Abstract—Horizontal gaze palsy with progressive scoliosis (HGPS) is a rare, autosomal recessive disorder characterized by a congenital absence of conjugate horizontal eye movement with progressive scoliosis developing in childhood or adolescence. The authors identified two unrelated consanguineous families with HGPS. Genomewide homozygosity mapping and linkage analysis mapped the disease locus to a 30-cM interval on chromosome 11q23-25 (combined maximum multipoint lod score Z = 5.46).

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Horizontal gaze palsy with progressive scoliosis (HGPS) is a rare, inherited disorder characterized by a congenital absence of conjugate horizontal eye movement with progressive scoliosis developing in childhood and adolescence1,2 (Online Mendelian Inheritance in Man [OMIM] 555000). The presence of consanguinity, the absence of scoliosis or any abnormality in horizontal eye movement in antecedent generations, and equal involvement of both sexes are strongly suggestive of an autosomal recessive inheritance pattern.

Two consanguineous pedigrees with HGPS were identified. We performed genomewide homozygosity mapping3 using polymorphic genetic markers. In both pedigrees, the same region of 30 cM on chromosome 11 showed excess homozygosity in affected individuals but not unaffected relatives, strongly suggesting that the disease gene lies in this region.

Patients and methods. Clinical profile. Horizontal gaze palsy was identified in two ethnically and racially unrelated inbred families now residing in Saudi Arabia: one from India and the other from Saudi Arabia (figure 1). All six affected individuals (4 males and 2 females, aged 2 weeks to 18 years) had no horizontal gaze from birth by family report, and no horizontal gaze was noted in one 2-week-old affected infant. Affected patients had no conjugate horizontal smooth pursuit, saccades, or vestibulo-ocular reflex, whereas vertical eye movements were full in excursion and normal in character. One patient had a few degrees of adduction on attempted horizontal gaze to either side that may have represented convergence. Two of the six affected individuals had a modest comitant esotropia present by report from early life, and four patients had minimal amplitude horizontal pendular nystagmus most compatible with congenital nystagmus. Afferent visual system was normal in all affected individuals, and no subject had either head thrusts or obvious retraction of the globe noted on attempted horizontal gaze. No facial contractions, myokymia, facial diplegia, or unilateral facial weakness was noted in any affected individual.

All affected individuals other than the infant had mild to moderate scoliosis by visual inspection or spine x-ray that was progressive by report. No patient had ocular colobomas or somatic abnormalities such as cleft palate, harelip, or Klippel-Fiel anomaly. Two subjects (one from each family) had mild to moderate mental retardation, and two others (one from each family) had mild delay of motor milestones by family report. One affected individual had a slightly increased ankle jerk on the right and a slightly broad-based gait that were probably the result of substantial progressive scoliosis. All unaffected parents and siblings had normal results on ophthalmologic and neurologic examinations.

Genotyping and linkage analysis. DNA was extracted from peripheral blood of consenting members of the two families. The study was approved by the institutional review boards at UCLA and the King Khaled Eye Specialist Hospital.

A known autosomal dominant Duane syndrome locus on chromosome 2 was excluded by genetic linkage analysis.4 A
A genome-wide screen for linkage was conducted to identify chromosomal regions consistently homozygous in all affected individuals but not in unaffected individuals. Genome scanning was performed using Weber Set 9 (Licor). Genomic amplification was performed with fluorescently labeled primers, with over 350 tri- and tetranucleotide microsatellite markers that span the genome in 10 cM intervals.

**Fine mapping of the candidate region.** A fine linkage study of the candidate region was performed using additional markers selected from GENETHON and the Center for Medical Genetics at the Marshfield Clinic to define the boundaries of the disease locus. Linkage analysis was performed to assess the likelihood that the disease locus lies within this chromosomal region. We made several assumptions for parametric analysis. A conservative estimate of the disease frequency was 10^-3 (0.001); thus, the frequency of the disease allele was 0.03. The mode of inheritance was assumed to be autosomal recessive. Mendel4 using the Elston-Stewart algorithm was employed to calculate two-point lod scores, for which we assumed equal frequencies for all alleles. The multipoint parametric lod score was calculated using SIMWALK2 (which permitted the consanguineous family structures in this study) yielded a significant result consistent with linkage (maximum lod of 5.46 near marker GATA140F03; figure 2); so did the two-point lod scores calculated using Mendel4 (maximum lod of 4.33 near marker D11S4132; See supplementary table on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the title link to this article.).

The boundaries for the mapping of the recessive HGPS are best determined from the minimal region that is homozygous in all six affected individuals on 11q23-25 (figure 2). The female affected individual in Family 1 is not homozygous at marker D11S1356, which sets the centromeric boundary. The female affected individual in Family 2 is not homozygous at marker D11S910, which sets the telomeric boundary. On the Genome Browser (http://genome.ucsc.edu) these boundaries are defined as

Figure 1. Pedigrees and most likely haplotypes for markers on chromosome 11q. Filled symbols represent affected individuals.

Results. From the initial 10 cM genome scan, we found only one region that fulfilled the criteria for homozygous inheritance of alleles in the affected individuals but not their unaffected relatives, located on chromosome 11q including markers D11S4464 and D11S912. Marker D11S1998 centromeric to D11S4464 did not appear linked to the disease locus, with several individuals showing recombination.

