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Clinical and molecular genetic study of a large German kindred with Gerstmann-Sträussler-Scheinker syndrome

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Article abstract—We have verified, by full open reading frame sequencing, the presence of an amino-acid-altering mutation in codon 102 of the scrapie amyloid protein gene in three affected members of a large and well-documented German family with experimentally transmitted Gerstmann-Sträussler-Scheinker syndrome. In addition, we identified the mutation by partial sequencing or DNA restriction enzyme analysis in three of 12 presently healthy family members with an affected parent, and none of 12 members without an affected parent. Thus, a total of six of 15 family members at risk for the disease (including the three established cases) had the same codon 102 mutation, a proportion consistent with the autosomal dominant inheritance pattern of disease expression. It is undetermined whether the mutation influences susceptibility to infection by an exogenous agent or is itself a proximate cause of disease.

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Gerstmann-Sträussler-Scheinker syndrome (GSS) is a transmissible spongiform encephalopathy of predominantly familial occurrence, characterized by a usually slowly progressive spinocerebellar dysfunction and dementia, and the neuropathologic findings of multicentric amyloid plaques and a variable degree of

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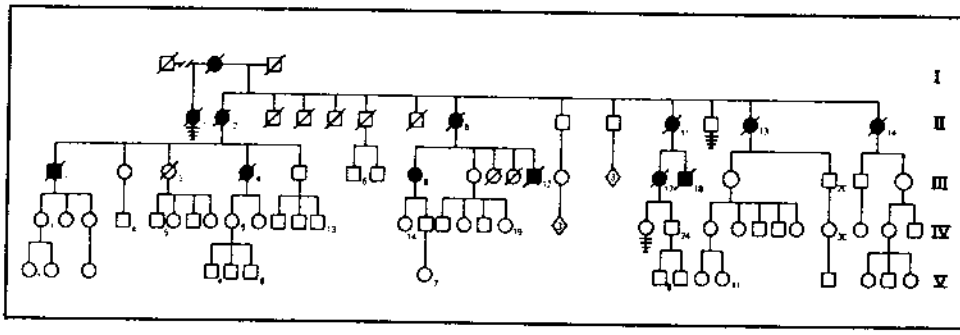


Figure 1. GSS family pedigree. Affected members are indicated by black symbols. The PRIP open reading frame was fully sequenced in patients III-1, III-8, and III-17. Restriction enzyme fragment analysis was performed for 24 unaffected family members in generations II, III, IV, and V.

spongiform change. A mutation in the scrapie amyloid protein gene (PRIP) on chromosome 20 has recently been identified in unrelated English, American, and Japanese families with the disease.[1,2] We earlier reported finding the same mutation in three affected members of a German family[3]; here we present a detailed molecular genetic analysis of this family, and speculate about the significance of the mutation.

Methods. *The family.* First reported in 1980,[4] and more extensively described in 1981,[5] this family is presently in its fifth generation since the first identified case of disease, as shown by the pedigree in figure 1. Six members in each of the second and third generations have died of the disease; four were neuropathologically confirmed cases, and brain tissue from one has transmitted a spongiform encephalopathy to mice.[6] The disease has occurred in an autosomal dominant pattern, and numerous members of the fourth generation are approaching the age of risk. All accessible living family members, including two affected (III-8 and III-17) and 24 unaffected individuals, were bled in 1987. The lymphocytes were separated, transformed with Epstein-Barr virus, and stored at −70 °C until extracted. Genomic DNA extractions from lymphoblast cultures were performed using conventional techniques described previously.[7] DNA was also extracted from stored frozen brain tissue of the transmitted case (III-1) according to a slightly modified protocol.[8]

DNA sequencing and restriction enzyme fragment analysis. Two oligonucleotides corresponding to opposite ends of the PRIP open reading frame (ORF) were synthesized and used in polymerase chain reaction (PCR) to amplify the ORF region from each DNA sample. The amplified DNA fragments were then subcloned into pGEM5z (f+) plasmids, and at least four subclones were sequenced in both directions and analyzed in acrylamide gels. The validity of restriction endonuclease *Dde* I for detecting the codon 102 mutation was tested in family members whose PRIP ORF had been sequenced, and the enzyme was then used to search for the mutation in additional family members whose ORF was not sequenced. Methodologic details for these procedures have been published previously.[1,3]

Immunohistochemistry. Formalin-fixed brain tissue was processed in standard fashion for histologic sections and immunostained using either a rabbit polyclonal antibody raised against gel-eluted hamster scrapie amyloid protein (reactive with human PrP), or a mouse polyclonal antibody raised against a synthetic 43-amino acid polypeptide homologous to the β-A4 amyloid protein of Alzheimer's disease. Appropriate alkaline phosphatase-conjugated secondary antibodies were developed with diaminobenzidine.

