A novel *PRNP*-P105S mutation associated with atypical prion disease and a rare PrP^{Sc} conformation

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ABSTRACT

Objective: To define the clinicopathologic, genetic, and pathogenic prion protein (PrP^{Sc}) characteristics associated with a novel mutation of the prion protein gene (*PRNP*).

Methods: The coding segment of *PRNP* from the proband and family members was sequenced and the brain of the proband was histologically studied. The Western blot profile of the proteinase K (PK) resistant fraction of PrP^{Sc}, an approximation of its conformation, or “PrP^{Sc}-type,” was determined.

Results: We detected a novel mutation at codon 105 of *PRNP* that results in a serine (S) substitution of proline (P) (P105S), in a young woman who developed progressive aphasia, behavioral changes, dementia, and parkinsonism, lasting 10 years to her death. Histopathologic findings included an intense focus of multicentric PrP-plaques within the hippocampus, punctate plaques scattered throughout the cerebellum, and intense spongiform degeneration focally within the putamen, suggesting a variant of Gerstmann-Sträussler-Scheinker syndrome (GSS). However, PrP^{Sc}-typing revealed two PK-resistant PrP^{Sc} fragments (~21 and 26 kDa), a pattern not previously detected in GSS.

Conclusions: This mutation is the third sequence variation at codon 105 of *PRNP*. The unusual phenotype and PrP^{Sc}-type distinguishes this genetic prion disease from typical Gerstmann-Sträussler-Scheinker syndrome and other codon 105 substitutions, suggesting that, in addition to the loss of proline at this position, the PrP^{Sc} conformation and phenotype is dependent on the specific amino acid substitution. **Neurology® 2008;71:1431-1438**

GLOSSARY

fCJD = familial Creutzfeldt-Jakob disease; **FFI** = familial fatal insomnia; **FTD** = frontotemporal dementia; **GSS** = Gerstmann-Sträussler-Scheinker syndrome; **PK** = proteinase K.

The prion diseases are a family of transmissible neurodegenerative disorders that result from the accumulation of a misfolded isoform (PrP^{Sc}) of the normal prion protein (PrP^C).¹ Over 30 missense and insertional mutations of the PrP gene (*PRNP*) lead to the varied expression of three major heritable forms of disease, including familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and familial fatal insomnia (FFI).² These prion subtypes are distinguished from each other somewhat by their clinical presentation, but primarily by their associated histopathology. Extensive spongiform degeneration denotes CJD, focal thalamic gliosis and neuronal loss defines FFI, and PrP amyloid plaque deposits characterize GSS. Evidence suggests these phenotypes are enciphered in the conformation of the associated misfolded PrP (PrP^{Sc}),³⁻⁵ which can be approximated by the Western blot pattern of proteinase K (PK) resistant PrP^{Sc} (rPrP^{Sc}) within the affected brain. In fCJD and FFI, rPrP^{Sc} displays three fractions with migration rates (M_r) ranging from ~19 or 21–33 kiloDaltons (kDa), representing un-, mono-, and di-glycosylated rPrP^{Sc}, whereas a single unglycosylated fragment of ~6–11 kDa is typically detected in GSS.⁶

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We report a novel serine (S) substitution of proline (P) at codon 105 of *PRNP* in association with a clinical presentation that suggested frontotemporal dementia (FTD) with parkinsonism, a histopathologic profile consistent with atypical GSS, and a rare rPrP^{Sc} pattern not previously detected with GSS. Whether this genetic-based prion disease constitutes an atypical variant of GSS or a new subtype of prion disease is debatable; however, its recognition not only broadens the clinical spectrum of prion disease but also supports the consideration of prion disease in the differential diagnosis of virtually any presentation of dementia.

METHODS *PRNP* gene analysis. DNA samples were prepared from whole blood, as previously described.⁷ The *PRNP* coding sequence was amplified as a single ~850 base pair amplicon using a previously reported primer pair⁵ and ~100 ng of genomic DNA in a 25 μ L reaction volume. PCR products were gel purified using Gene-Clean (Q-Biogene) and bidirectional sequenced using Big Dye fluorescent dye terminators and a 3730XL automated DNA Sequencer (ABI). To determine allelic phase, the *PRNP* coding segment was T/A ligated into pGEM-T plasmid (Promega, Madison, WI), transformed into DH5 α competent cells, and positive clones were selected by *Eco*R1 screening for the PrP insert, followed by *Nsp*I digestion for selection of 129M and 129V containing clones. Multiple clones were sequenced using T7 short sense and SP6 antisense primers. Chromatograms were analyzed and the sequence was aligned against human *PRNP* (GenBank accession no. 4506112), using BLAST2 software.

