HOMOZYGOUS EXPRESSION OF A DOMINANT GENE CAUSING PERONEAL MUSCULAR ATROPHY (CHARCOT-MARIE-TOOTH DISEASE)

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This study involves the presentation of a kindred from Southwestern Louisiana showing 66 individuals who were heterozygous for a rare dominant gene for a type of Charcot-Marie-Tooth disease with hypertrophy of peripheral nerves. Two marriages between heterozygotes resulted in the occurrence of five homozygous offsprings. Clinical features of these previously undescribed homozygotes are compared to the clinical features of the classic type of heterozygote. The value of using nerve-conduction time to detect the asymptomatic heterozygote for Charcot-Marie-Tooth disease is discussed.

To our knowledge no previous report has described the features associated with a double dose of a dominant gene for peroneal muscular atrophy (Charcot-Marie-Tooth disease). Indeed, there are few descriptions of the homozygous genotype for any condition caused by a rare autosomal dominant gene. Such descriptions include two types of brachydactyly (Mohr and Wriedt 1919, and Edwards and Gale 1970); multiple telangiectasia (Snyder and Doan 1944); a type of distal myopathy (Welander 1957); and a type of achondroplastic dwarf (Hall et al. 1969).

The kindred represented in the figure was ascertained through the unusual features presented by No. 66 at age 36 years. Field trips with neurological examinations disclosed a diagnosis of classical Charcot-Marie-Tooth disease in both parents of the propositus and in 64 other relatives, although a year earlier electromyography and nerve conduction studies supported a diagnosis of hypertrophic interstitial polyneuritis in the propositus.

As can be seen from the pedigree, 2 heterozygous parents (No. 28 and No. 29) had 2 similarly affected offsprings (No. 61 and No. 67); 1 unaffected offspring (No. 64), and 4 homozygotes (Nos. 62, 63, 66, and 68) with features simulating Dejerine-Sottas syndrome. According to family information, No. 63 was a homozygote who had 4 heterozygous children (3 boys and 1 girl). The mother (No. 63) and all 4 of her offsprings were killed in Hurricane Camile in 1957. Please note the error in the pedigree for symbol No. 108 which should have shown 3 of these heterozygous offsprings. No. 62 and No. 82 also were reported by the family to have had the symptoms of the homozygote. All heterozygotes in this pedigree were traced to progenitors No. 1 and No. 2 who, according to Church records, were married in Southwestern Louisiana in 1845 where most living descendants reside today.

The two living homozygotes (No. 66 and No. 68) available for study showed a severe mixed sensory and motor polyneuropathy with associated involvement of the facial nerves. There was a severe kyphoscoliosis, markedly thickened peripheral nerves, strabismus, and pes cavus. Cerebrospinal fluid protein was markedly elevated and a peripheral nerve biopsy of No. 66 was consistent with hypertrophic interstitial neuritis. These two cases clearly conformed clinically to the classical descrip-

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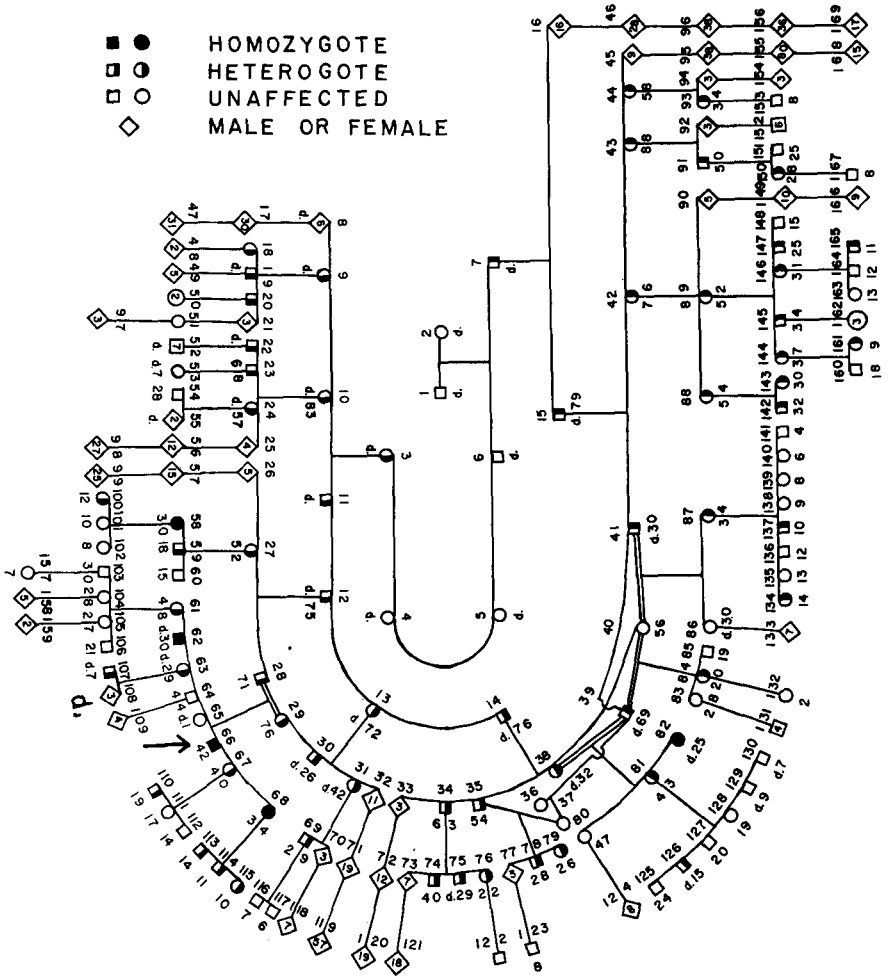

