ARTICLE

Loss of paraplegin drives spasticity rather than ataxia in a cohort of 241 patients with *SPG7*

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Neurology® 2019;92:e2679-e2690. doi:10.1212/WNL.0000000000007606

Abstract

Objective

We took advantage of a large multinational recruitment to delineate genotype-phenotype correlations in a large, trans-European multicenter cohort of patients with spastic paraplegia gene 7 (*SPG7*).

Methods

We analyzed clinical and genetic data from 241 patients with *SPG7*, integrating neurologic follow-up data. One case was examined neuropathologically.

Results

Patients with *SPG7* had a mean age of 35.5 ± 14.3 years (n = 233) at onset and presented with spasticity (n = 89), ataxia (n = 74), or both (n = 45). At the first visit, patients with a longer disease duration (>20 years, n = 62) showed more cerebellar dysarthria ($p < 0.05$), deep sensory loss ($p < 0.01$), muscle wasting ($p < 0.01$), ophthalmoplegia ($p < 0.05$), and sphincter dysfunction ($p < 0.05$) than those with a shorter duration (<10 years, n = 93). Progression, measured by Scale for the Assessment and Rating of Ataxia evaluations, showed a mean annual increase of 1.0 ± 1.4 points in a subgroup of 30 patients. Patients homozygous for loss of function (LOF) variants (n = 65) presented significantly more often with pyramidal signs ($p < 0.05$), diminished visual acuity due to optic atrophy ($p < 0.0001$), and deep sensory loss ($p < 0.0001$) than those with at least 1 missense variant (n = 176). Patients with at least 1 Ala510Val variant (58%) were older (age 37.6 ± 13.7 vs 32.8 ± 14.6 years, $p < 0.05$) and showed ataxia at onset ($p < 0.05$). Neuropathologic examination revealed reduction of the pyramidal tract in the medulla oblongata and moderate loss of Purkinje cells and substantia nigra neurons.

Conclusions

This is the largest *SPG7* cohort study to date and shows a spasticity-predominant phenotype of LOF variants and more frequent cerebellar ataxia and later onset in patients carrying at least 1 Ala510Val variant.

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Glossary

HSP = hereditary spastic paraplegia; **LOF** = loss of function; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCA** = spinocerebellar ataxia; **SPG** = spastic paraplegia gene.

The key feature of hereditary spastic paraplegia (HSP) is the progressive degeneration of corticospinal tracts.[1] To date, 79 loci are known to be involved and are classified as spastic paraplegia genes (*SPG1–SPG79*).[2] The first identified gene among autosomal recessively transmitted spastic paraparesis was *SPG7*.[3] Cerebellar atrophy does not always translate into cerebellar signs in patients.[4–6] However, cerebellar ataxia may be the predominant symptom, as confirmed by reports that found *SPG7* to be responsible for up to 19% of undiagnosed cerebellar ataxias.[7,8] Cerebellar atrophy and peripheral neuropathy have also been reported in heterozygous relatives of patients with *SPG7*.[6]

SPG7 encodes paraplegin, a mitochondrial inner membrane metalloprotease.[9,10] This protein forms the heterooligomeric protease complexes with the homologous ATPase AFG3L2.[9] Consequences of an impaired complex include mitochondrial dysfunctions.[9] *SPG7* and AFG3L2 levels are high in Purkinje neurons[11]; in addition, *SPG7* is expressed in pyramidal cortical neurons and spinal motor neurons.[12]

The *SPG7* gene has 17 exons and variants of unknown significance have been frequently reported.[4,5,13,] A recurrent variant, Ala510Val, shows a minor allele frequency of 0.5% in public databases such as GnomAD. Initially considered to be a nonpathologic variant, its pathogenicity was established by yeast complementation assay.[14] Moreover, this variant is found more frequently in patients than controls.[8,15–17]

Despite extensive clinical variability, few genotype-phenotype correlations have been established.[18] We aimed to delineate the progression of clinical features and to define correlations between genotypes and phenotypes by exploring a large population with *SPG7* from several European centers that includes follow-up data for many patients.

