Fine Linkage Mapping of a Novel Hereditary Spastic Paraplegia Gene Locus

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Hereditary Spastic Paraplegia (HSP) is an inherited human disease characterized by degeneration of the upper motor neurons resulting in spasticity and limb paralysis. HSP is inherited as either an autosomal dominant, autosomal recessive, or X-linked trait. Genes associated with HSP have been mapped to at least 15 different loci. My research Fall Semester 2000 was focused on mapping the location of a novel HSP gene in a kindred containing 15 individuals affected by this disease.

Genotyping of individuals in the kindred using polymorphic microsatellite markers allows for linkage analysis to be performed which determines whether an association exists between the inheritance of a given allele and the disease. Previously, genotyping and linkage analysis eliminated the already described HSP loci as possible disease causing loci in this kindred. A genome-wide screen using approximately 240 polymorphic microsatellite markers evenly spaced throughout the genome resulted in the identification of several candidate gene regions. More detailed genotyping and linkage analysis of markers within each region identified a single disease locus on chromosome 7q, termed SPG17.

identify new polymorphic markers within the locus, which will narrow the region further. Candidate genes at this locus are being identified from the Human Genome Project database. We are pursuing mutational analysis of these genes by direct sequencing of the coding regions. No mutations have been found in the affected individuals of the kindred in genes tested to date.

Molecular characterization of the gene responsible for HSP linked to the SPG17 locus will help gain a better understanding of the human nervous system, an understanding that could lead to better treatments and cures for this and other neurological disorders.