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Gene identification in autosomal dominant disorders.

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LETTERS

Gene Identification in Autosomal Dominant Disorders

We first want to congratulate the authors and the *AJNR* for the interesting case in "The Association between Tuberous Sclerosis and Insulinoma" (1). In this age of molecular genetics, these unusual cases have been shown to lead to major discoveries, as exemplified by the cloning of the neurofibromatosis type 1 gene. In the "Discussion," the authors state, "Although multiple endocrine neoplasia [MEN] type II has been linked to chromosome 10, the genetic linkage of multiple endocrine neoplasia type I has not yet been delineated." We would like to point out that the MEN2 gene was cloned in 1993 (2) and that the MEN1 gene was mapped to chromosomal region 11q13 in 1988 (3). Two tuberous sclerosis genes have been mapped, one to 9q (TSC1) and the other to 16p (TSC2), and the TSC2 gene was cloned in 1993 (4). The case could be related to either one of them. To date, more than 80 MEN1 families have been genotyped and no genetic heterogeneity has been detected (5), so the authors' suggestion that MEN1 might be linked to chromosome 9 (tuberous sclerosis type 1 gene) is unlikely, although the possible relationship between tuberous sclerosis and MEN1 at the molecular level cannot be denied, but can be ascertained only after the genes are cloned and analyzed. However, it would be very interesting to carry out cytogenetic studies on this patient, because any karyotypic abnormality that might involve chromosomes 9, 16, or 11 will greatly contribute to the cloning of the tuberous sclerosis type 1 gene in 9q and the MEN1 gene in 11q13.

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Editor's note.—Dr Kerr and his colleagues did not wish to reply. The letter was referred to David Kwiatkowski, whose comments follow.

Comment

The report by Kerr et al highlights the occurrence of pancreatic neoplasms in patients with tuberous sclerosis. The letter from Teh et al serves to highlight the current state of gene location/identification for the tuberous sclerosis and MEN syndromes. To put these reports in perspective, it is appropriate to characterize briefly the syndromes under discussion (see the Table). All three syndromes (tuberous sclerosis and both forms of MEN) are autosomal dominant disorders, meaning that inheritance of a single defective gene leads to the syndrome. In tuberous sclerosis, two different genes cause an identical clinical syndrome, and most patients have sporadic cases without family history, likely attributable to new mutations. All three syndromes are characterized by both benign tumors and, less often, malignant metastasizing tumors. For MEN2, the causative gene is a mutated, activated ret gene. In MEN1 and tuberous sclerosis, there is good evidence that the inherited gene is inactivated and the second copy must be lost by somatic mutation in the tumors that develop.

Tuberous sclerosis is a highly pleomorphic syndrome, in which hamartomas develop in numerous organs (1, 2). Small series and case reports have documented that a wide variety of malignant neoplasms can be seen in tuberous sclerosis, including those of nearly every endocrine organ. Because of the rarity of tuberous sclerosis, it is difficult to know whether these are chance occurrences or real associations. Renal cell cancer is clearly associated with tuberous sclerosis and can arise in the angiomyolipomas commonly seen in this syndrome (3). Kerr et al's article underscores that pancreatic islet cell and related tumors occur at an appreciable frequency in tuberous sclerosis. From a management standpoint, the observation is perhaps most important because it emphasizes that the blood glucose should be analyzed whenever a patient with tuberous sclerosis experiences mental status or personality changes or worsening seizures.

Teh et al suggest that it is possible that the patient could have had both tuberous sclerosis and MEN1 through a chromosomal translocation disrupting the MEN1 gene on 11p13 and either of the tuberous sclerosis genes. Although possible, given the association of tuberous sclerosis with

Features of three autosomal dominant disorders

| Syndrome | Inheritance Pattern/Gene | Clinical Features |
|--------------------|--|---|
| MEN1 | Autosomal dominant/gene not identified, localized to 11q13 | Major: hyperparathyroidism, pituitary adenomas, pancreatic islet tumors Minor: duodenal gastrinoma, carcinoid tumors, adrenal and thyroid tumors |
| MEN2* | Autosomal dominant/ret (10q11) | Major: medullary thyroid carcinoma, pheochromocytoma Minor: parathyroid hyperplasia |
| Tuberous sclerosis | Autosomal dominant/TSC2 (tuberin, 16p13); TSC1 not identified, localized to 9q34 | Major: facial angiofibromas, ungual fibromas, cortical tubers, subependymal nodule/giant cell astrocytoma, cardiac rhabdomyoma, renal angiomyolipoma Minor: numerous |

