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Gerstmann-Sträussler-Scheinker disease in an Alsatian family: clinical and genetic studies

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Abstract

The clinical progression of Gerstmann-Sträussler-Scheinker disease in a family of Alsatian origin is reported. The age of onset and the duration of evolution were variable. The clinical picture became more complex over the generations: in the first generations, isolated dementia and in later generations a triad of pyramidal, pseudobulbar syndromes and dementia associated with spinal cord and cerebellar features. Prion gene analysis showed that four surviving patients carry double missense changes at codons 117 and 129, identical to those found in one case at necropsy and 10 other healthy members of the family. The missense changes were not found in 100 controls. No member of the family had modification of codons 102, 178, or 200. The lod score suggests linkage between the missense change at codon 117 and Gerstmann-Sträussler-Scheinker disease in this family.

In 1982, Warter *et al*¹ reported observations on a family of Alsatian origin in which at least eight members presented with Gerstmann-Sträussler-Scheinker (GSS) disease. This familial disease of autosomal dominant transmission^{2,3} can sometimes be transmitted to laboratory animals via intracerebral inoculation of brain homogenates from GSS patients whose disease has incubated for periods of months to years. The infectious agent has not as yet been identified, but a protease-resistant isoform of the prion protein,^{4,5} PrP, has been found in these patients' brains. Molecular genetic studies have recently detected a polymorphism of the PrP gene in GSS families,⁶ in particular a missense variant at codon 102 resulting in a substitution of leucine (leu 102) for proline (pro 102).⁷⁻⁹ Tateishi *et al* have reported in one member of the Alsatian family, a missense PrP variant with an alanine (GCA) to valine (GTG) change at codon 117 and a methionine (ATG) to valine (GTG) change at codon 129 on the same PrP allele. In this case, the attempts to transmit GSS to animals were negative.⁵ We summarise here the clinical and genetic studies in this family (AND family).

Subjects and methods

The family tree includes 76 subjects over six generations. We have usable clinical and genetic data for 65 (fig).

PrP gene analyses—High molecular weight

DNA was prepared from the frozen brain tissue of patient IV-28 and from leucocytes of 47 living family members. The PrP coding region was amplified by the polymerase chain reaction (PCR) method, and the substitutions in codons 102, 117, 129, 178, and 200 were detected by dot-blot hybridisation and PvuII restriction mapping of the PCR-amplified DNA.⁸ The results were compared with those from 100 control patients: 20 patients from the same town as the GSS family, half of whom had Alzheimers' disease, and 80 white subjects healthy or having other neurological diseases. *Genetic study*—The family data were analysed for genetic linkage with the linkage programs version 4.7 (R).¹⁰ We assumed that the disease followed a dominant mode of inheritance with penetrance depending non-linearly on age, from 0% at age 19 to 100% at 60 and over.

Results

The eight cases previously reported¹ and four new cases are summarised in table 1. In three cases (IV-3, IV-9, and IV-28) a cerebral biopsy specimen showed numerous multicentric or unicentric amyloid plaques¹ which were PrP positive to immunohistochemical stains,⁵ axonal degeneration at or surrounding the plaques, neuronal degeneration, and a moderately intense spongiosis. Patient III-3, mother of IV-9, and hospitalised at present, began her illness at 64 years of age, in 1984, with a right hemiparesis followed by a pseudobulbar syndrome, a cerebellar syndrome, dementia, and an extrapyramidal syndrome. For the last 18 months, the patient has been bedridden and demented; she now has epileptic seizures. Patient III-13 died aged 48 years after one year's progression characterised by a pseudobulbar syndrome, an asymmetrical pyramidal syndrome, and intellectual deterioration which in six months led to a bedridden state. There was no necropsy. Patient IV-25 became ill four years ago at 33 years of age, starting with an asymmetrical pyramidal syndrome followed by extrapyramidal and pseudobulbar syndromes, a state of dementia, and a cerebellar syndrome. For the past year he has been bedridden. Finally, one year ago, at 57 years of age, patient III-11, mother of IV-26 and IV-28, presented walking difficulties, dysarthria, and intellectual deterioration. She has been bedridden and demented for a few weeks.

