Infantile bilateral striatal necrosis maps to chromosome 19q

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Abstract—*Background:* Infantile bilateral striatal necrosis (IBSN) encompasses several syndromes of bilateral symmetric degeneration of the caudate nucleus, putamen, and globus pallidus. Autosomal recessive IBSN is characterized clinically by developmental arrest beginning at age 7 to 15 months, dysphagia, choreoathetosis, pendular nystagmus and optic atrophy, and severe progressive atrophy of the basal ganglia on MRI. *Objective:* To map the gene causing IBSN. *Methods:* A 10-cM genome-wide linkage scan was initially performed on five affected and five unaffected individuals. The extended family was included in the analysis to narrow the candidate region. Logarithm of odds (LOD) score was calculated using the SUPERLINK program. *Results:* Linkage to the chromosomal region 19q13.32-13.41 was established (Z_{max} = 6.27 at theta = 0.02 at locus D19S412). Recombination events and a common disease-bearing haplotype defined a critical region of 1.2 Mb between the loci D19S596 proximally and D19S867 distally. *Conclusion:* IBSN maps to the chromosomal region 19q13.32-13.41. The presence of a common haplotype in all the patients suggests that the disease is caused by a single mutation derived from a single ancestral founder in all the families.

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Infantile bilateral striatal necrosis (IBSN; MIM-271930) is a rare neurologic disorder characterized by symmetric degeneration of the caudate nucleus, putamen, and occasionally the globus pallidus, with little or no involvement of the rest of the brain.[1] The clinical features of IBSN include developmental regression, choreoathetosis, dystonia, spasticity, dysphagia, failure to thrive, nystagmus, optic atrophy, and mental retardation.[2] Familial IBSN has rarely been reported.[3-8] In the families with mitochondrial inheritance, mutations of the adenosine triphosphatase 6 gene (complex V) were described.[9,10]

Subjects and methods. *Patients.* We ascertained six Israeli Bedouin families (five of them closely related) with IBSN. The clinical manifestations, radiologic evolution, and neuropathologic characteristics of the disease in the original family (figure 1) were described by Straussberg et al.[11] All the families are members of five interrelated Bedouin families belonging to a single kindred. The exact relationship of the sixth family to the other families is not known, but they bear the same family name and live in the same village as the other families.

The age at onset of the disease in the affected individuals ranged from 7 to 15 months. The most prominent neurologic findings were choreoathetoid movements of the face, trunk, and extremities, dystonia, horizontal pendular nystagmus, optic atrophy, and spastic quadriparesis. Gradual disappearance of the basal ganglia was evident on serial brain MRI scans (figure 2). Extensive metabolic workup was normal.[11]

We obtained informed consent either from all family members who agreed to participate in the study or from their legal guardians. The research study was reviewed and approved by the Human Subjects Committee of the Rabin Medical Center.

Microsatellite marker analysis. DNA was isolated from the blood samples by standard methods.[12] A 10-cM genome-wide linkage scan was initially performed at the Boston Children's Hospital Genomics Core Facility by use of a ABI PRISM linkage-mapping set (version 2.5; Applied Biosystems, Foster City, CA) marker set and standard techniques.

For additional microsatellite markers, primer sequences, marker order, and distances were obtained from the Center for Medical Genetics, Marshfield Medical Research Foundation, Genome Database, UCSC Genome Bioinformatics, and Ensembl databases. Markers were amplified from genomic DNA, according to methods specified by the manufacturers.

PCR products were separated on polyacrylamide gels and visualized by silver staining.

Linkage analysis. For the initial screening of linkage to the disease gene, genotyping of 10 family members (5 affected and 5 unaffected individuals) was performed. For each marker, visual comparison of the degree of homozygosity and genotype sharing in affected and unaffected individuals was performed.

In addition, genotyping of all family members and linkage analysis were performed for each marker that showed increased homozygosity or genotype sharing in the affected individuals.