Results. *Clinical and pathologic findings.* Detailed descriptions of the proband (III-4), her brother (III-1), and her cousin (III-18) have been published in the German literature[5]; we summarize them here, together with the two additional cousins for whom we have molecular genetic data.

E.R. (III-4). In late 1968, this 41-year-old woman first noted unsteadiness during long walks, and pain in the left leg; these symptoms were quickly followed by difficulty in speaking and swallowing. When first seen, 4 months later, she had bilateral lateral gaze nystagmus, dysarthria, dysphagia, decreased lower limb deep tendon reflexes, and an ataxic finger-to-nose test. No mental or emotional deterioration was noted. When next seen, in 1970, she had a more pronounced ataxic gait and marked dysarthria and dysphagia, plus a slight head-holding tremor. In 1972, she showed a severely ataxic gait, bilateral decrease in hearing, and a clearly abnormal mental status, with memory loss, compulsive crying, aggressivity, and an absence of reaction to questions and commands. An EEG showed diffuse abnormalities but no periodic activity. By early 1974, she had become cachectic, with constant ataxic, athetotic defensive movements of the arms, and a flaccid paralysis of the legs. She continued to have speaking and swallowing disturbances, and her hearing impairment progressed to complete deafness. She died in July 1974, 5 years after the onset of symptoms.

Neuropathology. The brain weighed 1,100 grams, with moderate diffuse atrophic changes. Microscopically, the cerebral cortex showed severe spongiform change, glial proliferation, and numerous multicentric amyloid plaques. Plaques also occurred in the brainstem nuclei, and were particularly prominent in the cerebellar cortex. The dentate nuclei, inferior olives, and posterior columns of the spinal cord all showed marked degenerative changes.

Immunohistochemistry. Amyloid plaques in sections of cerebral cortex stained with antibody to scrapie amyloid protein, but not with antibody to the β-A4 amyloid of Alzheimer's disease.

E.S. (III-1). In 1972, this 53-year-old man began to experience severe headaches, frequent stuttering, and occasional whispering speech, followed by weakness and unsteadiness when walking. In 1974, he was noted to have a moderately ataxic gait, bilateral nystagmus, dysphonia, and clear signs of mental deterioration, including irritability, memory loss, and compromised learning ability. During the next 5 years, ataxia progressed to the point that he became confined to his bed, with failing vision and hearing, hoarseness and dysarthria, and increasingly autistic behavior. Repeated EEG studies showed progressive generalized slowing but no periodic activity. When hospitalized in 1977, he had a global cerebellar syndrome, severe hearing and visual impairment (including bilateral abducens paresis, horizontal and vertical gaze nystagmus, saccadic eye movement, and reduced optokinetics), pyramidal signs, fine bilateral myoclonus of both forearms, and advanced dementia. He died in 1978, 6 years

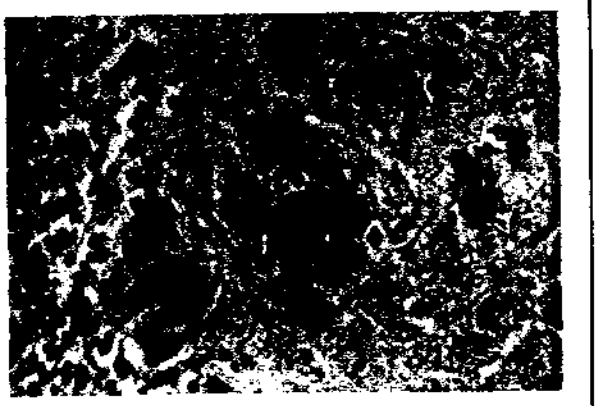


Figure 2. Immunohistologic study of a formalin-fixed section of cerebral cortex from patient A.N. (III-8). A multicentric plaque is stained with antibody to scrapie amyloid protein (PrP); photographed at ×128 magnification before 54% reduction. No staining was seen in an adjacent section incubated with antibody to the β-A4 amyloid protein of Alzheimer's disease.

after the onset of illness.