PrP gene analyses—No member of the family had either insertion-deletion mutation or substitutional mutation at codons 102, 178, or 200. Four patients still alive at present carried

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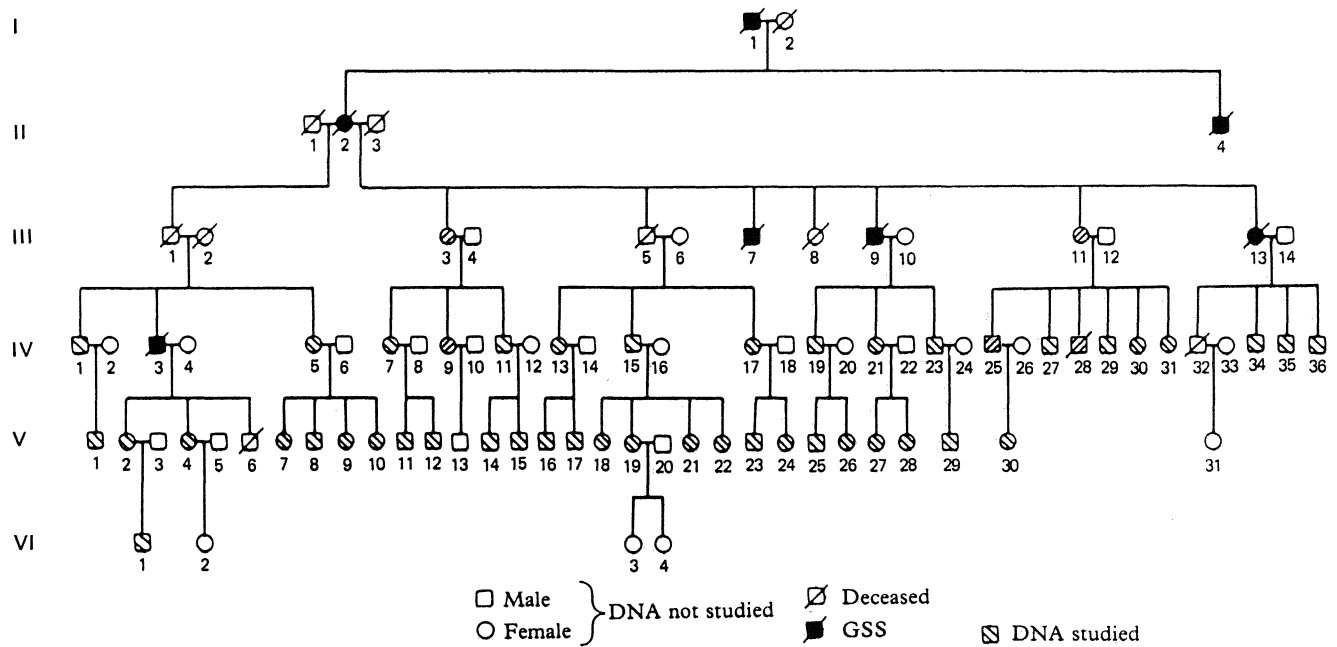


Figure Alsatian GSS family (AND family)

double missense changes at codons 117 and 129 like patient IV-28, as well as 10 healthy members of the family between 11 and 38 years of age whose condition is not discussed for reasons of confidentiality. The missense change at codon 117 was not found in 100 control patients. The missense change at codon 129 was, however, found in the family and the controls. Of the 100 control subjects, 43 had the double allele methionine, 40 had alleles methionine and valine, and 17 had double allele valine. In the GSS family, the missense change at codon 117 was always associated on the same allele with the methionine to valine substitution at the codon 129. This methionine to valine substitution was carried heterozygously by all the members of the family with the double missense, except one of the 10 healthy members, who carried it homozygously. *Genetic analysis*—According to these data, the population frequency p for the missense change at codon 117 was estimated as having a 95% confidence interval between 0 to 0.015. The 99% confidence interval for p extends from 0 to 0.023. As GSS is extremely rare (estimated one to 10 cases per 10^7) population frequency of $q = 1$ per 10^7 was assumed for the GSS gene. The log likelihood ratio (lod score) varied between $Z = 2.185$ at a recombination fraction of $\theta = 0$,

($p = 1 \times 10^{-7}$) and $Z = 2.023$ (recombination fraction $\theta = 0$, $p = 0.023$). The confidence interval for the recombination fraction θ , approximated by the lod score value $Z-1$, ranges from 0 to 0.28 for $p = 10^{-7}$ and from 0 to 0.26 for $p = 0.023$ (table 2).

Discussion

This family of vintners and artisans has lived in Alsace since at least 1795. Patient I-1's direct or allied ascendants are now being studied. No conclusion is yet possible. The family disease is transmitted in the autosomal dominant mode. There are three sets of clinical signs: dementia alone in the first generations and, later, dementia followed by progressive hemiparesis which then became bilateral and was accompanied by a pseudobulbar syndrome. In the most recent generations, there is dementia, a pseudobulbar syndrome, and the appearance of more complex neurological signs associating a cerebellar syndrome, an extrapyramidal syndrome (fixed faces, severely stooped posture, and hypertonia), motor neuron signs with fasciculations and amyotrophy, spontaneous or provoked myoclonia, and generalised tonic-clonic seizures. The age of onset, which at first appeared to be limited to the interval between 30 and 45 years, is in fact much

