Suggestive evidence for linkage to chromosome 13qter for autosomal dominant type 1 porencephaly

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Abstract—A large three-generation family with autosomal dominant type 1 porencephaly from southern Italy was studied. A high rate of miscarriages was observed. Of the nine affected individuals, four displayed a severe phenotype, and five had slight pyramidal signs or mild cognitive abnormalities. The MRI study disclosed unilateral porencephalic cyst, or colpocephaly. A genome-wide screen resulted in suggestive evidence for linkage to chromosome 13qter with a maximum logarithm-of-the-odds score of 3.16, from multipoint analysis, with marker D13S285.

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The term "porencephaly" describes any full-thickness defect within the cerebral mantle, irrespective of etiology and time of onset. According to the current classification,[1] type 1 porencephaly (T1P; encephaloclastic porencephaly) results from different destructive brain lesions. There have been reports of familial T1P,[2-7] which indicate that genetic factors may also play a role in its pathogenesis. It remains unclear if familial T1P represents a distinct clinical and genetic entity. Moreover, no multigenerational pedigree has been available, making it difficult to assess the pattern of inheritance and the clinical spectrum of this peculiar disorder. We describe here a large three-generation family with autosomal dominant T1P (ADT1P) in which a systematic genome-wide screen revealed suggestive evidence for linkage to chromosome 13qter.

Subjects and methods. *Pedigree assessment.* The family, consisting of 28 living members, was ascertained in Calabria, southern Italy. The pedigree is shown in figure E-1 in the supplementary material on the Neurology Web site (go to www.neurology.org). A subset of family members underwent detailed clinical, brain CT, and/or cranial MR investigation. Based on imaging studies, there were nine affected individuals (table). A high rate of miscarriages was observed (see figure E-1 on the *Neurology* Web site). There were no consanguineous marriages. Male-to-male transmission was observed. These data strongly support an autosomal dominant inheritance for the trait segregating in this pedigree.

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Genotyping. After informed consent was given, peripheral blood samples were obtained from 19 of 28 living members. Eight of them were affected, nine were unaffected, one patient (III27) refused imaging, and one (IV4) had inconclusive CT scan results (see figure E-1 on the *Neurology* Web site).

DNA isolation was performed using standard protocols. For genotyping, the ABI Prism Linkage Mapping Set MD10 was used (Applied Biosystems, Foster City, CA). Additional markers for fine mapping were obtained from the Marshfield genetic map (http://research.marshfieldclinic.org/genetics/) or developed by us (information available through P.H.).

Linkage analysis. Linkage analyses were performed using the MLINK and LINKMAP programs of the LINKAGE package (version 5.1).[8] Maximum logarithm-of-the-odds (lod) and location scores were calculated for each marker, assuming ADT1P to be an autosomal dominant disorder with 90% penetrance and a gene frequency of 1:10.000; no phenocopies were allowed. Mutation rate was set at zero. Recombination frequencies were assumed to be equal between males and females, and equal allele frequencies were used in the calculations. Changing allele frequencies did not significantly alter lod or location scores. Haplotypes were constructed manually, based on the minimal number of recombinations.

Results. *Clinical findings.* The main clinical findings of the nine affected individuals are summarized in the table. Only one patient (V15) was born prematurely (30 weeks). The most severely affected patients had partial epileptic seizures and low IQ. Other common neuropsychological abnormalities were reduced verbal fluency, reduced verbal learning or verbal memory or both, oral apraxia, and ideomotor and constructive apraxia. The subject (IV4) with doubtful CT brain scan abnormalities was born after a dystocic delivery and had slight neonatal asphyxia but normal psychomotor development.