Methods

We analyzed the clinical and genetic data of 241 patients (194 index patients, 47 affected relatives). Geographic origin was European in most (French n = 86, Netherlands n = 49, German n = 35, Belgium n = 23, Italy n = 8, Great Britain n = 2, Greece n = 1); some came from North Africa or Middle East (n = 10); and geographic origin was unknown for 26 patients. All patients with *SPG7* carried 2 disease-causing variants and had at least 1 neurologic examination. Patients were followed up at the French National Reference Center for Rare Diseases "Neurogenetics" in Paris (n = 106) and Strasbourg (n = 2), the German Center for Neurodegenerative Diseases (Tubingen, Bonn, Munich, Rostock, University Hospitals) and collaborating German hospitals (Kiel, Bochum) (n = 53), Radboud University Nijmegen Medical Centre (n = 49), Antwerp University Hospital (n = 24), and the Medea Institute in Conegliano and Bosisio Parini (n = 7). Some patients (n = 90) have been previously reported: n = 8[4]; n = 7[19]; n = 16[6]; n = 49[18]; n = 1[20]; n = 9[8]. Data were collected systematically with the ataxia and spastic paraparesis databases of each center, for clinical follow-up and research purposes (Spatax network), between 1995 and 2018. Clinical and imaging data were retrieved and critically reviewed. Genetic diagnosis was reached differently, depending on the local facilities and year of sampling, by either direct sequencing of *SPG7* coding regions or high-throughput panel sequencing and exome sequencing, sometimes completed by multiplex ligation-dependent probe amplification to detect deletions or duplications within the *SPG7* gene.

We compared clinical features of patients with homozygous missense variants, with homozygous loss-of-function (LOF) variants, or with a nonsense variant on 1 allele and missense variants on the other allele. We studied the clinical consequences of the Ala510Val variant and identified genetic differences in patients with cerebellar ataxia or spasticity at onset. We analyzed the progression of the clinical signs in patients who had follow-up and by comparing the clinical signs at the first visit in 3 groups of patients: with disease onset at the most 10 years before the clinical examination, between 10 and 19 years, and >19 years.

Patients were assessed with a standardized evaluation form. The categorical scale of disability was as follows: 0, no functional handicap; 1 = no functional handicap but signs at examination; 2 = mild, able to run, unlimited walking; 3 = moderate, unable to run, limited walking without aid; 4 = severe, walking with 1 stick; 5 = walking with 2 sticks; 6 = unable to walk, requiring a wheelchair; and 7 = confined to bed. The disease progression index was calculated as the ratio between the disability stage and disease duration in years. Symptoms at onset such as stiff legs/spastic gait or unsteadiness and gait/balance impairment were collected as reported by the patients. A subgroup of patients were evaluated with the Scale for the Assessment and Rating of Ataxia (SARA; maximum score 40).[21] Transmission was classified as autosomal recessive, autosomal dominant (based on a positive first-degree familial history combined with the presence of 2 variants in the *SPG7* gene), or sporadic (only 1 index in the family and absence of consanguinity). Segregation of the variants was assessed in family members for suspected

autosomal dominant cases when DNA was available. Variants were classified as missense or LOF (including nonsense, splicing, frameshift variants, deletions, duplications, and in-frame deletions). Pathogenicity of the variants was obtained by an in silico approach by 5 prediction programs (SIFT, PolyPhen, LRT, M-Cap, and MutationTaster). Brain MRIs and EMGs were collected when available. The degree of cerebellar atrophy was evaluated by the physicians involved in this study on T1- or T2-weighted sagittal sequences.

Neuropathology

One patient was involved in a brain donation program and signed an informed consent form for brain neuropathologic examination and research. The brain was removed post-mortem, and the right hemisphere and right half of the brainstem were fixed by immersion in 4% formaldehyde (10% formalin); systematic samples from the other hemisphere were frozen at −80°C. After formalin fixation, a systematic sampling protocol was applied. The samples involved the vermis and the cerebellar hemisphere, the whole hemi-brainstem (8 samples), the spinal cord at the upper cervical level, the basal nuclei, the hippocampus, and the cerebral cortex. The samples were embedded in paraffin and cut at a thickness of 5 μm. The sections were deparaffinized in graded alcohol and stained with hematoxylin & eosin and Luxol Fast Blue for myelin. Immunohistochemistry was performed on selected samples with primary antibodies for tau protein, β-amyloid, α-synuclein, TAR DNA-binding protein 43, ubiquitin, p62, and CD68 (for activated microglia). Double immunostaining for myelin (myelin basic protein) and phosphorylated neurofilaments was performed to assess myelin pallor and to distinguish demyelination from degeneration.