Neuropathology. The brain weighed 1,180 grams, and was without gyral atrophy or dilated ventricles. Microscopically, the main finding was a diffuse distribution of multicentric and kuru-type amyloid plaques, particularly abundant in the cerebellar cortex. There was also a marked diffuse gliosis, but no spongiform change and no spinocerebellar degeneration.

Animal transmission studies. Frozen brain-tissue homogenate was inoculated into a rhesus monkey and a squirrel monkey at our NIH laboratory: both animals died without neurologic disease 6 to 7 years after inoculation. Homogenate from a different frozen brain sample was inoculated into mice by Tateishi et al[6]; 20 of 28 mice developed neuropathologically verified spongiform encephalopathy that was transmitted on subsequent passage in mice.

S.F. (III-18). In 1977, this 35-year-old man became aware of unsteadiness of gait and trouble articulating words when excited. First examined in 1978, he showed marked cerebellar dysfunction: right-sided nystagmus, saccadic eye movements, poorly articulated speech, and an ataxic gait. Although emotionally labile, his intellect was unimpaired. Physical disability progressed over the next year, and he became cachectic, weak, unable to walk more than a few meters, and had increasing speech difficulty. His mental status declined, with a limited attention span and slowed performance time; recent memory was now also slightly impaired. All laboratory tests were normal, including EEGs recorded in 1978 and 1980. He died in 1981, 4 years after the onset of illness. Autopsy was not performed.

A.N. (III-8). In 1980, this 52-year-old woman visited her local physician because of anxiety and an inability to concentrate. She was not seen again until 1983, with a complaint of difficulty in walking down stairs. She was evaluated neurologically in 1984, with findings of gait and truncal ataxia and stuttering speech. The remainder of the examination was normal, as were CT and an EEG. Thereafter, her cerebellar syndrome very slowly worsened, so that by late 1987 she had become bedridden, with barely understandable speech and athetotic arm movements. By May 1989, her ataxia had rendered her completely helpless, in spite of which she appeared euphoric and without concern for her physical deterioration. In January 1990, she was mute, had marked grip ataxia, generalized spasticity, intention tremor, nystagmus, and severe muscle atrophy. She died in July 1990, 7 to 10 years after the onset of illness.

Neuropathology. The brain weighed 1,120 g, and was grossly unremarkable except for mild diffuse cerebral atrophy and depigmentation of the substantia nigra. Microscopic examination is not yet complete, but preliminary observations revealed a profusion of faintly eosinophilic amyloid plaques throughout the cerebellar and cerebral gray matter, and the cerebral cortex also showed mild spongiform change with occasional intraneuronal vacuolation, neuronal loss, and astrocytic proliferation.

Immunohistochemistry. Plaques in sections of cerebral and cerebellar cortex stained with antibody to scrapie amyloid protein (figure 2) but not with antibody to the β-A4 amyloid of Alzheimer's disease.

K.F. (III-17). Early in 1986, this 58-year-old woman lost her footing while wading in the ocean, and soon after experienced progressive unsteadiness on her feet, often needing support, and occasionally falling. She was evaluated in December 1986 and again in April 1987; she was found to have a grossly ataxic gait and poor general coordination, as well as a mild dysphasia and memory loss. MRI, CT, and EEG studies were normal. She remained at home for the duration of her clinical course, which was marked by a relentless progression of cerebellar symptoms, with eventually disabling difficulties in walking, talking, and swallowing, and an uncharacteristically aggressive and hostile attitude toward her family. She died in August 1988, 2½ years after the onset of illness. Autopsy was not performed.

Other affected family members, for whom medical reports are not available, were described by their relatives as having the same general clinical course, characterized by a slowly progressive cerebellar syndrome that was usually associated with some degree of mental or behavioral deterioration in the later stages of disease. For the entire group of 13 affected family members, the age at onset of illness ranged from 30 to 57 years (mean, 46 years), and the clinical duration extended from 3 to 9 years (mean, 6 years).