Statistical analysis. The results of the two-point linkage analysis performed using the program SUPERLINK[13] with these markers are given in the table. We assumed a susceptibility allele with frequency 0.02 and a recessive mode of inheritance with penetrance 0.99. Marker allele frequencies were not available in this specific Bedouin population, and equal allele frequencies were

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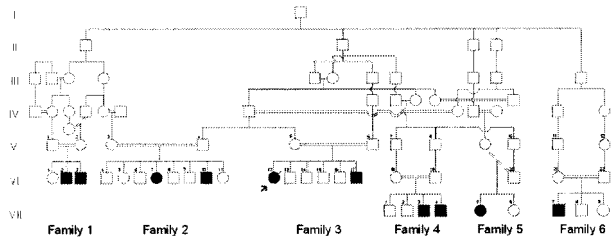

Figure 1. Pedigree of the family with infantile bilateral striatal necrosis. The exact relationship of Family 6 to the rest of the families is unknown. The filled symbols indicate affected individuals, and the arrow indicates the proband.

assumed. For logarithm of odds (LOD) score calculations, the number of alleles was set as the number observed in the pedigree, rather than the number observed elsewhere, to provide a conservative estimate of the LOD score. The LOD score calculations included all known parts of the pedigrees. Where exact connections between parts of the pedigree were not explicitly known, it was assumed that the parts of the pedigrees were unrelated.

Results. At the initial genome-wide screen, all five affected children were homozygous for the same allele for the marker D19S420 (not shown). On the basis of these results, we further genotyped the extended family for additional microsatellite markers near D19S420 (figure 3). Statistical analysis provided strong evidence for linkage of IBSN to chromosome 19q13.32-q13.41. Several markers yielded pooled 2-point LOD scores of >3.0 (see the table). A few recombination events were observed in the pedigrees, narrowing the candidate region to the chromosomal region of 7.4 cM between D19S412 (Individual II-3, Family 1) and D19S867 (Individual II-4, Family 2) (see figure 3). Haplotype sharing studies revealed complete homozygosity in all affected individuals for the markers cen-D19S604-D19S867-D19S553-D19S571-tel (see figure 3). Informative recombinations and the presence of the common haplotype indicated a minimal candidate interval for ISBN between D19S596 and D19S867.

Discussion. In this study, we evaluated six related consanguineous Israeli Bedouin families with autosomal recessive ISBN. Linkage of the disease to the chromosomal region 19q13.32-13.41 was established. The presence of the common disease haplotype strongly suggests the existence of a single founder mutation in all the families, as expected owing to the common origin of all the families.

Informative recombinations and the presence of the common haplotype indicated a minimal candidate interval for ISBN of a 1.2-Mb region that contains 63 known or predicted genes.

Research is underway to search for the disease-causing gene. The function of the candidate gene might be involvement in neuronal apoptosis or necrosis pathways. Because of the clinical similarities in our patients and the patients with mutations of the adenosine triphosphatase 6 gene (complex V),[9,10] genes encoding proteins involved in mitochondrial function should also be considered.

The focus will be on those genes that are ubiquitously expressed in the brain. One of the candidate genes in the region is the gene encoding ferritin light chain. A mutation in this gene causes a dominantly inherited adult-onset basal ganglia disease (MIM 606159), which presents with extrapyramidal features similar to those of Huntington disease. MRI scan in these patients is characterized by cavitation of the basal ganglia, and abnormal aggregates of ferritin and iron are detected on brain histochemistry. Sequencing of this gene revealed no disease-causing mutations in our patients.

Several of the other known genes are of potential interest as candidates, including *AP2A1*, *PNKP*, *SLC17A7*, and *NTF5*.

Adaptor-related protein complex 2, α1 subunit (AP2A1; MIM 601026), is a subunit of the clathrin-associated adaptor protein complex 2 that plays a role in protein sorting in the late-Golgi/trans-Golgi network and/or endosomes and recycling of synaptic vesicle membranes from the presynaptic surface. AP2A1 was found to be associated with Huntingtin-interacting protein 1 (HIP1; MIM 601767).[14] HIP1 potentially interacts with the protein causing Huntington's disease. Huntington's disease is characterized by atrophy of the caudate nucleus, progressive chorea, rigidity, and dementia.