* MEN2 is split into 2A and 2B based on additional features in MEN2B (multiple mucosal neuromas, intestinal ganglioneuromatosis, and Marfanoid habitus).

multiple forms of neoplasia, it seems much more likely that this patient had tuberous sclerosis alone.

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Cerebral MR and Craniofacial Syndromes

We read with interest the paper of Tokumaru et al (1), "Skull Base and Calvarial Deformities: Association with Intracranial Changes in Craniofacial Syndromes." We studied with cerebral magnetic resonance (MR) 62 patients affected by malformation syndromes, of which five had craniofacial syndromes (two Saethre-Chotzen, one Pfeiffer, one Crouzon, and one Apert). In these we have observed (a) in Pfeiffer syndrome, white matter alterations and increased flip angle (2) of the corpus callosum, (b) in Crouzon syndrome, ventriculomegaly and reduced thickness of the splenium, (c) in Saethre-Chotzen syndrome, one case of corpus callosum with modified shape estimated by Talairach grid application (3) and optic nerve atrophy, and (d) in Apert syndrome, lateral ventricular dilatation and enlarged cisterna cerebellomedullaris. We did not detect lesions in the second case of Saethre-Chotzen syndrome. Contrary to Tokumaru et al in their nine cases studied with MR, we have not found any tonsillar herniation (Chiari anomaly), defects of the septum pellucidum, anomalies of the temporal lobe, or atypical gyral pattern.

We have also used cerebral MR in 57 other subjects with different malformation syndromes with mental retardation. We observed a high frequency of cerebral anomalies not related to the specific malformation syndrome studied (seven cases of Silver-Russel syndrome, six of Williams syndrome, five of Noonan syndrome, four of Engelmann syndrome, four of Beckwith-Wiedemann syndrome, and three of de Lange syndrome). Eleven patients did not have cerebral anomalies.

We agree with Tokumaru et al in recognizing the utility of MR in the study of the craniofacial syndromes, and in general of all malformation syndromes. Nevertheless, at present, the identification of specific patterns of cerebral anomalies in definite syndromes is not possible. Only with the availability of a copious amount of statistically significant data will it be possible to rearrange the classification, which is now based only on clinical data and few autopsy findings.

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Ocular Enhancement in Sturge-Weber Syndrome

I read with interest the recent *AJNR* article on the presence of choroid hemangioma in patients with Sturge-Weber syndrome (1). Griffiths et al present this finding in seven of eight patients in whom the hemangiomas were shown at fundoscopy. In the "Discussion," they comment that in our paper (2) is presented a patient of unspecified age with the ocular enhancement on contrast-enhanced MR.

Actually, we included an illustration (Figure 2 in our article) of retinal hemangioma, but we do not mention that this finding was observed in only one patient. In the abstract and in the "Results," we comment that contrast-enhanced MR was performed in 11 cases, and disclosed the cerebral, leptomeningeal, and ocular lesions before the first evidence of neurologic abnormality. In another part of the "Results" we say that "only patients with nevus flammeus affecting the upper eyelid had glaucoma; the lesion in the retina was documented by MRI with Gd-DTPA. Neither of these alterations were present in patients without palpebral angioma." Although we did not specify the number of patients, retinal hemangioma was found in all patients with nevus flammeus affecting the upper eyelid. With this explanation, we try to clarify the facts and would rather have the authors write, "Pascual-Castroviejo et al described an unknown or a unmentioned number of patients."

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Reply

We are grateful for the comments of Dr Pascual-Castroviejo. We accept totally the semantic error in the "Discussion" portion of our paper. We agree that the final sentence offered in the above letter is most appropriate.

