Hereditary Spastic Paraplegia With Thin Corpus Callosum

Reduction of the SPG11 Interval and Evidence for Further Genetic Heterogeneity

Alexander Lossos, MD; Giovanni Stevanin, PhD; Vardiella Meiner, MD; Zohar Argov, MD; Naima Bouslam, MS; J. P. Newman, PhD; John M. Gomori, MD; Stephan Klebe, MD; Israela Lerer, MSc; Nizar Elleuch, MD; Shira Silverstein, MSc; Alexandra Durr, MD; Oded Abramsky, MD, PhD; Ziva Ben-Nariah, MD; Alexis Brice, MD

Background: Hereditary spastic paraplegia (HSP) with thin corpus callosum (TCC) is an autosomal recessive form of complicated HSP mainly characterized by slowly progressive spastic paraparesis and mental deterioration beginning in the second decade of life. The locus for HSP-TCC, designated SPG11, was mapped to chromosome 15q13-15 in some of the affected families from Japan, Europe, and North America, spanning an interval of 17.5 megabases (Mb).

Objective: To perform a clinical and genetic study of HSP-TCC.

Design and Setting: Case series; multi-institutional study.

Patients: Seven patients with HSP-TCC who belong to 3 consanguineous families of Arab origin residing in Israel.

Results: The 7 patients manifested a relatively similar combination of adolescence-onset cognitive decline and spastic paraparesis with TCC on brain magnetic resonance imaging. After excluding the SPG7 locus, we tested the 3 families for linkage to the SPG11, SPG21/MAST, and ACCPN loci associated with autosomal recessive disorders with TCC. Two families showed evidence for linkage to SPG11 (Zmax = 5.55) and reduced the candidate region to 13 Mb.

Conclusions: Our findings in HSP-TCC further confirm its worldwide distribution and genetic heterogeneity, and they significantly reduce the candidate SPG11 interval.

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Hereditary spastic paraplegia (HSP) with thin corpus callosum (TCC) (Online Mendelian Inheritance in Man [OMIM] #604360) is an autosomal recessive form of complicated HSP characterized clinically by slowly progressive spastic paraparesis and mental deterioration beginning in the second decade of life. Additional manifestations include urinary incontinence, sensory deficit in the legs, late distal amyotrophy, occasional seizures, extrapyramidal signs, and cerebellar ataxia. Although the appearance of TCC on cerebral magnetic resonance imaging is typical of HSP-TCC, it also occurs in some of the other HSPs, including those related to SPG7, SPG21, and SPG4, and in peripheral neuropathy with agenesis of the corpus callosum, making genetic analysis essential for diagnosis.

The locus for HSP-TCC, designated SPG11, was originally assigned to chromosome 15q13-15 overlapping the ACCPN locus in 7 families from Italy and North America. Onset in early childhood, normal intelligence, and the absence of TCC in some of these families suggested clinical variability. Later studies defined a 20-centimorgan interval in this region in 10 of 13 Japanese families with HSP-TCC and in 5 of 12 Italian families with HSP-TCC, demonstrating genetic heterogeneity. We present the results of genetic analysis in 3 Arab families from Israel with HSP-TCC.

We evaluated 7 patients with HSP-TCC who belong to 3 consanguineous families of Arab origin residing in Israel. Of the 31 living family members, 8 parents and 11 clinically unaffected siblings ranging in age from 15 to 35 years (mean age, 23 years) were also available for the study. The study was approved by the Ethics Committee, Hadassah Medical Organization, Jerusalem, Israel.