Genotyping additional markers near D11S1998, D11S4464, and D11S912 was performed to fine map the disease locus and to define the boundaries of the candidate region (figures 1 and 2). The multipoint parametric lod score calculated using SIMWALK2 (which permitted the consanguineous family structures in this study) yielded a significant result consistent with linkage (maximum lod of 5.46 near marker GATA140F03; figure 2); so did the two-point lod scores calculated using Mendel4 (maximum lod of 4.33 near marker D11S4132; See supplementary table on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the title link to this article.).

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Discussion. HGPS is a rare disorder for which the genetic basis has not been determined previously. Affected patients described in earlier reports were thought to develop progressive external ophthalmoplegia because not all had been examined during infancy to ascertain whether horizontal gaze was intact\(^1,2\) (OMIM 555000). The overlapping feature of progressive external ophthalmoplegia between HGPS and Kearns-Sayre syndrome raised the possibility of mitochondrial cytopathy as an etiology (OMIM 555000). In fact, affected individuals in the two families in this report were noted to have no horizontal gaze since birth, rather than a progressive limitation in horizontal gaze. Furthermore, the absence of affected individuals in antecedent generations, the equal involvement of both sexes, and the presence of consanguinity in HGPS are most consistent with an autosomal recessive pattern of inheritance.

A number of inherited syndromes involving horizontal eye movement have been reported but it is unclear whether these represent unique phenotypes or a spectrum of phenotypes. Duane syndrome is usually characterized by limitation of abduction, but there are variants with impaired adduction. Patients with HGPS have absent conjugate horizontal gaze with preserved vertical gaze and convergence.\(^2,7\) All patients with Duane syndrome have variable globe retraction with attempted horizontal gaze, which was not observed in the patients reported here. Pathologic studies in cases of Duane syndrome identified congenital maldevelopment of abducens nuclei and absence of abducens nerves. Because the abducens nuclei contains both motor neurons supplying the lateral rectus and interneurons that send their axons in the medial longitudinal fasciculus (MLF) to the contralateral third cranial nerve nucleus, lack of development of the entire abducens nucleus could lead to loss of all conjugate horizontal eye movements.\(^7\) In those cases where just abduction paralysis occurs (as with most cases of Duane syndrome), then the maldevelopment must be restricted to the motor neurons in the abducens nucleus. The locus previously identified on chromosome 2 in a large autosomal dominant family with Duane syndrome\(^4\) was excluded in our two families with HGPS, so at least two different chromosomal loci are associated with congenital horizontal gaze restriction.

With a prevalence of 2 to 3\% in the general population, scoliosis is one of the most common neuromuscular disorders. Numerous families with scoliosis have been reported in the literature, and population studies documented an increased incidence of scoliosis within families with affected individuals compared with that in the general population. Dominant, recessive, and X-linked transmission has been described, whereas a multifactorial mode of inheritance seems most likely in other families.\(^8\) To date, there is no known gene or chromosomal locus definitely associated with scoliosis, although a genome-wide linkage survey in two large families with dominantly inherited scoliosis identified suspect loci on chromosome 6p, 10q, and 18q.\(^9\) Identifying the gene associated with HGPS should provide new insight into the pathophysiology of inherited scoliosis and suggest likely candidate genes for the more commonly inherited syndromes.

Although it is possible that separate genes underlie congenital horizontal gaze palsy and progressive scoliosis in these patients, it is far more likely that defects within the same gene are responsible for the entire syndrome. How could a single gene mutation result in maldevelopment of brainstem gaze mechanisms followed by delayed development of scoliosis? Associated development abnormalities in the spinal cord might predispose to the subsequent development of scoliosis. However, none of our patients with HGPS had signs of segmental spinal neuromuscular involvement that would suggest a neurogenic mechanism for scoliosis. Chronic muscle tone abnormality resulting from a primary brainstem pathology may lead to scoliosis over time. Two mouse mutants with
The association between migraine and ischemic stroke remains unexplained. Whether this association is similar across the various subtypes of ischemic stroke, or whether there is a specific association with one subtype, is unknown. Cervical artery dissection (CAD) is a possible candidate as the underlying arterial wall disease could predispose to migraine. We therefore studied the association between migraine and CAD within a case-control study.

Patients and methods. We undertook a hospital-based case-control study in two neurology departments, one at Lariboisière Hospital in Paris and the other at Laënnec hospital in Nantes, France. Patients with CAD (case subjects) and patients hospitalized for a cerebral ischemic event not related to CAD (control subjects) were prospectively recruited during a 20-month period. Patients eligible for inclusion were between 18 to 65 years of age and gave their informed consent for the study. There were no other inclusion or exclusion criteria. The study was approved by the local ethics committee and a signed informed consent was obtained for all participants.

Forty-seven patients with CAD were consecutively recruited, including 21 women and 26 men; mean age was 44.8 (SD 7.4, range 27 to 62). CAD was confirmed by duplex scanning and by MRI and MR angiography (n = 46) or conventional angiography (n = 1). All patients with CAD were without recent major whiplash injury and were therefore considered as spontaneous cases. Dissection involved a single artery in 33 patients (carotid artery in 24; vertebral artery in 9). Fourteen patients had more than one dissection: both carotid arteries in nine, both vertebral arteries in three, and one or both carotid arteries and one or both vertebral arteries in two. No patient had an associated intracranial dissection. A cerebral ischemic event occurred with CAD in 33 patients: 24 had an ischemic stroke, eight a TIA, and one a transient monocular blindness. All the remaining 14 patients had a painful Horner syndrome without ischemic event. Overall, 96% (44/46) of the pa-