Statistical analyses

Statistical analyses were performed with SAS software 9.4. Data are expressed as mean ± SD or frequency (number). Qualitative variables were compared between groups with the Fisher exact test, and quantitative variables were compared by analysis of variance, followed by a post hoc test when necessary. We compared clinical examinations at the first visit to account for disease duration (<10, 10–19, ≥20 years). We used the McNemar exact test for qualitative variables to compare the clinical characteristics of the patients between 2 consecutive visits.

Standard protocol approvals, registrations, and patient consents

All patients have been examined in clinical settings during their usual follow-up. Informed consent was obtained according to the regulations of each European country and the local ethics committee.

Data availability

Anonymized data presented in this article will be made available at the request of a qualified investigator. Requests should be made to Alexandra Durr (alexandra.durr@icm-institute.org).

Results

At the first visit, 241 patients with *SPG7* (136 men and 105 women) were included, with a mean age at examination of 50.4 ± 14.1 years. The mean age at reported disease onset was 35.5 ± 14.3 years (n = 233), and the mean disease duration was 15.1 ± 13 years (n = 233). The patients had a mean disability stage of 3.3 ± 1.2 (n = 223) and a mean SARA score of 10.6 ± 6 (n = 55).

There were 167 familial cases, 64 without other affected in their families, and 10 with unknown familial history. There were 12 families (6%) with transmission of the disease from 1 generation to the next despite the presence of 2 variants in the index case (figure 1). These apparently dominantly inherited forms were more often reported in patients who had cerebellar symptoms at onset (10 patients with cerebellar onset vs 3 patients with spastic onset, $p < 0.05$). Segregation of 1 of the 2 variants from the index case was confirmed for only 2 families (AAD-796 and FSP-554) and was reported elsewhere.[6] In these 2 families, the heterozygous parent showed mild cerebellar atrophy and cerebellar signs, and both parents carried the p.Arg485_Glu487del variant.[6] DNA was not available for the other families to analyze segregation.

Overall genotype-phenotype correlations

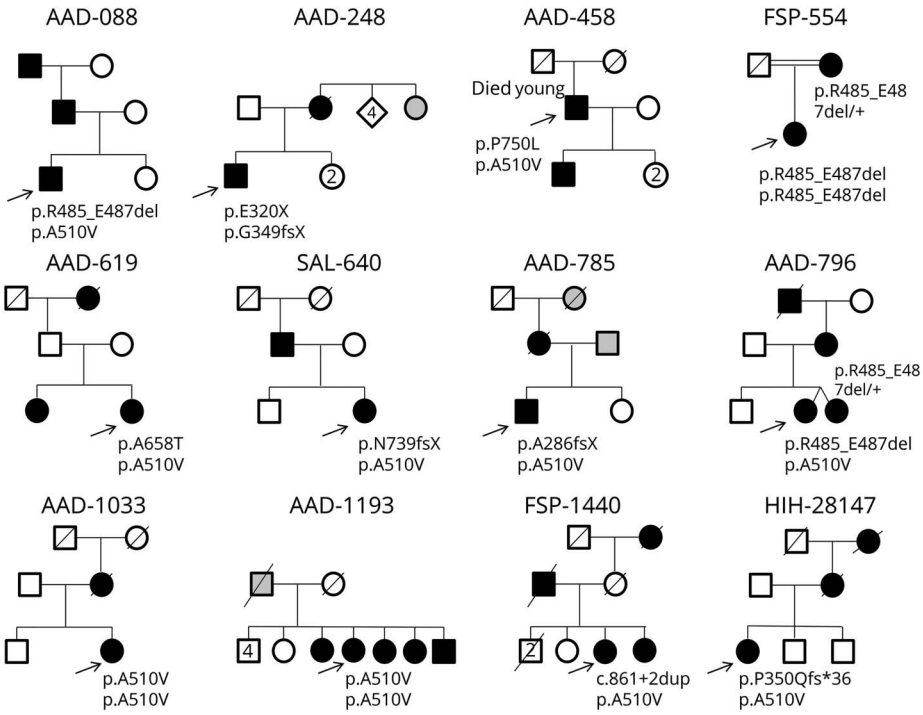
All variants are shown in figure 2, with the presence of a cluster of missense variants in the peptidase domain (between the 13th and 16th exons, amino acid positions 555–727). New variants are listed in supplementary table 4 (available from Dryad, doi.org/10.5061/dryad.sb4kr01).