Diagnosis of HSP-TCC was established according to the published criteria. Age at symptom onset was obtained from the parents or the available medical records. Because of language limitations, we used the Test of Nonverbal Intelligence for the assessment of mental status. This language-free test of visual logical reasoning yields predicted IQ scores when other batteries cannot be applied. High-molecular-weight DNA was extracted from peripheral blood samples of 26...
Clinical findings at last examination are summarized in the Table. All of the 7 patients manifested slowly progressive spastic paraparesis, distal hand and foot muscle atrophy and weakness, signs of pseudobulbar dysfunction, and progressive mental impairment. The functional disability tended to correlate with age. While no patients had sensory deficits, seizures, signs of cerebellar dysfunction, or cataracts, some clinical variability was apparent in family 671. Although patient 671-10 initially had gait disturbance and urinary incontinence at age 13 years, she was reported to have mild mental retardation since early childhood. Patient 671-5 had extrapyramidal rigidity in the hands associated with mild hand tremor, and patient 671-4 developed urinary incontinence late in the course of her disease. Additional features included high-arched palate in patients 670-4, 670-5, and 671-4, obesity with a body mass index above 33 (where BMI is the weight in kilograms divided by the height in meters squared) in patients 672-3 and 672-5, and wide interdental spaces and Raynaud phenomenon in patient 671-4.

Consistent with the clinical findings, all of the 4 patients studied by magnetic resonance imaging had TCC most prominent in the rostrum, genu, and body associated with confluent and symmetric signal hyperintensities on T2-weighted and fluid-attenuated inversion recovery sequences in the cerebral white matter (Table). Widening of the anterior interhemispheric fissure was present in the 3 oldest patients, possibly the consequence of a mild frontal atrophy. Basal ganglia, brainstem, cerebellum, and the cervical spinal cord appeared normal. Only brain computed tomography was available in patient 671-10, and it showed TCC. Results of peripheral nerve conduction studies were consistent with borderline-to-mild predominantly axonal polyneuropathy in patients 670-4, 670-5, and 671-4 and were normal in patients 671-10 and 671-5. Sural nerve biopsy in patients 670-4 and 671-4 showed signs of axonal degeneration, and a quadriceps muscle biopsy specimen in patient 670-5 showed chronic neurogenic changes without specific alterations.

Abbreviations: B, body; CMAP, compound motor action potential amplitude; F, frontal; G, genu; LL, lower limb; MNCV, motor nerve conduction velocity; MRI, magnetic resonance imaging; NA, not available; ND, not done; O, occipital; Pv, periventricular; R, rostrum; S, splenium; SNAP, sensory nerve action potential amplitude; SNCV, sensory nerve conduction velocity; UL, upper limb; WMA, white matter abnormalities; *Disability stage at last examination: 2 indicates moderate gait stiffness without consistent use of assistive device; 3, marked gait stiffness with consistent use of assistive device; and 4, wheelchair bound.

### CLINICAL FINDINGS

Clinical findings at last examination are summarized in the Table. All of the 7 patients manifested slowly progressive spastic paraparesis, distal hand and foot muscle atrophy and weakness, signs of pseudobulbar dysfunction, and progressive mental impairment. The functional disability tended to correlate with age. While no patients had sensory deficits, seizures, signs of cerebellar dysfunction, or cataracts, some clinical variability was apparent in family 671. Although patient 671-10 initially had gait disturbance and urinary incontinence at age 13 years, she was reported to have mild mental retardation since early childhood. Patient 671-5 had extrapyramidal rigidity in the hands associated with mild hand tremor, and patient 671-4 developed urinary incontinence late in the course of her disease. Additional features included high-arched palate in patients 670-4, 670-5, and 671-4, obesity with a body mass index above 33 (where BMI is the weight in kilograms divided by the height in meters squared) in patients 672-3 and 672-5, and wide interdental spaces and Raynaud phenomenon in patient 671-4.

Consistent with the clinical findings, all of the 4 patients studied by magnetic resonance imaging had TCC most prominent in the rostrum, genu, and body associated with confluent and symmetric signal hyperintensities on T2-weighted and fluid-attenuated inversion recovery sequences in the cerebral white matter (Table). Widening of the anterior interhemispheric fissure was present in the 3 oldest patients, possibly the consequence of a mild frontal atrophy. Basal ganglia, brainstem, cerebellum, and the cervical spinal cord appeared normal. Only brain computed tomography was available in patient 671-10, and it showed TCC. Results of peripheral nerve conduction studies were consistent with borderline-to-mild predominantly axonal polyneuropathy in patients 670-4, 670-5, and 671-4 and were normal in patients 671-10 and 671-5. Sural nerve biopsy in patients 670-4 and 671-4 showed signs of axonal degeneration, and a quadriceps muscle biopsy specimen in patient 670-5 showed chronic neurogenic changes without specific alterations.
MOLECULAR ANALYSIS