Western analysis. Sections of frozen brain cortex from several regions were used to prepare 10% (W/V) brain homogenates in lysis buffer. Samples were dounce homogenized, cleared by low speed centrifugation (1,500 rpm $\times$ 5 minutes), then digested with PK (20 μ g/mL) for 1 hour at 37°C, and the reaction terminated with 2 mM phenylmethylsulfonylfluoride. Western blotting was performed as previously described, using 3F4 monoclonal antibody (DAKO) at 1:3,000 dilution and Super Signal West Pico chemiluminescence substrate (Pierce) and documented with a Biorad XRS digital document imager.⁷

Cellular studies. PrP mutations were introduced into a mouse PrP cDNA in a pSP72 (Promega) plasmid by site directed mutagenesis, PCR amplified with primers carrying Bam HI and Hind III restriction sites, and cloned into a pCB6 based mammalian expression vector, and transfected into HeLa cells using Lipofectamine 2000 (Invitrogen, Inc.), as previously described.⁸ Following 24 hours of expression, cells were harvested directly in lysis buffer, Western blot was performed, and the membrane was probed with anti-mouse PrP antibody, D13 (InPro, South San Francisco, CA).

Histologic studies. At autopsy, brain tissue was fixed in 10% formalin for 48 hours. After formalin fixation the tissue was immersed in 97% formic acid for 90 minutes, washed several times in 10% formalin, dehydrated in graded alcohols and xylene, and infiltrated with paraffin at 60 degrees. Sections were cut 5 μ m thick for standard hematoxylin-eosin, thioflavin, and immuno-

histochemistry, and 10 μ m for Congo red staining. Identification and localization of protease resistant PrP^{Sc} in aldehyde-fixed tissue sections was achieved by the hydrolytic autoclaving technique.⁹ Eight- μ m-thick paraffin-embedded tissue sections mounted on coated glass slides were deparaffinized and endogenous peroxidase activity blocked by incubation in methanol containing 0.3% H₂O₂. The slides were then immersed in 1–30 mM HCl in distilled water and autoclaved for 10 minutes at 121°C. When the autoclave pressure returns to atmospheric and the temperature to about 60°C, the slides are washed with tap water and 50 mM Tris-HCl buffer (pH 7.5), followed by incubation with the primary 3F4 PrP antibody¹⁰ diluted in 25 mM Tris HCl buffer (pH 7.6) containing 0.05% Tween 20, 0.5 mol/L NaCl, and 5% nonfat milk at 4°C. Detection is performed by peroxidase-linked secondary antibody and diaminobenzidine. This technique enhances detection of the PrP^{Sc} signal.

Clinical phenotype. Over a 2-year period, a 30-year-old right handed woman struggled with the names of her regular customers at work, became withdrawn, neglected her personal hygiene, failed in managing her finances, and developed difficulties with bicycle riding, driving, and using keys. Examination at the time noted a complacent woman who smiled inappropriately, maintained excessive eye contact, spoke slowly, and lacked insight into her problem. She scored 15 out of 30 on a Folstein Mini-Mental State Examination.¹¹ Neuropsychological assessment revealed prominent receptive and expressive aphasia and mild to moderate impairment in orientation, attention, and verbal and visual memory. Her affect was restricted. Neurologic examination was otherwise normal. Of note, neither ataxia nor dysarthria were evident. Extensive serologic and CSF examination was unrevealing, with the exception of a mildly elevated sedimentation rate of 42 mm/hour. CSF total protein was not elevated and the 14-3-3 protein was not tested. MRI of the brain revealed only generalized sulcal prominence. SPECT scan revealed diffusely decreased activity, especially prominent in the mid temporal regions, bilaterally. The EEG displayed mild to moderate diffuse slow waves. Cerebral angiogram was normal.

