months, below the 3rd percentile. MRI showed lissencephaly, thick cortex, small basal ganglia, subependymal cysts, and absent corpus callosum (ACC) and septum pellucidum. Abnormal signs also included micropenis, hypospadias, cryptorchidism, and hypothermic episodes. Case 2 index patient developed microcephaly by 2 years and was born with a head circumference in the 25th percentile, myoclonic seizures, abnormal genitalia, and subsequent episodic hypothermia. MRI showed lissencephaly and ACC, and echocardiogram revealed a persistent patent ductus arteriosus and foramen ovale. Sequencing of the ARX gene showed in case 1 a single nucleotide deletion and in case 2 a missense mutation. Three known ARX mutations within the homeodomain are associated with a XLAG phenotype. Patients with XLAG show severe clinical deficits and cerebral malformations. Female carriers (mother of index case 1) with mutations leading to XLAG phenotype in males show partial or complete ACC. (Uyanik G, Aigner L, Martin P et al. ARX mutations in X-linked lissencephaly with abnormal genitalia. *Neurology* 22 July 2003;61:232-235). (Reprints: Dr Juergen Winkler, Department of Neurology, University of Regensburg, Universitätsstr. 84, D-93053 Regensburg, Germany).

COMMENT. XLAG is characterized by lissencephaly, complete agenesis of the corpus callosum, and hypogenitalism (Berry-Kravis, Israel, 1994). Posterior agyria, anterior pachygyria, and intermediate thickening of the cortex distinguish this syndrome from lissencephaly type I, in which the cortex is thicker, and the corpus callosum is hypoplastic but not absent. Females related to boys with XLAG may be mentally retarded, and have epilepsy and agenesis of the corpus callosum (Bonneau D et al. see *Ped Neur Briefs* March 2002;16:22). ARX is a causative gene for X-linked mental retardation, X-linked infantile spasms, and X-linked lissencephaly with abnormal genitalia. Two different point mutations in the ARX gene are reported here in two pedigrees of XLAG. A report from Japan finds a polyalanine expansion of ARX associated with cryptogenic West syndrome in one of 8 patients tested (Kato M et al. *Neurology* 22 July 2003;61:267-268). The detection of this mutation is helpful in genetic counseling.