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Prevalence of Arachnoid Granulations as Detected with CT Venography of the Dural Sinuses

In a recent article in *AJNR*, Roche and Warner (1) found the incidence of arachnoid granulations in adults undergoing imaging to be 0.3% to 1%. They correctly viewed these numbers as a conservative estimate in part limited by CT or MR section thickness. We read their article with interest because we have encountered these granulations frequently in our use of cerebral CT venography of the dural sinuses (2). Our retrospective review of a series of CT venograms suggests a much greater prevalence, with granulations identifiable in 55% of patients.

CT venography is performed with 1-mm collimation in a helical scan with a pitch of 2. The examination covers the entire head in a 60-second axial acquisition from the cranial vertex down to the skull base during a rapid intravenous bolus of contrast material. Presently our protocol consists of a biphasic injection of nonionic contrast material into an antecubital vein, beginning with a rate of 2.8 mL/s for 60 mL and dropping to a rate of 1.0 mL/s for an additional 30 mL. A 30-second prescan delay is used. The data are retrospectively reconstructed to 148 overlapping sections at 0.8-mm intervals. These sections can be reformatted into multiplanar sections or 3-D models (using maximum intensity projection [MIP] algorithms).

We retrospectively reviewed cerebral CT venograms in 20 patients for the presence of arachnoid granulations. These studies had been performed to evaluate the presence of dural sinus thrombosis and had been interpreted as normal. We used criteria derived from Roche and Warner's article to identify small dural sinus filling defects as arachnoid granulations. We also used region-of-interest measurements to ensure that granulations had densities near that of cerebrospinal fluid (0 to 20 Hounsfield units). To avoid overestimation, suspected granulations at least had to invaginate into the dural sinus and have no more than one side not bordered by the contrast-enhancing sinus. Eleven of 20 patients were found to have a total of 13 arachnoid granulations. These were found most commonly at the junction between the middle and lateral thirds of the transverse sinuses and measured 2 to 6 mm in diameter. They were best seen on the source images or on multiplanar reformations (Fig 1A). The 3-D MIP reformations tend to depict these small almost entirely intraluminal granulations suboptimally, because the arachnoid granulations are obscured by the surrounding contrast-enhancing blood within the dural sinus (Fig 1B). Despite this flaw, the 3-D MIP reformations, from a practical point of view, decrease the possibility that these small intraluminal granulations will be mistaken for dural sinus thrombus.

As a result of its very thin collimation and cross-sectional nature, CT venography has an advantage for the demonstration of small dural sinus filling defects such as arachnoid granulations. Because of their small size and low density, these granulations are not usually confused with thrombus. In summary, our retrospective review of a

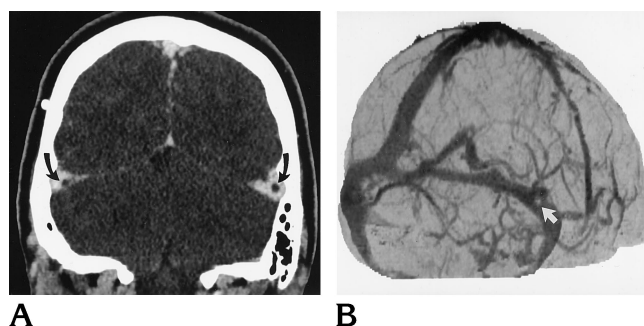


Fig 1. A, Coronal reformation from a CT venogram shows granulations in the lateral third of the transverse sinus on each side (arrows).

B, MIP 3-D reformation of the same CT venogram (right anterior oblique projection) shows only the granulation in the left transverse sinus (arrow). MIP images obscure the small intraluminal arachnoid granulation within the right transverse sinus.

small sample of patients reveal visible arachnoid granulations, of 2 mm or greater diameter, to be a frequent normal finding on CT venography, with the prevalence being approximately 55%.

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Reply

We welcome the response of Casey et al to our observations about arachnoid granulations. Our estimates of the prevalence of these lesions were inevitably inaccurate because of (a) the nonsystematic nature of our sampling of patients, (b) the nature of both CT and MR sampling with thick cuts (3 mm or more) often with intersection gaps, and (c) our inability within our hospital to carry out a formal search for granulations.