Table 1 Clinical characteristics of family members with Gerstmann-Sträussler-Scheinker disease

| Family member | Onset age (years) | Disease development (years) | Sex | Codon 117 mutation | Dementia | Progressive hemiparesis | Pseudo bulbar syndrome | Ataxia | Extra pyramidal syndrome | Fasciculations | Seizures of myoclonus |
|---------------|-------------------|-----------------------------|-----|--------------------|----------|-------------------------|------------------------|--------|--------------------------|----------------|-----------------------|
| I 1 | 44 | 3 | M | NA | + | | | | | | |
| II 2 | 43 | 3 | F | NA | + | | | | | | |
| II 4 | 40 | 3 | M | NA | + | | | | | | |
| III 7 | 26 | 5 | M | NA | + | | | | + | | |
| III 9 | 43 | 3 | M | NA | + | + | + | | | | |
| IV 3 | 35* | 2 | M | NA | + | + | + | + | | + | |
| IV 9 | 35* | 11† | F | + | + | + | + | + | + | | + |
| IV 28 | 20* | 4 | M | + | + | ± | + | + | + | + | + |
| III 3 | 64 | 6† | F | + | + | + | + | + | + | | + |
| III 13 | 47 | 1 | F | NA | + | | + | | | | |
| IV 25 | 33 | 4† | M | + | + | + | | + | + | | |
| III 11 | 56 | 1† | F | + | + | | + | | | | |

NA: information not available.
 *From biopsy specimen.
 †Patient still living.

Table 2 Lod scores for several values of θ , the valine substitution frequency

| P | $\theta = 0$ | $\theta = 0.01$ | $\theta = 0.05$ | $\theta = 0.1$ | $\theta = 0.2$ | $\theta = 0.3$ |
|------------|--------------|-----------------|-----------------|----------------|----------------|----------------|
| 0.023 | 2.023 | 2.018 | 1.962 | 1.835 | 1.464 | 0.980 |
| 0.015 | 2.076 | 2.071 | 2.015 | 1.888 | 1.514 | 1.022 |
| 10^{-4} | 2.184 | 2.180 | 2.126 | 1.998 | 1.617 | 1.112 |
| 10^{-10} | 2.185 | 2.181 | 2.127 | 1.999 | 1.618 | 1.112 |

θ recombination fraction.

wider: 20 years at the youngest, 64 at the oldest. The duration of disease, three to five years in the first cases, may vary from one year to at least 10 years in the case of one patient still alive. No correlations could be established between onset age, sex, symptomatology, and generation. In several cases the disease started in the children before their parents (patients IV-28 and IV-25 before III-11 and patient IV-9 before III-3) and, among sisters and brothers, the older after the younger. The histopathological lesions examined in three patients, on the other hand, are similar.¹ The AND family's clinical features lie between the ataxic form^{5,8,11} and the dementing form of GSS.¹² Experimental transmission of the disease from patient IV-28 to mice was negative, as reported previously.⁵ The negative transmissions from this patient and other GSS patients contrast with the almost 100% positivity from sporadic Creutzfeldt-Jakob disease patients.⁵ The low infectivity also contrasts with the high penetrance of the disease in GSS families such as this one.

The analysis of the PrP gene has shown a GCA-to-GTG mutation at codon 117. This missense mutation seems to be specific to this family; it has never been described in any other GSS family or any control subject. The loss of the PvuII restriction site, probably by a silent GCA-to-GCG transition at the third base of codon 117 apparently represents a normal polymorphism of the gene which is found in 10% of white people.¹³ The missense mutation at codon 117 reported here is presumably due to a C-to-T transition at the CpG dinucleotide mutation hot spot¹⁴ of this GCG sequence at codon 117. The missense change at codon 129 was carried not only by the patients but also by over half (57) of controls, suggesting that it might be a normal polymorphism of the gene. We have to take into account, however, that the missense change at codon 117 was always combined with the change at codon 129 in this family. The lod score suggests a correlation between the valine change at codon 117 and the GSS disease gene in this family. The value of 2.185 is certainly below the threshold of the $Z = 3$ value generally admitted as significant, but in this extremely rare disease, there can be difficulties about estimating the frequency of the PrP variant in the population.

The role of the PrP variant is unclear. In AND family, it apparently influences neither the duration of incubation nor the progression of the disorder, unlike certain polymorphisms in animal pathology.¹⁵⁻¹⁷ Contrary to the suggestions of Baker *et al.*¹⁸ amino-acid polymorphism at codon 129 in the normal allele seems not to influence

these clinical data. It is also too soon to know whether the codons 117 and 129 variants in this family or the codon 102 variant in other families are a predisposing factor or the factor responsible for the disease.^{19,20}

Continued clinical observation may give the answer. Follow up of the families with GSS patients, and above all of the now healthy carriers of a mutation of the prion gene, should suggest the potential role of the prion in the induction of the disorder. If all the healthy carriers develop GSS the mutation may be considered to be sufficient for disease development; if not, it must be interpreted as necessary but not sufficient.

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