Given the clinical presentation, we tested these families for linkage to the 3 loci on chromosome 15 that are associated with autosomal recessive disorders with TCC: SPG21/MAST (OMIM #248900), ACCPN (OMIM #218000), and SPG11. Linkage analyses generated negative lod scores with markers flanking the ACP33/MAST (D15S108, D15S1507) and SLC12A6/KCC3 (D15S1040, D15S971) genes in accordance with haplotype reconstructions (Figure 1 and Figure 2), excluding their involvement in the disease. However, families 670 and 672...
demonstrated positive lod scores for the 7 markers spanning the SPG11 candidate interval with combined pairwise lod scores greater than 3 at D15S778, D15S783, and D15S182. A significant multipoint lod score of 3.1 was obtained in this region in family 670 whereas it reached 2.5 for family 672. Haplotype reconstructions revealed the existence of a recombination event between D15S971 and D15S1044 in family 670, setting the centromeric boundary to D15S971 (Figure 1). The telomeric boundary was defined at D15S143 because of the loss of homozygosity between this marker and D15S1508 in family 672. In contrast, linkages to SPG11 (Figure 2) and SPG4 (data not shown) were excluded in family 671.

To our knowledge, this is the first description of HSP-TCC in patients of Arab origin. Originally described in Japan,1 HSP-TCC apparently shows a worldwide distribution and probably represents a common form of autosomal recessive HSP.7,8 Our patients share similar clinical and imaging manifestations with those described in other populations, and they add minor orofacial dysmorphism to the list of associated abnormalities. In addition, although Raynaud phenomenon in one of our patients may be coincidental, obesity was also noticed in a family from Germany linked to SPG11.9

We found no mutations in the coding sequence of the SPG7 gene or linkage to the SPG21/MAST or ACCPN loci in the 3 families, which supports the previous conclusion that peripheral neuropathy with agenesis of the corpus callosum and SPG11 are not allelic disorders.10 However, 2 of our 3 families demonstrated significant linkage to the SPG11 locus. Haplotype reconstruction in these families allows for the reduction of the candidate interval from 17.5 megabases (Mb) (approximately 25 centimorgans)7,8 to 13 Mb (approximately 17 centimorgans) flanked by markers D15S971 and D15S143. This region contains more than 120 known genes. The exclusion of linkage to SPG11 in the third family further demonstrates genetic heterogeneity in this disorder.7,8

Retrospective analysis of the clinical phenotype in light of these results reveals relatively similar neurological and imaging findings in the SPG11-linked and SPG11-unlinked families, suggesting that responsible genes may be functionally related. Still, there are a few subtle differences. Whereas patients from the 2 linked families initially had cognitive decline and later developed a highly homogeneous combination of motor deficit and mental impairment, patients from the unlinked family somewhat differed in the early manifestations as well as in the range of additional features. Two of the patients had gait disturbance, 1 was reported to have mild mental retardation since early childhood, 1 had extrapyramidal signs, and 2 showed no electrophysiologic evidence of peripheral neuropathy. Because each of these features and some variability between the affected siblings may be present in SPG11,7,8 these findings probably do not have discriminative clinical value and cannot distinguish our SPG11-linked and SPG11-unlinked families. Furthermore, parkinsonism was previously described in a South Korean family with HSP-TCC.11

In conclusion, our findings in HSP-TCC in Israel further confirm its worldwide distribution and genetic heterogeneity, and they significantly reduce the candidate SPG11 interval.

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Correspondence: Alexander Lossos, MD, Department of Neurology, Hadassah University Hospital, PO Box 12000, Jerusalem 91120, Israel (alos@hadassah.org.il).
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Figure 2. Multipoint linkage analysis. Lod scores are plotted according to the genetic map of chromosome 15 (http://research.marshfieldclinic.org/genetics) for the SG11-linked families 670 and 672 (solid line) and for the unlinked family 671 (dashed line). Arrows indicate the position of the SLC12A6 and ACP33 genes; CM, centimorgan.
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REFERENCES