Laboratory findings. Echocardiogram revealed slight mitral valve regurgitation in four of six examined patients. In 11 examined subjects (III3, III9, III23, III26, IV8, IV12,

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Table *Clinical findings in nine patients with autosomal dominant type 1 porencephaly*

	Patients								
Findings	III3	III9	III16	IV8	IV12	IV16	IV20	IV23	V15
Age, y	56	49	70	28	18	9	40	30	15
Sex	F	M	M	F	F	M	F	F	M
Perinatal asphyxia					Yes	Yes			Yes
Pyramidal signs	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Tetraparesis					Yes	Yes			Yes
Limb dystonia				Yes	Yes	Yes			Yes
Seizures				Yes	Yes	Yes			Yes
Exotropia	Yes			Yes	Yes	Yes			
Campimetric defects		Yes	Yes		Yes	Yes	Yes		NE
Neuropychological anomalies	Yes	Yes	NE	Yes	Yes	Yes		NE	Yes
Mitral valve prolapse	Yes	Yes	NE	Yes		Yes		NE	

NE = not examined.

IV14, IV15, IV16, IV20, V15), the hemostatic workup including complete blood count, prothrombin time, partial thromboplastin time, protein C, protein S, APC resistance, bleeding time, homocystinemia, and testing for mutations in the prothrombin, factor V, and methyltetrahydrofolate reductase genes showed no abnormalities. In four subjects (IV8, IV12, IV16, V15), the cytogenetic study (G-banding method using peripheral lymphocytes) was normal.

Neuroimaging findings. A CT brain scan was performed in all 28 investigated individuals but 1 (III27). It was normal in 18 of 28 subjects. Nine of the remaining 10 subjects (III3, III9, III16, IV8, IV12, IV16, IV20, IV23, V15) had an abnormal CT scan. In the last subject (IV4), it showed a small hypodense periventricular cavity nearby the centrum ovale of doubtful significance, which could be related to the perinatal asphyxia. Brain MR studies were performed in six of nine patients (III3, III9, IV8, IV12, IV16, V15). Three of four most severely affected patients showed a large unilateral porencephalic cyst (figure, A), whereas the fourth had marked colpocephaly. In one patient (IV16), crossed cerebellar atrophy was also found (see the figure, B). In the two less affected members, MRI study revealed only unilateral enlargement of a ventricular occipital horn (see the figure, C), reflecting loss of periventricular white matter. Overall, the patterns of brain abnormalities, as detected by MR study, were consistent with in utero insults, which had mainly occurred late in the second trimester. Indeed, there was no evidence of concomitant astrocytic response to injury such as astrocytic proliferation or glial septations within the area of damaged brain, which are seen in the third trimester of mature brain as reaction to injury.[9] Similarly, we never depicted malformations of the overlying cortex or dysplastic gray matter lining the porencephalic cavity, which result from earlier brain destruction.[9] MR arteriography, performed in three patients (III3, III9, IV12), showed nor-