Over the next year, the patient developed inappropriate and impulsive behaviors, including excessive shopping, giving away her used undergarments and clothing as Christmas gifts, undressing in public, and eating directly from the dinner plates of others. Her food intake increased dramatically, as did, for a short time, alcohol consumption.

Three years after onset, she was moderately obese, developed a persistent pruritus, was minimally oriented, and giggled excessively. She displayed severe nonfluent aphasia, profound echolalia, and prominent frontal release signs. Paratonia was evident throughout and deep tendon reflexes were slightly increased, but strength was full, there was no clonus, and plantar responses were flexor. Gait was slow and slightly wide-based, but obvious truncal and limb ataxia was not evident. At this time, genetic prion disease was considered, despite the atypical presentation. Family history was not well known, but was reported to include a great uncle with schizophrenia on one side of the family, and on the opposite side, a grandmother who died in her 30s from presumed cancer, an uncle who died in his 30s, and a great grandfather who died in his 50s from “unspecified causes” (figure 1A). Neither parent was reported to have symptoms, although no formal neurologic or neuropsychological testing was performed.

Seven years after onset, the patient developed an oral fixation for non-food items, prominent and diffuse cogwheel rigidity, and mutism. Because of severe bradykinesia and inattention to her gait, she

Figure 1 Pedigree of the *PRNP*-P105S family (A) and brain MRI of the proband (B)

(A) Pedigree of *PRNP*-P105S family. The proband is indicated by an arrow. Individuals I-3 and II-3 (dark gray) died young of "unspecified causes" and II-4 died of presumed cancer at age 34, but the accuracy of these diagnoses is limited by the lack of close family contact. These presumptive carriers are relatives of the proband's parent that carries the P105S/129V genotype (III-5), while the other parent (III-9) carries the 24-bp deletion/129 M allele. The carrier parent (age ~60) has not been formally assessed at this time, but is reported to be in general good health. Gender of the parents is withheld for confidentiality. (B) Brain MRI of proband. Axial FLAIR (left image) and diffusion-weighted imaging of the proband performed 7 years after onset of symptoms. Signal hyperintensities are present within the caudate/putamen (arrows) and cortical ribbon (arrowheads). These features are characteristic of Creutzfeldt-Jakob disease. Such data for Gerstmann-Sträussler-Scheinker are limited. Motion artifact is present. SZP = schizophrenia; MI = myocardial infarction; CA = cancer; ?Dx = diagnosis unclear.

was confined to a wheelchair for safety. At this time, an MRI of the brain revealed hyperintensity of the caudate and putamen, in addition to gyriform high signal in the parieto-occipital junction and frontal lobes by FLAIR and diffusion weighted imaging (figure 1B). Ten years after onset the patient died in an akinetic mute state.

RESULTS Genetic analysis of *PRNP*. The entire coding segment of *PRNP* was sequenced from the pro-

band and parents. No other family members were available. At the first nucleotide of codon 105, a C to T transition, resulting in a serine (S) substitution of proline (P), was detected in the proband. The polymorphic codon 129 was Met/Val heterozygous and a deletion of a single 24 base pair (bp) octarepeat segment was detected. Subcloning revealed that the P105S mutation was allelic with valine at codon 129 (129V) and the normal allele carried the 24-bp deletion and 129M coding. One parent carried the P105S/129V allele and the other carried the 24-bp deletion/129M allele. The 24-bp deletion is a polymorphism not known to affect risk to prion disease.^{12,13}

Pathologic features. The brain was markedly atrophic at 725 g. All cortical and subcortical regions, including basal ganglia, thalamus, and central white matter, were significantly and symmetrically atrophic, whereas brainstem and cerebellum were relatively spared. Histologic examination demonstrated severe atrophy in all cortical laminae with loss of more than 90% of pyramidal neurons. Severe neuronal loss was prominent in layer 2 of the gray matter of most neocortical regions, a feature reminiscent of FTD (figure 2A). Spongiform degeneration was sparse, but patchy throughout multiple cortical layers of all brain regions (figure 2B). It was more prominent within the entorhinal cortex and pyramidal layer of the hippocampus (figure 2C), and intense within the basal ganglia, especially putamen (figure 2D). The appearance in the putamen was comparable to the coarse spongiform degeneration observed in sporadic CJD with homozygosity for Met at codon 129 (i.e., CJDMM2).⁴ Within the cerebellum, only mild spongiform degeneration was evident and limited to the molecular layer (figure 2E). In the brainstem, the tectum was mildly affected by spongiform change (not shown).