Sequence of PRIP open reading frame. In order to assess directly the presence of mutations, full sequencing of the PRIP ORF was performed for three affected family members (III-1, III-8, and III-17); in addition, sequencing limited to the region containing codon 102 was performed for five unaffected family members. Figure 3 presents these results. Each of the affected members had an identical C to T single base substitution in codon 102, resulting in a change of the encoded amino acid from proline to leucine. The substitution was found in three of four subclones in III-1, three of seven subclones in III-8, and three of six subclones in III-17, indicating that all three patients were heterozygous for this mutation.

Four of the five unaffected family members had the correct codon 102 CCG sequence in all examined subclones. The fifth unaffected member (III-6) had a CCG to CCC substitution in two of eight subclones, which does not result in an amino acid alteration because both CCG and CCC code for proline. At 60 years of age, he is older than the oldest age at onset in any member affected to date and thus may no longer be at risk.

Restriction fragment analysis of PRIP open reading frame. The mutation in codon 102 creates a third re-

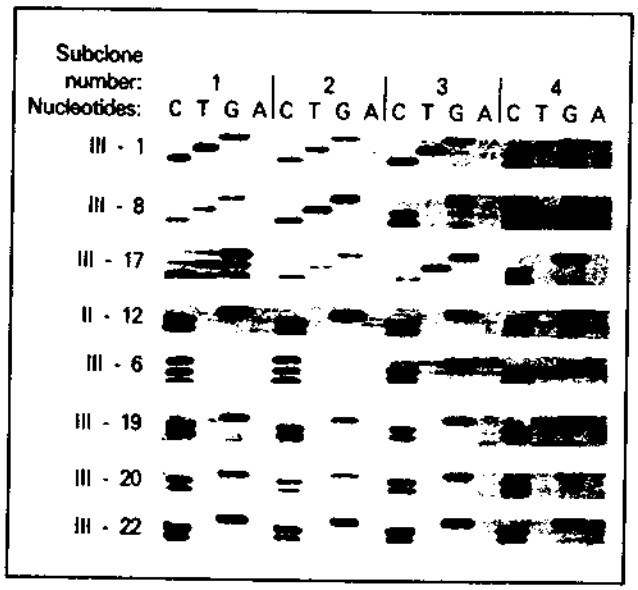


Figure 3. Nucleotide sequence in codon 102 of the PRIP open reading frame in three GSS cases (III-1, 8, and 17) and five unaffected (II-12, III-6, 19, 20, and 22) family members. The mutated CTG sequence in the GSS cases occurred in three subclones from III-1 and III-17, and in two subclones from III-8. The normal CCG sequence occurred in the remaining subclones from these patients, and in all subclones from the five unaffected members (except for two subclones from III-6 which had an unusual CCC sequence).

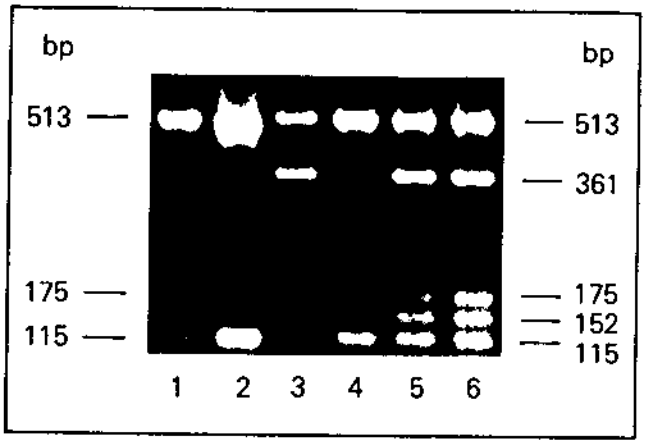


Figure 4. Gel separation of restriction enzyme Dde I-cleaved PRIP open reading frame fragments in six healthy GSS family members at risk for the disease; three have the mutation (lanes 3, 5, and 6), and three are normal (lanes 1, 2, and 4).

striction site for *Dde* I, in addition to the two naturally existing *Dde* I sites in this sequence. A normal allele is cut into three fragments of 175, 513, and 115 nucleotides, but in a mutated allele the middle 513-nucleotide fragment is cut into two pieces of 152 and 361 nucleotides. After DNA fragment patterns had been established for the three affected family members,[9] we screened *Dde* I-digested PRIP ORF fragments in 24 unaffected members of the family; the mutation was present in 3/12 members with an affected parent, and 0/12 members with an unaffected parent (results from six of these individuals are shown in figure 4).