On the basis of genotype, patients homozygous for LOF variants presented significantly more often with pyramidal signs and diminished visual acuity (table 1) than patients homozygous for missense variants.

Comparison between patients carrying the Ala510Val variant and those carrying other variants

The Ala510Val variant was the most frequent variant in our patients (table 2). Indeed, 141 patients (58.5%) carried at least 1 Ala510Val variant, including 45 patients (18.7%) homozygous for this variant. The presence of the Ala510Val variant, even on 1 allele, was associated with significantly later disease onset than in noncarriers of this variant (37.6 ± 13.7 vs 32.8 ± 14.6 years, $p = 0.01$, n = 233), with no further differences in patients homozygous for Ala510Val . Clinically, at the first examination, the Ala510Val carriers did not differ in disease severity measured by disability stage (3.2 ± 1.1 vs 3.3 ± 1.2, $p = 0.5$, n = 223) or SARA score (10.8 ± 6.1 vs 10.1 ± 5.5, $p = 0.7$, n = 55) compared to patients carrying other variants. However, patients carrying the Ala510Val variant had a lower frequency of pyramidal signs (86% vs 97%, $p = 0.01$), including brisk reflexes (76% vs 92%, $p = 0.01$) and sphincter dysfunction (38% vs 53%, $p = 0.02$); diminished visual acuity (6% vs 24%, $p < 0.001$); and pes cavus (17% vs 30%, $p = 0.02$).

Figure 1 Pedigrees of the 12 families with a dominant inheritance pattern



Index case is indicated by an arrow.

Symptoms at onset: Cerebellar ataxia vs spasticity

At onset, more patients reported stiff legs and spastic gait (n = 89) than unsteadiness and gait or balance impairment (n = 74). A third group presented either a combination of cerebellar ataxia and spastic gait (n = 45) or other features such as dysarthria, diplopia, diminished visual acuity, and neuropathic pain. The presence of the Ala510Val variant was significantly associated with cerebellar signs at onset ($p = 0.01$).