Figure. Pedigree of an autosomal dominant gene in a kindred of Acadian descent for peroneal muscular atrophy (Charcot-Marie-Tooth disease) with hypertrophy of peripheral nerves. Homozygotes simulate Dejerine-Sottas Syndrome.
Number above symbol identifies symbol; number below symbol represents age or age of death in years; number within symbol indicates number of individuals represented by the symbol. Please note that, due to pedigree-construction error, identification symbol 108 should have indicated 2 male and 1 female heterozygote who were deceased.

tions of Dejerine-Sottas syndrome, but histologically biopsy of nerve was more similar to Charcot-Marie-Tooth disease.

Typical features of heterozygotes included a mild to moderate motor polyneuropathy with principle involvement of the lower extremities. Occasional sensory abnormalities were noted with mild scoliosis and pes cavus. Variable degrees of nerve thickening were noted in the majority of cases.

Age of onset of symptoms appeared in early childhood in the homozygotes with consequent crippling neuropathy evident by age 10 years. The heterozygotes were usually asymptomatic until 20 to 30 years of age. With some exceptions, they were never severely affected.

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TABLE

COMPARATIVE FEATURES OF HETEROZYGOTES AND HOMOZYGOTES

	Heterozygotes	Homozygotes
Stature	normal	short
Pes cavus	present	present
Kyphoscoliosis	absent	present
Scoliosis	variable	present
Facial weakness	absent	present
Thickened nerves	variable	very marked
Sensory abnormalities	variable	marked
Strabismus	absent	present
Exotropia	absent	present
Motor and sensory neuropathy	mild to moderate	severe
Slowing of nerve conduction	moderate	severe
Elevated cerebrospinal protein	mild and variable	marked

Nerve-conduction studies were slowed markedly in the 2 homozygotes to less than 25% of normal (7 and 1 M/sec in the arm). Severe denervation was present in all extremities and the facial muscles. Heterozygotes showed slowing of nerve conduction to less than 50% of normal with ranges of 10 to 35 M/sec in the arm (normal 49-65 M/sec) with a mean of 18 M/sec. Ranges of 10 to 22 M/sec were noted in the peroneal nerves with no essential difference in the range of conduction velocities according to age or sex. Some velocities were nonmeasurable due to severe atrophy of the intrinsic foot or hand muscles. (See Table for comparative features of heterozygotes and homozygotes.)

Although this report was not designed to include a case history of a homozygote or a heterozygote, it is of interest to note from a review of previous admissions the diagnostic problem which prevailed in the propositus prior to age 35 years. With a diagnosis of Friedreich's ataxia, tic douloureux, and bilateral partial nerve deafness, an operation was performed on cranial nerve V at age 27 years to relieve severe shooting pains in the right jaw and right temple. These pains reoccurred at age 32. At age 30 the superior rectus muscle was excised from the sclera and reinserted 7 mm posterior to the original insertion to correct an alternating exotropia.

Like many rare dominant genes for neurological disorders which typically are recognized only in the heterozygote, there was a great range of expressivity from no apparent clinical features to barely recognizable or slight effects, to effects which not only were readily recognized but also impaired job opportunities. Based on clinical observations, the heterozygous state of the gene for Charcot-Marie-Tooth disease was not 100% penetrant. Heterozygotes with nerve-conduction time less than 50% typically were unaware of affection and could not be detected clinically, but penetrance was 100% when subclinical cases were identified by reduced nerve-conduction time of less than 50%. This observation confirmed the findings of Dyck et al. (1963) who recognized the value of nerve-conduction studies to identify the apenetrant carrier of this autosomal dominant gene.

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