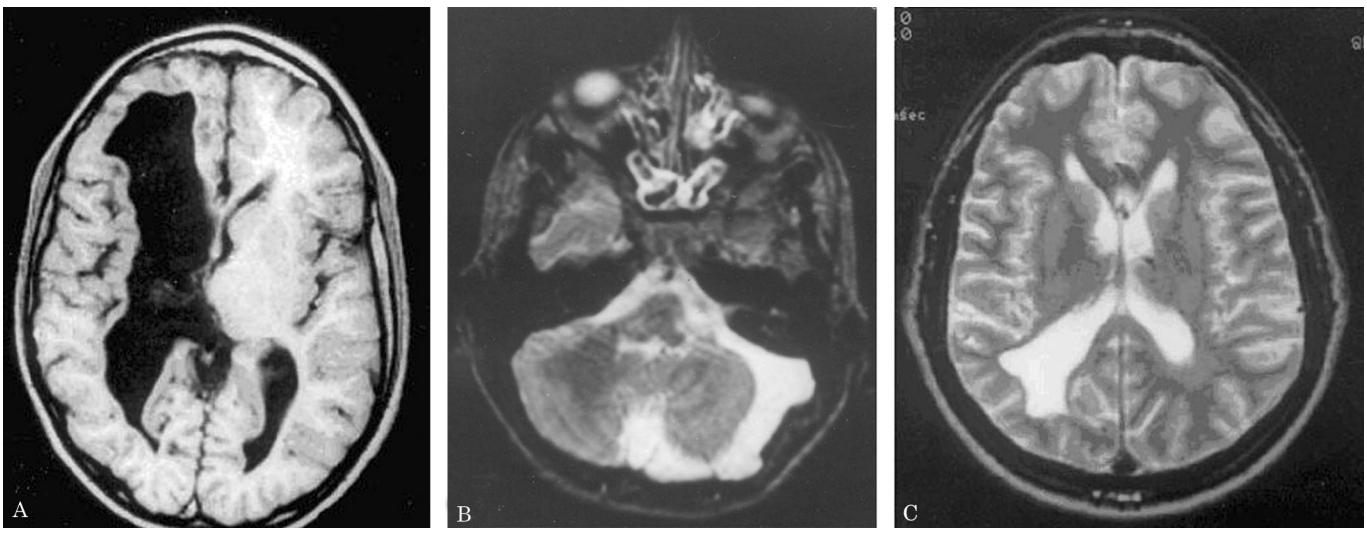

Figure. (A and B) MRI of severe autosomal dominant type 1 porencephaly: Patient IV16. There is a large porencephalic cyst involving both subcortical gray and white matter of the whole right hemisphere (A). Crossed cerebellar atrophy is evident (B). (C) MRI of mild autosomal dominant type 1 porencephaly: Patient III9. There is slight enlargement of a ventricle's occipital horn. No other brain abnormalities and no MRI evidence of abnormal cortical gyral pattern are seen.

mal arterial flow in both extracranial and intracranial circulation.

Linkage analysis. Employing a systematic genome scan for linkage for this family, we obtained the highest positive lod score ($Z_{max} = 2.33$, $\theta = 0$) with marker D13S261 on chromosome 13qter (see table E-1 on the *Neurology* Web site). Additional markers were typed from the Marshfield genetic map, and a multipoint linkage analysis was performed with the following markers: D13S1315, D13S261, D13S1295, D13S285, D13S293, D13S1825. The maximum lod score was $Z_{max} = 3.16$ at $\theta = 0$ of D13S285. By using these and several newly generated markers from our laboratory, a critical region could be defined distal to marker D13S293 due to a recombination event between marker D13S293 and CGR91 in Patient III16. No recombinant marker was found to determine a telomeric border for the possible porencephaly locus. Unaffected Patient III5 carries also the risk haplotype and is therefore assumed to be a carrier of the ADT1P mutation. Finally, FISH analysis utilizing several probes of chromosome 13 gave no evidence of rearrangements.

Discussion. Examination of this family allowed us to uncover the genetic, clinical spectrum, and natural history of ADT1P and to confirm that this hereditary disorder represents a distinct clinical and genetic entity with an autosomal dominant pattern of inheritance. Combined linkage and haplotype analyses for this family resulted in suggestive evidence for linkage for ADT1P to chromosome 13qter with a maximum lod score of $Z_{max} = 3.16$ at $\theta = 0$ of D13S285 following the criteria to report linkage findings proposed by Lander and Kruglyak.[10] The exact size of the critical region could not be easily defined owing to the fact that the available genetic and physical map data are unfinished (National Center for Biotechnology Information build 33, Celera Discovery System 3.9, March 2, 2003), but it is at least 1 Mb. As ADT1P may result from destructive lesions such as fetal vascular occlusion, hemiplegic cerebral palsy candidate genes could be involved in the coagulation of blood. Candidate genes for porencephaly could also have a function in brain or vascular development or both. From the seven genes, which are located in the critical region, *LOC283489* (which has some homology with a Zn finger C2H2-type domain, known to play a role in brain development), *CDC16* (which plays a role in proliferation of cells and regulation in ubiquitin cell division), and *GAP1IP4BP* (a member of the GAP1 family of GTPase-activating proteins that may act in cellular proliferation and differentiation) are the candidate genes for porencephaly. However, there is first the need to obtain significant lod scores for this chromosome 13qter region and to confirm this suggestive evidence for linkage. For this, more families with ADT1P should be tested for linkage to chromosome 13qter. Finding the responsible mutation(s) for ADT1P will provide new tools for the initiation of studies toward understanding the origin of this disorder.

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