GFAP immunohistochemistry revealed intense fibrillary astrocytosis in most brain regions sampled, regardless of the degree of spongiform degeneration (figure 2, F-H). Astrocytosis was more intense in frontal lobes (figure 2F) compared with hippocampus (figure 2G), while putamen was comparable to entorhinal cortex (figure 2H).

PrP deposits were evident by hematoxylin-eosin staining, but clearly revealed by immunohistochemical staining with anti-PrP 3F4 monoclonal antibody (figure 3, A-C). These were especially dense in the pyramidal layer of the hippocampus (figure 3A) and in the parahippocampal cortex (figure 3B). Plaque morphology was mixed, ranging from large (~30 μ m) multicentric plaques in the hippocampus, to punctate irregular, dense aggregates (~5-10 μ m) in all layers of the cerebellum (figure 3C), and a mixture of plaque types in the neocortex. Smaller PrP deposits

Figure 2 Histopathologic features of *PRNP*-P105S

Hematoxylin-eosin staining shows (A) severe atrophy of frontal cortex with neuronal loss (40×), (B) patchy spongiform degeneration that was present throughout all neocortical regions (100×), (C) spongiform degeneration of moderate intensity in the hippocampus (100×), (D) a section of putamen, which displayed the most intense spongiform degeneration (100×), and (E) mild vacuolar degeneration in the molecular layer of the cerebellar cortex, reflecting an overall minimally involved cerebellum (40×). Glial fibrillary acidic protein IHC revealed fibrillary astrocytosis that was most intense within the frontal lobe (F), but prominent in most brain regions sampled, including hippocampus (G) and putamen (H) (100×). Solid bar in B represents 75 μm for all panels except A and E (250 μm).

were also seen within the gray matter of the midbrain, pons, and medulla. Congo red (figure 3D) and thioflavin S (figure 3E) staining of several regions, including cerebellum, hippocampus, and subiculum, confirmed the plaques were true amyloid. In contrast to other GSS, tau immunohistochemistry was negative.

PrP analysis. The Western blot pattern of rPrP^{Sc} approximates the conformation of PrP^{Sc}, which is

Figure 3 PrP amyloid in *PRNP*-P105S

PrP plaques revealed by IHC, using monoclonal antibody 3F4. (A) Large (~30–50 μm) multicentric plaques, typical of GSS, were at the highest density in the hippocampus. (B) PrP plaques were also prevalent in the parahippocampus, but at a lower density than the hippocampus. Morphology is similar to those in frontal cortex. (C) Smaller (~5–10 μm) punctate plaques predominated in all cerebellar layers and throughout gray matter structures in midbrain, pons, and medulla (not shown). (D) Congo red staining (shown) of subiculum shows plaques that displayed green birefringence in polarized light (not shown). (E) Thioflavin S staining shows intense fluorescence from a section of hippocampus. The last two figures confirm these plaques are true amyloid. Solid bar in D represents 75 μm.

linked to the phenotype of prion disease.^{5,14} Several PrP^{Sc} types have been described, based primarily on the migration rate (M_r) of the unglycosylated frac-