Data reviewed in our paper from Knudsen referred to filling defects in three of 14 volunteers, and suggested to us that the prevalence was much higher than we had observed. With the data available to us, we were loathe to make a claim for a higher prevalence. We would have guessed a prevalence of 10% to 20%, but find the report of Casey et al unsurprising. The smallest granulations we

assessed were 3 mm. With their ability to see granulations of 2 mm, their claim of a prevalence of 55% causes us only mild surprise. We wonder whether their age distribution was the same as ours, because the number of granulations is supposed to increase with age.

We thank them for their valuable contribution to our observations. It would be of interest to know whether they saw arachnoid granulations in the superior sagittal sinus, the straight sinus, or other sites.

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MR Findings of Neonatal Hypoglycemia

We had the pleasure of reading a recent article in *AJNR* by Spar et al (1). They reported a case of neonatal hypoglycemia and suggested that the findings of significant parenchymal loss, most prominent in the occipital regions, seemed to be somewhat specific for neonatal hypoglycemia. We report a newborn with hypoglycemia who has similar MR findings.

A 32-hour-old girl was referred to our Neonatal Intensive Care Unit with irritability, poor feeding, and seizures. She was delivered as the fourth uncomplicated gestation of a nondiabetic mother 10 days before term. The infant's Apgar scores were 9/10 at 1 and 5 minutes. Her parents were healthy and first-degree consanguineous. The parents reported that the infant initially fed well, but they noted increasing irritability and poor feeding 24 hours after delivery. She had seizures at approximately 30 and 31 hours of her life.

On physical examination, she exhibited irritability and poor feeding. Her birth weight was 3400 g, height 51 cm, and head circumference 35 cm. Blood glucose level was 7 mg/dL and intravenous infusion of 1 mL/kg of 20% dextrose solution was administered immediately over 1 minute followed by continuous dextrose infusion at a rate of 8 mg/kg per minute. Although the dextrose concentration was adjusted by 2 mg/kg per minute every 4 to 6 hours (maximum 12 mg/kg per minute), glucose levels had not increased to over 30 mg/dL. Therefore hydrocortisone 10 mg/kg per day intravenously was started at 44 hours of age and given for 3 days. Blood glucose level was 42 mg/dL at 58 hours after delivery and stabilized at 70 to 120 mg/dL at 92 hours of age. At 58 hours after delivery, continuous nasogastric drip feeding was started. The infant's seizure activity recurred despite the improved glucose levels; therefore, phenobarbital therapy was added.

Etiologic investigations for hypoglycemia revealed normal findings. Electroencephalography showed a flat and periodic abnormality pattern. MR images at 10 days of age showed diffuse parenchymal loss and hypointense areas that resembled infarction in both occipital regions, and

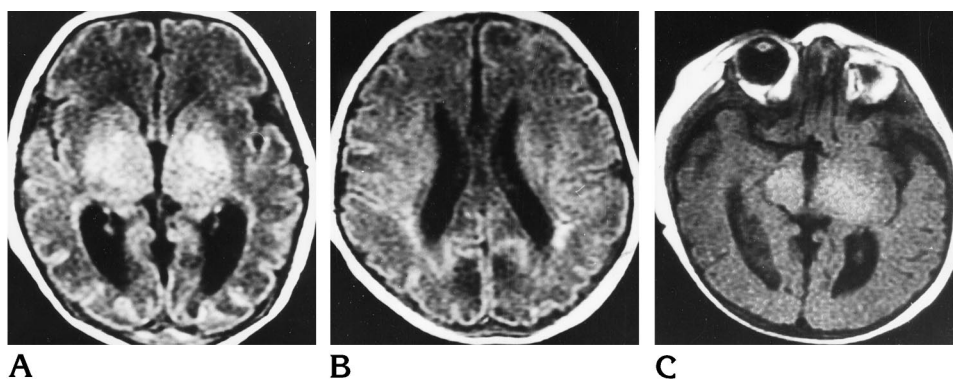


Fig 2. Unenhanced short-repetition-time (400/20 [repetition time/echo time]) axial MR images.