Clinical progression between the first and the second clinical examinations

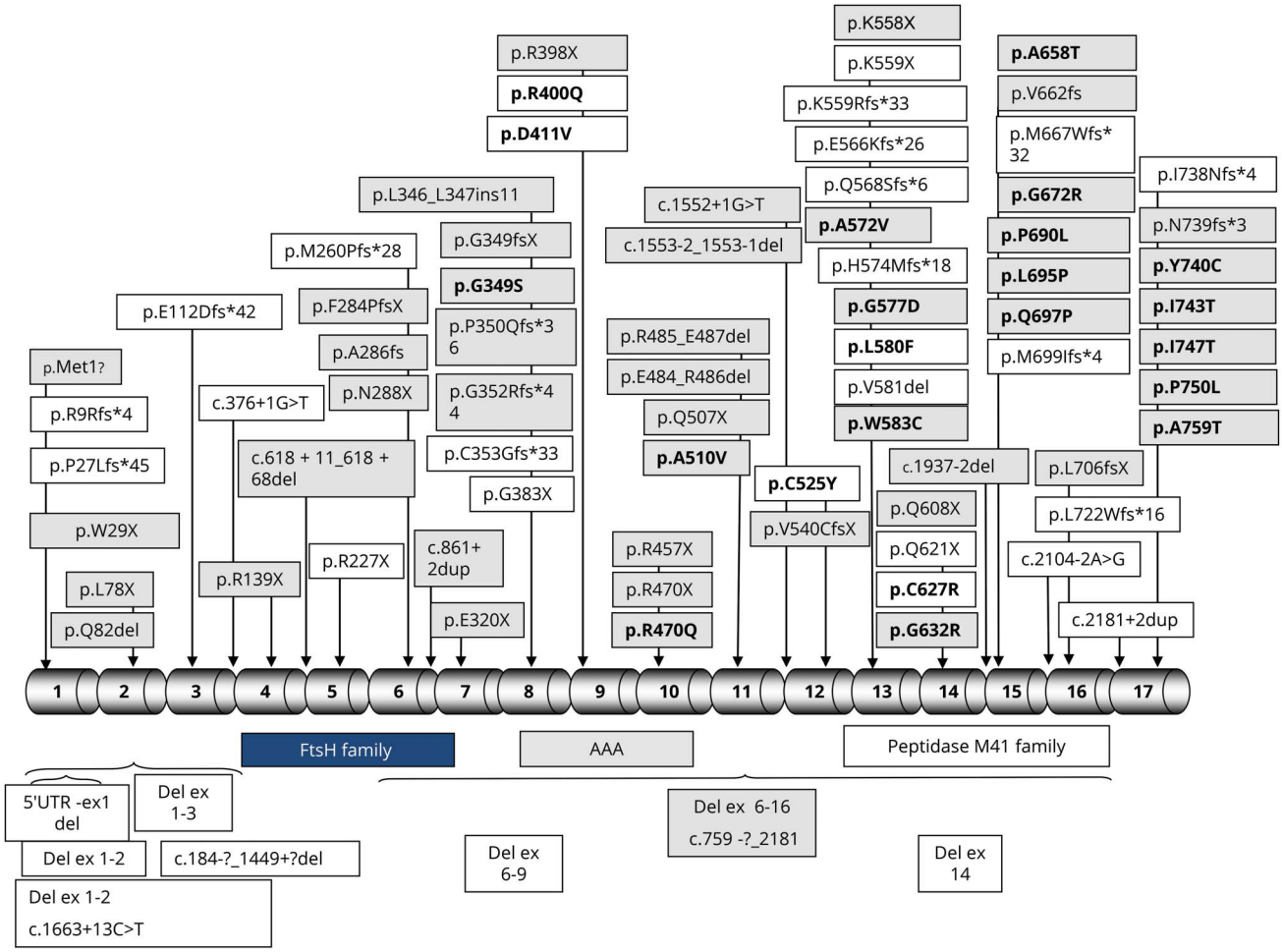
Data from 2 consecutive follow-up examinations were available for 98 patients, with a mean interval between the 2 examinations of 5.0 ± 5.9 years (median 3 years [quartile 1 = 1 year; quartile 3 = 7 years]). The number of associated clinical signs increased significantly in the second evaluation, especially cerebellar ataxia (66.3% vs 78.3%, $p = 0.003$, n = 92), cerebellar dysarthria (42% vs 57%, $p < 0.001$, n = 93), and pyramidal syndrome (89.3% vs 96.8%, $p < 0.05$, n = 94), with increased presence of the extensor plantar reflex (71.6% vs 81.5%, $p < 0.05$, n = 81), dystonia (2.3% vs 11.5%, $p < 0.01$, n = 87), muscle wasting (10.3% vs 29.9%, $p < 0.001$, n = 87), ptosis (4.7% vs 16.7%, $p < 0.01$, n = 84), dysphagia (15.3% vs 28.2%, $p < 0.01$, n = 78), decreased vibration sense at the ankles (44.3% vs 64.8%, $p < 0.001$, n = 88), cognitive impairment (8% vs 19.3%, $p < 0.01$, n = 88), and diminished visual acuity (7.4% vs 14.1%, $p < 0.05$, n = 81). In the subgroup of patients with at least 2 SARA scores (n = 30), the mean progression of cerebellar ataxia measured by SARA score was 4.0 ± 4.0 with a mean annual progression of 1.0 ± 1.4.

Retrospectively, there was no change in disability, measured by functional stage, between the 2 visits for 48% (43 of 89) of the patients. Among the 46 patients for whom the disability stage increased, the mean annual increase of the disability progression index was 0.08 ± 0.31 per year. The stability in half of the patients over time indicated a slowly progressive disease.