Figure 4 PrP^{Sc} typing and characterization of PrP^{-P105S}

(A) Western blot comparing rPrP^{Sc} of sporadic Creutzfeldt-Jakob disease (CJD) (Type 1 PrP^{Sc}, M_r ~21 kDa) (lane 1) to the PRNP-P105S case (lane 2, M_r ~21 kDa). rPrP^{Sc}-P105S lacks the high molecular weight diglycosylated fraction typically present in CJD. (B) Regional brain levels of rPrP^{Sc} observed following treatment with 20 μ g/mL proteinase K (PK). Despite different pathologic features in these six brain regions, the pattern of rPrP^{Sc} is consistent. Frontal (Fr), temporal (Te), occipital (Oc), basal ganglia (BG), cerebellum (Cb), thalamus (Th). (C) Western blot comparing the typical pattern of rPrP^{Sc} from sporadic CJD (Type 2 PrP^{Sc}, M_r ~19 kDa), and the atypical patterns of rPrP^{Sc} from each of the three genetic prion diseases that lack an obvious diglycosylated fraction. Note the slight difference in M_r and relative intensity of the two fractions among the mutations, suggesting subtle differences in PrP^{Sc} conformation or physiologic fate of each. (D) HeLa cells were transfected to express wild type (WT) PrP, PrP^{-P105S} (P105S), or PrP^{-T183A} (T183A) for 24 hours prior to immunohistofluorescence with D13 anti-PrP antibody, to detect plasmalemma localized PrP. In contrast to PrP^{-T183A}, WT and PrP^{-P105S} are detected on the cell surface, suggesting the P105S mutation does not grossly impair PrP trafficking. (E) Western blot of HeLa cells expressing WT, PrP^{-P105S}, and PrP^{-T183A} for 24 hours, probed with D13. PrP^{-P105S} appears similarly glycosylated as WT, whereas PrP^{-T183A} lacks the diglycosylated fraction, suggesting the absence of diglycosylated rPrP^{Sc}-P105S is not a result of grossly impaired glycosylation, but rather selected conversion of unglycosylated and monoglycosylated PrP^{Sc}.

tion, but also on the relative predominance of the higher molecular weight glycoforms.^{4,15} In general, CJD and FFI are linked to rPrP^{Sc} with three glycoforms ranging from ~19 or 21–33 kDa, although the unglycosylated fraction of FFI is consistently 19 kDa. In GSS, rPrP^{Sc} is typically represented as a single smaller unglycosylated fragment, ranging between ~6 and 13 kDa.^{6,16,17} The rPrP^{Sc} pattern found in the current case consisted of two fragments of ~21 and 26 kDa (figure 4A), representing unglycosylated and monoglycosylated rPrP^{Sc}. To determine if this pattern was associated with a specific

underlying pathologic feature, we analyzed several brain regions that displayed the range of pathologies present in this case. In all regions, the pattern was the same (figure 4B).

Although this unusual rPrP^{Sc} pattern has not been reported in GSS, it has been observed in two other genetic prion diseases. Substitutions of alanine (A) for threonine (T) at codon 183 (T183A) and isoleucine (I) for valine (V) at codon 180 (V180I)^{18,19} are associated with rPrP^{Sc} that lacks the diglycosylated fraction. To determine if they all represent a common PrP^{Sc} type, we compared the rPrP^{Sc} of

Table <i>PRNP</i> codon 105 mutations						
Substitutions at position 105	Codon sequence	Mutation event	Codon 129	Key clinical phenotype	Key pathologic phenotype	PrP ^{Sc} type
Pro	CCA	Normal	Met or Val			None
Leu	CTA	C to T transition, pos. 2	Val	Dementia, dysarthria, spastic paraparesis, some action myoclonus, ataxia, tremor, and chorea	Mixture of multicentric and punctate PrP plaques diffusely in cerebrum; no SD	~6 kDa unglycosylated
Thr	ACA	C to A transversion, pos. 1	Met	Ataxia and dementia, some psychiatric	Not reported	Not reported
Ser	TCA	C to T transition, pos. 1	Val	Aphasia, behavior, dementia, parkinsonian features	Multicentric PrP plaques in hippocampus, punctate plaques in cerebellum, intense SD in basal ganglia	21 kDa unglycosylated + 26 kDa monoglycosylated

SD = spongiform degeneration.

these mutations with that of P105S. Although the unglycosylated fraction of rPrP^{Sc-P105S} may be very slightly larger than rPrP^{Sc-V180I}, they are ~21 kDa, whereas rPrP^{Sc-T183A} is ~19 kDa. In addition, in contrast to V180I and P105S mutations, which display relatively equal proportions of the two rPrP^{Sc} fractions, the monoglycosylated fraction of rPrP^{Sc-T183A} is much more prominent (figure 4C), confirming these represent different PrP^{Sc}-types.