At 10 days of age, there is diffuse occipital parenchymal loss and dilatation of the occipital horns of the lateral ventricles (A) and hypointense areas in the occipital regions bilaterally (B).

C, At 4 months of age, there is diffuse parenchymal loss in the occipital lobes and dilatation of the occipital horns of the lateral ventricles.

dilatation of the occipital horns of the lateral ventricles (Fig 2A and B). She was discharged at age 14 days.

On examination at 4 months of age, she exhibited bad performance on the Denver Developmental Screening Test. Electroencephalography showed a pattern with mild voltage suppression and moderate periodic abnormality. Flash visual evoked response studies showed a decreased latency. MR studies revealed extensive occipital cortical loss and dilatation of the occipital horns of the lateral ventricles (Fig 2C).

Multiple studies have documented neuropathologic and neurochemical abnormalities in infants and children with hypoglycemia (2, 3). CT findings of hypoglycemia were demonstrated in a few reports. Isono et al (4) reported an adult patient with hypoglycemia who had CT findings of multiple low-density areas throughout the cerebral cortex resembling multiple cortical infarctions, and concluded that these findings were specific for hypoglycemic encephalopathy. However, Spar et al (1) reported that CT findings of neonatal hypoglycemia are generalized edema in the early period, and parenchymal loss or hypodensities in the occipital regions in the late period.

An adult patient showing extensive cortical and subcortical atrophy, particularly in the frontoparietal and parietooccipital regions bilaterally, with dilated lateral ventricles on MR has been reported (4). The newborn hypoglycemic infant reported by Spar et al (1) revealed a predominance of brain parenchymal loss in the occipital lobes bilaterally with nearly complete absence of cortex in the posterior parietal and occipital regions and generalized thinning of the cortex throughout the brain.

The present case's hypointense areas on MR images at 10 days of age were correlated with that of a case previously reported by Isono et al (4). The other MR findings of our case, such as diffuse occipital parenchymal loss bilaterally and dilatation of the occipital horns of the lateral ventricles, were consistent with previously reported findings of Spar et al. Finally, we also think that the presented

MR findings are the result of neonatal hypoglycemic brain damage.

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Reply

Acute and long-term radiologic abnormalities associated with hypoglycemic episodes in children and adults are well documented, but the details of the situation for neonatal hypoglycemia are still emerging. In our article and a previous report (1), it was noted that occipital involvement is more severe than that seen in the temporal or frontal lobes. The letter by Aslan and Dinc confirms the consistency of this observation and provides supporting evidence for our hypothesis that the selective occipital vulnerability is related to the high degree of axonal migration and synaptogenesis occurring within the occipital lobe during the neonatal period.

A unique aspect of the study by Aslan and Dinc was sequential MR scanning at 10 days and 4 months of age. This revealed what appears to be a progressive deterioration of the occipital cortex, triggered by a relatively acute hypoglycemic episode during the first week of life. It is not simply the case that the regions of the occipital lobe shown to be compromised at 10 days failed to mature. Rather, there seems to have been a pervasive effect of hypoglycemia throughout the occipital lobe. We believe that this finding is consistent with the type of developmental process we have outlined, in which an acute catastrophic event disrupts the full pattern of occipital development, including axonal migration and myelination. If cortical neurons within the occipital lobe are deprived of their expected geniculostriate innervation (and associated trophic factors), there is a progressive atrophy of the cortex, as is seen.

The electroencephalographic findings in the present study are also supportive of our developmental proposal. At 4 months of age, Aslan and Dinc found a latency delay in the flash visual evoked response. This probably reflects a combination of several factors, all of which are consistent with the notion of disrupted occipital development. Specifically, the latency delay is likely to reflect (a) abnormal synaptic patterns, (b) decreased myelination along the retinal-geniculostriate pathway, and (c) selective loss

of rapidly conducting magnocellular neurons (large neurons of this type are more sensitive to hypoglycemia than smaller neurons, because of their greater metabolic demands).

We look forward to additional case reports on the topic of neonatal hypoglycemia, with the hope that they will continue to shed light on the etiology of the occipital vulnerability.

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