Polynucleotide kinase 3'-phosphatase (MIM 605610) belongs to the mammalian polynucleotide kinase family. Polynucleotide kinases catalyze the 5' phosphorylation of nucleic acids and can have associated 3' phosphatase activity, predictive of an important function in DNA repair following ionizing radiation or oxidative damage.[15] This type of damage arises endogenously during normal cellular metabolism, and its repair is essential for cellular, including neuronal, survival.

Solute carrier family 17, member 7 (MIM 605208), encodes a human brain sodium-dependent inorganic

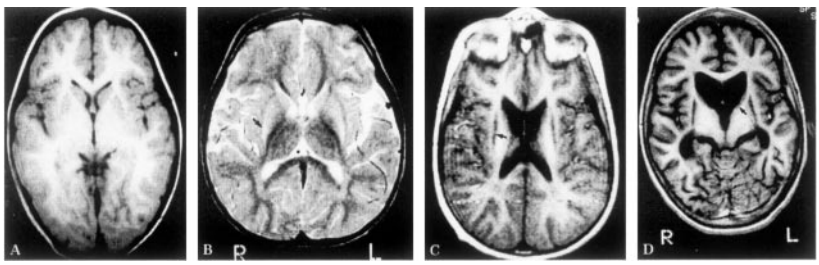

Figure 2. (A) Axial T1-weighted images of Patient VI-12 at 15 months. No abnormalities are seen. (B) Axial T2-weighted images of Patient VI-10 at 21 months. Note localized high signals only in the posterior putamen. There is no volume loss in the striatum (arrow). (C) Axial T1-weighted images of Patient VI-7 at 6 years. The caudate and putamina have diminished in size. Note the low signals from the putamina (arrow). (D) Axial T1-weighted images of Patient VI-12 at age 11 years. Only minimal residual caudate (arrow) and putamina are visualized. Note the diffuse parenchymal loss. (Reprinted with permission from Straussberg et al).[11]

Table *Two-point limit-of-detection scores for chromosome 19q markers*

	Recombination fraction θ											
Locus	0.000	0.001	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	Z_{max}	θ_{max}
D19S408	−∞	−2.46	1.53	2.48	2.97	3.26	3.44	3.55	3.61	3.63	3.63	.08
D19S900	−∞	4.96	5.87	5.99	6.00	5.95	5.86	5.75	5.63	5.49	6.00	.03
D19S574	−∞	2.65	4.57	4.95	5.11	5.15	5.14	5.10	5.02	4.93	5.15	.04
DMPK	−∞	3.09	4.22	4.51	4.63	4.68	4.67	4.63	4.57	4.48	4.68	.04
D19S412	−∞	5.28	6.16	6.27	6.26	6.19	6.10	5.98	5.84	5.70	6.27	.02
D19S606	−∞	2.09	2.60	2.81	2.92	2.96	2.97	2.96	2.93	2.88	2.97	.05
D19S596	2.74	2.66	2.80	2.85	2.85	2.82	2.79	2.74	2.68	2.62	2.85	.03
D19S604	4.80	4.88	4.73	4.58	4.44	4.29	4.15	4.00	3.86	3.72	4.88	.01
D19S867	−∞	4.99	5.80	5.85	5.79	5.68	5.55	5.40	5.23	5.07	5.85	.02
D19S553	−∞	0.43	3.31	3.90	4.17	4.29	4.33	4.32	4.28	4.21	4.33	.05
D19S571	−∞	−0.16	1.78	2.21	2.42	2.53	2.58	2.61	2.60	2.57	2.61	.06

phosphate cotransporter that transports glutamate into synaptic vesicles.[16] This gene is highly conserved during vertebrate evolution.[17] MRNA is most abundant in neuron-enriched regions such as the amygdala and hippocampus, moderate levels of expression are observed in glial-enriched areas such as the corpus callosum, and low levels are observed in the substantia nigra, subthalamic nuclei, and thalamus. Glutamate transport malfunction can lead to the accumulation of excessive glutamate in the synapse, with subsequent neurotoxicity. It was suggested that disturbed glutamate transport can be partly involved in the motor neuron devastation and latent thalamic degeneration in human neurologic diseases such as spinal muscular atrophy type 1,[18] ALS,[19] Alzheimer's disease,[20] and Parkinson's disease.[21]