Discussion. We documented a point mutation in codon 102 of the PRIP coding region by full sequencing in three affected members of a large and well-studied German family with GSS, including a patient from whose brain the disease was transmitted to experimental animals. We also found, by partial sequencing or restriction enzyme analysis, the same mutation in three of 12 presently healthy family members with an affected parent. Thus, a total of six of 15 family members at risk for GSS (including the three established clinical cases) carry the mutation, a proportion consistent with the autosomal dominant inheritance pattern shown by the disease itself.

Because the mutation in codon 102 is not found in Creutzfeldt-Jakob disease (CJD) or kuru,[9] or even in all families with GSS,[2,10,11] it is clearly not a sine qua non for the transmissible (or replicative) property of the agent that causes spongiform encephalopathy. It and other mutations recently identified in patients with GSS[2,10] and CJD[3,12-18] may all perform the same function of altering the structure of the encoded precursor protein just enough to facilitate its conversion to the insoluble β-pleated sheet of amyloid fibrils. In this regard, it may be significant that an older member of our GSS family, with a CCC sequence in codon 102 that does not result in an amino acid change, has not developed the disease.

Whether the mutation in codon 102 of the PRIP gene is responsible for the clinical and pathologic characteristics of GSS is another question. We are disinclined to agree with the proposal that the presence of the mutation is characteristic of an ataxic form of GSS.[1] Some affected members of the French family[19] and most affected members of the American (Indiana) kinship[11] without this mutation also had a major cerebellar component to their illness, and ataxia is prominent in all patients with kuru[20] and a majority of patients with CJD,[21] but none shows the codon 102 mutation.[3,9]

Moreover, there is considerable individual clinical and pathologic variation among affected members within a single kinship, as is also true in CJD families. In our German kindred with the mutation, as well as in the Indiana kindred without the mutation, no single clinical sign was invariably present in all affected members; dementia, behavioral disturbances, cerebellar and corticospinal signs, and abnormal movements all varied from patient to patient, as did age at onset (3rd to 7th decade) and the duration of illness (3 to 10 years). Even the pathology is variable; although all patients appear to have prominent multicentric plaques composed of the scrapie amyloid protein, the spongiform changes in our three autopsied patients varied from severe to absent, and two patients in the Indiana kindred had widespread neurofibrillary tangles with minimal spongiform change.[22] None of these pathologic features appears to be correlated with the clinical course (or with experimental transmissibility) in these or other reported families, but the number of patients for which such comparisons can be made is still very limited.

It is possible that mutations in the amyloid precursor gene influence the time frame of disease, analogous to

the polymorphisms linked to genes determining short and long incubation times of scrapie-infected mice[23-25] and sheep.[26] Such mutations might be responsible for the comparatively short incubation period (early age at onset) and long clinical course of GSS, which in turn could promote the development of plaques in the brain. Precedent for a relationship between disease duration and plaque formation is suggested by the fact that, in Japan, a form of CJD with plaques transmits both spongiform change and plaques to mice on primary isolation, which typically takes 2 to 3 years, but on subsequent passages, with much shorter incubation times, the plaques disappear.[27] However, the individual variability from patient to patient noted above and the absence of any amyloid precursor gene mutations in the clinically comparable Indiana kindred mean that such mutations cannot be the only determining factors even of this characteristic.

In point of fact, it is probably premature at this time to emphasize any clinical subclassifications of GSS, or to attempt to redefine GSS, solely on the basis of molecular genetics. The syndrome was originally described on clinical-pathologic grounds that are sufficiently distinctive to warrant their continued use as diagnostic criteria,[28] and transmission to experimentally inoculated animals secures its position as a variety of transmissible spongiform encephalopathy.[6,29] What is needed now is a renewed attention to the careful clinical-pathologic documentation of cases and families[10,11,19,22,30-32] together with complete gene sequencing data and transmission studies, in order to build a base upon which genetic correlations may eventually be made.

Acknowledgments

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