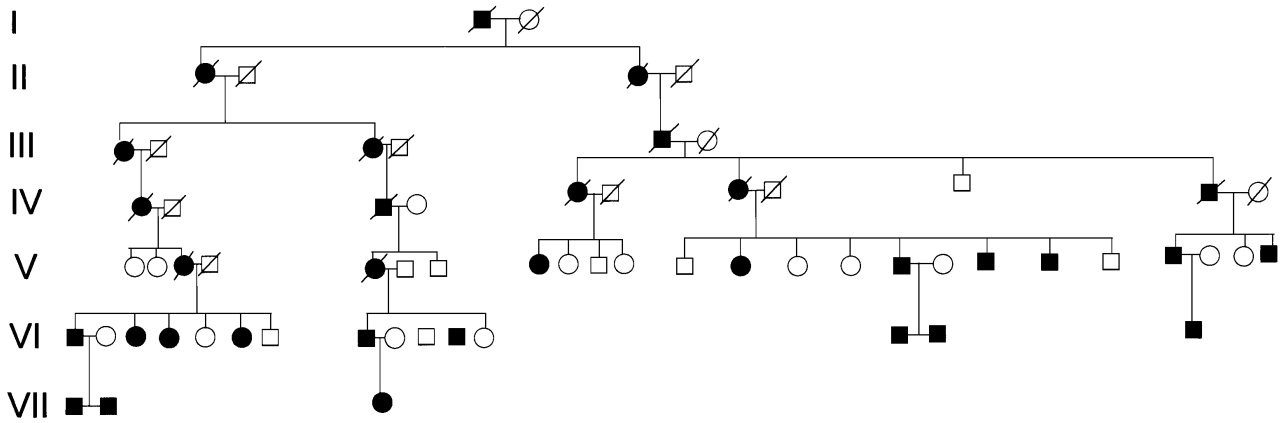
Clinical Genetics, I



Partial pedigree from the Venezuelan Huntington's disease family. DNA from transformed lymphoblastoid cell lines developed from these families was used to identify the Huntington's disease chromosome and the Huntington's disease gene. Data used by permission of Nature Medicine (Gusella JF et al: Nature 1983; 306:234–238).

Huntington's Disease: From Disease to Gene

Huntington's disease is an autosomal-dominant neurodegenerative disease originally described by George Huntington in 1872. Its pathology is restricted to the brain, with selective regional atrophy of medium spiny neurons in the caudate and putamen and loss of large neurons in the deep layers of the cerebral cortex, but with relative sparing of the basal forebrain and the hippocampus. Disease manifestations include abnormal involuntary movements (chorea and dystonia), cognitive deterioration (intellectual slowing progressing to profound dementia), and emotional abnormalities (depression, psychosis, and/or pervasive personality changes). Symptoms generally begin in middle age, although onset in the very young or the very old has been described. The disease progresses to death over 15–20 years.

In 1983, on the basis of a study of two Huntington's disease families, linkage between the Huntington's disease gene and a DNA marker that mapped to the human chromosome 4 was established. One family formed an American pedigree. The other family was from the largest known Huntington's disease pedigree, living on Lake Maracaibo, Venezuela, and numbering over 3,000 members and extending from the early 1800s, who inherited the disease from a common ancestor (see figure). An anonymous DNA marker detected the abnormal restriction fragment length polymorphism (RFLP), which showed close linkage to the Huntington's disease gene in the two families. However, it was not until 1993 that painstaking study of this area of chromosome 4 resulted in identification of the Huntington's disease gene.

The Huntington's disease gene, IT15, includes a polymorphic trinucleotide repeat that is expanded and unstable in Huntington's disease. Whereas persons without Huntington's disease have about 11–35 CAG repeats at the IT15 gene, people with Huntington's disease have 36 to more than 80 CAG repeats (see table). Longer repeats are associated with earlier onset and more severe disease. Current research focuses on the question of how the trinucleotide repeat expansion in Huntington's disease causes disease symptoms. Most likely, the protein product of the Huntington's disease gene, called huntingtin, in its mutant form binds to essential cell proteins. This pathologic interaction eventually causes nerve cell death through as yet undefined destructive processes.

Range of Allele Sizes (Number of Repeats)	Normal Chromosomes		Huntington's Disease Chromosomes	
	Number	Frequency	Number	Frequency
≥48	0	0	44	0.59
42–47	0	0	30	0.41
30–41	2	0.01	0	0
25–30	2	0.01	0	0
≤24	169	0.98	0	0
Total	173	1.00	74	1.0

Number and frequency of CAG repeats near the 5′ end of the IT15 gene in Huntington's disease and normal subjects; the triplet codes for glutamine. Most normal chromosomes have ≤24 repeats, whereas most Huntington's disease chromosomes have ≥42 repeats. Data used by permission of Cell Press (MacDonald ME et al: Cell 1993; 72:971–983).

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