Evolution of neurologic signs based on disease duration

The clinical presentation of the patients with *SPG7* at first visit differed significantly, depending on disease duration (<10 years n = 93, 10–19 years n = 79, ≥20 years n = 62). Cerebellar dysarthria, deep sensory loss, and peripheral wasting were more predominant in the group who had the disease the longest. Ophthalmoplegia was observed more frequently with longer disease duration, as well as sphincter dysfunction (table 3). The stage of disability increased with disease duration, but taking into consideration the disease progression index, progression was significantly faster in the group with the shortest duration of disease than in the others. The rapid progression in the first stage of the disease appears to reach a plateau in the advanced phases; these data should be confirmed in a longitudinal study.

Figure 2 Representation of all detected variants of this study



Representation of the *SPG7* gene with functional domains (FtsH family, ATPases associated with diverse cellular activities, peptidase M41 family) and all detected variants. Previously reported variants are shown in gray; missense variants are shown in bold. UTR = untranslated region.

Brain MRI and EMG

During follow-up, we collected 137 individual brain MRIs. Cerebellar atrophy of varying severity was present in 80 patients (58.4%) (figure 3). There was no correlation between severity of atrophy and specific variants. EMG data were available for a small group of patients (n = 23) with a mean age at examination of 55 ± 13.9 years and a mean disability stage of 3.7 ± 1.1 and showed the main peripheral involvement to be sensorimotor axonal neuropathy (n = 20).

Neuropathologic findings in *SPG7*

Individual AAR-247-004 died of pancreatic cancer at the age of 56 years. The parents were not related and had a normal neurologic examination at 68 and 66 years of age. The onset of *SPG7* disease occurred at 30 years of age with gait instability. She subsequently suffered from stiff legs. She needed walking aids by 45 years of age and a wheelchair by 50 years of age. She was dysarthric without swallowing difficulties. Clinical evaluation at the age of 55 years showed pyramidal syndrome with spasticity of the lower limbs, bilateral extensor plantar reflex, and a mild proximal weakness of the lower limbs. Deep sensation was impaired, and she had a cerebellar syndrome (SARA score 16.5 of 40). Oculomotor examination showed asymmetric ptosis, saccadic pursuit, and a limitation of vertical gaze. Brain MRI was performed at 40 and 55 years of age and revealed cerebellar atrophy with vermis predominance. Nerve conduction studies were normal at both 43 and 55 years of age. Neuropsychological assessment was performed at 55 years of age, showing normal cognitive efficiency but apathy and depressive signs. Muscular biopsy revealed mitochondrial abnormalities with cytochrome oxidase– negative fibers. The genetic test, at 56 years of age, confirmed the presence of compound heterozygote variants c.1749G>C(p.Trp583Cys) in exon 13 and c.2181+2dup(p.?) in exon 16.

Neuropathologic examination

The brain weight was 1,256 g. The vermis of the cerebellum was atrophic (figure 4A). The pyramids of the medulla

Table 1 Clinical comparison at the first visit between patients harboring different genotypes