Neurotrophin 4/5 (NTF5; MIM 162662) plays a physiologic role essential for hippocampus- and amygdala-dependent long-term memory, as was shown in the NT4−/− mice by using fear conditioning.[22]

All these genes are potential candidates for IBSN, and continuing studies will, it is hoped, lead to the identification of the disease-causing gene.

Electronic database information. Accession numbers and URL for data presented herein are as follows:

Center for Inherited Disease Research: http://www.cidr.jhmi.edu/ (for the Weber version 9 marker set)

Center for Medical Genetics, Marshfield Medical Research Foundation: http://research.marshfieldclinic.org/genetics/ (for identification and order of microsatellite markers)

Ensembl: http://www.ensembl.org/ (for identification of candidate genes)

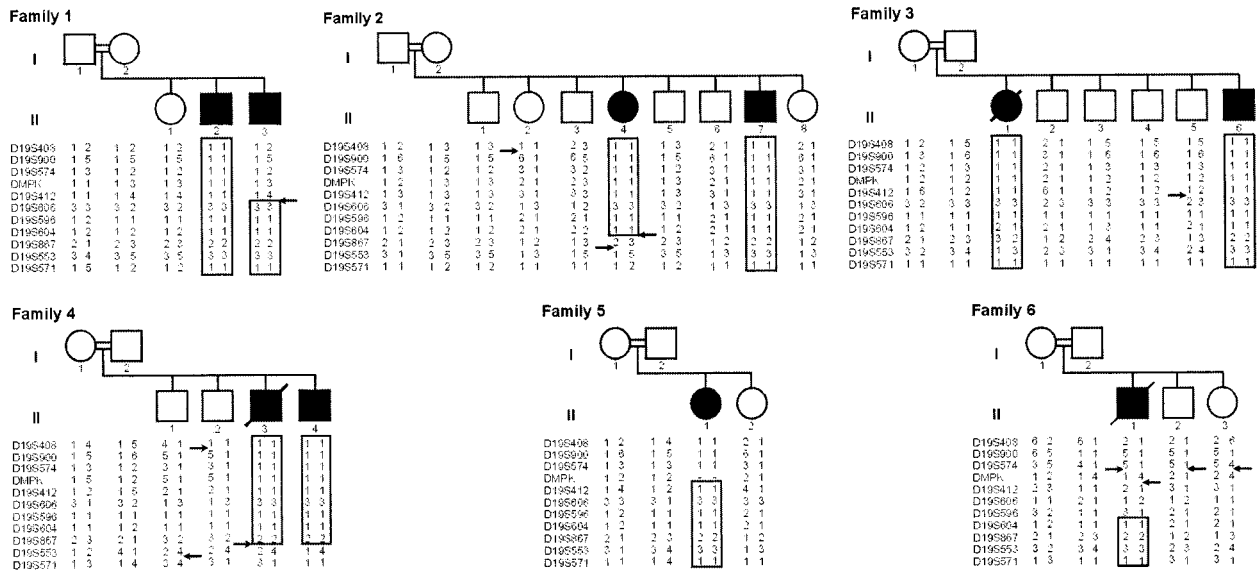

Figure 3. Haplotype analysis of the individual pedigrees for chromosome 19q13.32-q13.41. The marker order is cen-D19S408-D19S571-tel. The boxed regions indicate the homozygous regions in each affected individual. Arrows indicate informative recombinations.

Genome Database: http://www.gdb.org/

Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/Omim/ (for IBSN [MIM-271930])

UCSC Genome Bioinformatics: http://genome.cse.ucsc.edu/ (for identification of candidate genes)

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