The T183A mutation precludes glycosylation at position 181 and impairs trafficking of PrP to the plasma membrane, the normal cellular destination of PrP.^{20,21} Although residue 105 is distant from the glycosylation sites at positions 181 and 196, an indirect effect on glycosylation might result from an effect on the normal cellular trafficking of PrP. To determine if the P105S mutation directly impairs PrP glycosylation, we expressed PrP carrying the P105S mutation in cultured HeLa cells and compared the glycosylation profile and plasma membrane localization with PrP carrying the T183A mutation. After 24 hours of expression the cells were either fixed for immunofluorescence staining (figure 4D) or lysed for Western blot analysis (figure 4E). In contrast to PrP^{T183A}, PrP^{P105S} displays a normal glycosylation profile and is delivered to the plasma membrane, supporting a selective conversion of mono- and unglycosylated fractions of PrP^{C-P105S} to rPrP^{Sc-P105S}, rather than a direct effect on glycosylation.

DISCUSSION We characterized the clinicopathologic phenotype and PrP^{Sc} type in the proband of an American family that carries a novel P105S mutation of *PRNP*. Although this is the first documented case of prion disease in this family, several factors support the gene defect as causal, including 1) the young age at onset in the proband and the

prolonged disease duration, both of which are typical of familial prion disease, 2) the family history of early deaths from unclear causes within the lineage of the carrier parent, 3) the mutation occurs at a codon previously linked to familial prion disease, and 4) the presence of GSS-type plaques has thus far only been observed in association with a mutation of *PRNP*. The absence of disease in the carrier parent suggests a variable age at onset, a feature not uncommon in prion disease.

P105S represents the third distinct base pair alteration at codon 105 of *PRNP* that is associated with prion disease (table). A leucine substitution (P105L) was initially reported in several Japanese families²²⁻²⁴ and a threonine substitution (P105T) was subsequently detected in a Canadian family.²⁵ The polymorphic codon 129, which is known to affect prion disease phenotype, is Val on the mutated allele in both P105S and P105L, but Met on the P105T allele. The clinicopathologic picture most associated with P105L has been the development of spastic paraparesis in the absence of prominent ataxia, the diffuse deposition of GSS-type plaques, and the absence of spongiform degeneration.²⁴ Although the histologic profile of P105T has not been described, ataxia and dementia were the principal clinical features reported.²⁵ These descriptions differ from our case that presented with features initially suggesting FTD with parkinsonism, including aphasia, prominent behavioral changes, and severe parkinsonism, and a histologic profile that includes an unusual distribution of GSS type plaques and intense focus of spongiform degeneration in the putamen. Despite these differences, one could argue that this picture may fall within the limits of phenotypic variability associ-

ated with prion disease²⁶ and could, therefore, be observed with any mutation of codon 105. The identification of additional cases of each of these mutations will assist in this regard. By current standards of prion classification, this would be categorized as a GSS variant. However, the unusual rPrP^{Sc} pattern, a measure of PrP^{Sc} conformation, clearly distinguishes this disease not only from P105L-related disease, but all other cases of GSS and other GSS variants.²⁴ As such, it could also be argued that this represents a distinct prion subtype. Strain testing by transmission to susceptible transgenic mice is under way to assist in this determination. Beyond this, our case supports the idea that the loss of Pro at residue 105 is sufficient to induce prion disease (which appears to favor GSS-type pathology), and the specific amino acid substitution contributes to the PrP^{Sc} conformation and ultimate phenotype.

It is not clear why rPrP^{Sc-P105S} lacks the diglycosylated fraction; however, our cell-based studies suggest that, in contrast to PrP^{T183A},^{20,21} PrP^{P105S}, like PrP^{V180I}, is fully glycosylated and properly delivered to the plasma membrane. Thus, either the diglycosylated fraction of PrP^{P105S} and PrP^{V180I} is resistant to conversion, or the unglycosylated and monoglycosylated forms are selectively favored. This preference for conversion of specific glycoforms parallels observations with variant CJD in which, paradoxically, the diglycosylated fraction is favored (reviewed elsewhere²⁷).

Of note, a similar PrP^{Sc} type was recently reported in association with a sporadic CJD case.²⁸ In this case, the unglycosylated fragment predominates over the monoglycosylated fragment, suggesting that it may represent yet another PrP^{Sc} type than the ones discussed here. In support of this, the histopathology of that case is distinct from P105S, in that intraneuronal accumulation of PrP was evident, but not extracellular PrP plaque deposits.

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