	Homozygous missense (n = 77)	Heterozygous missense LOF (n = 99)	Homozygous LOF (n = 65)	*p* Value
Age at disease onset, mean ± SD (n = 233), y	38.2 ± 14.3 (n = 73)	35.4 ± 13.6 (n = 96)	32.7 ± 14.7 (n = 64)	0.08
Disease duration, mean ± SD (n = 233), y	16.2 ± 12.4 (n = 73)	15.2 ± 15.3 (n = 96)	13.6 ± 9.8 (n = 64)	0.49
SARA score, mean ± SD (n = 65)	10 ± 5.2 (n = 20)	10.7 ± 6.9 (n = 25)	11.6 ± 5.2 (n = 10)	0.80
Disability stage (maximum value 7), mean ± SD (n = 223)	3.3 ± 1.1 (n = 73)	3.1 ± 1.2 (n = 91)	3.4 ± 1.2 (n = 59)	0.25
Women/men, % (n)	40/60 (31/46)	42/58 (42/57)	49/51 (32/33)	0.54
Sporadic case (n = 64), n (%)	17 (26)	29 (45)	18 (28)	0.70
Autosomal recessive (n = 154), n (%)	51 (33)	60 (39)	43 (28)	
Autosomal dominant (n = 13) n (%)	4 (31)	7 (54)	2 (15)	
Cerebellar ataxia, % (n)	66 (48/73)	61 (57/93)	60 (38/63)	0.80
Cerebellar dysarthria, % (n)	40 (29/72)	37 (34/92)	36 (23/63)	0.89
Brisk reflexes, % (n)	82 (55/67)	80 (70/88)	88 (51/58)	0.44
Babinski sign, % (n)	63 (42/67)	80 (70/87)	75 (43/57)	0.04
Pyramidal syndrome, % (n)	82 (60/73)	95 (89/94)	95 (60/63)	0.01
Pes cavus, % (n)	14 (10/69)	23 (21/91)	31 (19/61)	0.07
Parkinsonism, % (n)	6 (4/69)	4 (4/94)	3 (2/62)	0.84
Dystonia, % (n)	1 (1/71)	4 (4/95)	3 (2/62)	0.63
Muscle wasting, % (n)	18 (13/71)	17 (16/93)	13 (8/61)	0.74
Abnormal vibration at ankles, % (n)	59 (43/73)	29 (27/92)	57 (35/61)	<0.0001
Ophthalmoplegia, % (n)	14 (9/65)	15 (13/88)	19 (10/54)	0.78
Ptosis, % (n)	6 (3/54)	2 (2/77)	6 (3/50)	0.60
Diminished visual acuity, % (n)	7 (4/55)	6 (5/84)	31 (19/62)	<0.0001
Dysphagia, % (n)	16 (9/58)	10 (8/79)	17 (8/48)	0.51
Sphincter dysfunction, % (n)	39 (27/69)	41 (38/92)	55 (32/58)	0.15
Cognitive impairment, % (n)	6 (4/71)	8 (8/95)	8 (5/63)	0.81

Abbreviations: LOF = loss of function; SARA = Scale for the Assessment and Rating of Ataxia.

oblongata were small. The spinal cord at the cervical level was slightly altered; there was no myelin pallor in the lateral, anterior, or posterior columns. The anterior horns were normal. The pyramids of the medulla oblongata were small but without myelin pallor. The vermis of the cerebellum was severely atrophic; there was a loss of Purkinje cells with empty baskets, torpedos, and Bergmann glia (figure 4, B–D). The cerebellar hemispheres, the dentate nucleus, and the inferior, middle, and superior cerebellar peduncles were normal, as well as the pontine nuclei and the locus coeruleus. There was some degree of neuronal loss in the pars compacta of the substantia nigra, as shown by the presence of extrapyramidal pigments (figure 4E). The pars reticulata was also affected and appeared gliotic. The subthalamic nucleus, striatum, and pallidum were normal. The hippocampus was remarkable with a thin dentate gyrus (figure 4F). There were some Betz cells in the motor cortex; one of them appeared chromatolytic. There was unusual thinning of the granular layer of the dentate gyrus. The CD68 antibody did not show inflammation foci; the pyramidal tract did not contain an abnormal number of microglia. Tau, β-amyloid, TAR DNA-binding protein 43, and α-synuclein immunostaining was negative. The anti-ubiquitin and p62 staining did not label any inclusion.

Discussion

We report data from 241 European patients with *SPG7*, including 98 with neurologic follow-up, in a collaborative effort

Table 2 Clinical comparison at the first visit between patients harboring at least 1 Ala510Val variant and patients with other variants

	p.Ala510Val (n = 141)	Other variants (n = 100)	*P* Value
Age at disease onset, mean ± SD (n = 233), y	37.6 ± 13.7 (n = 134)	32.8 ± 14.6 (n = 99)	0.01
Age at examination, mean ± SD (n = 241), y	52.6 ± 12.7 (n = 141)	47.4 ± 15.4 (n = 100)	0.03
Disease duration, mean ± SD (n = 234), y	15.2 ± 13.6 (n = 135)	14.9 ± 12.3 (n = 99)	0.82
SARA score, mean ± SD (n = 55)	10.8 ± 6.2 (n = 40)	10.1 ± 5.5 (n = 15)	0.73
Disability stage (maximum value 7), mean ± SD (n = 223)	3.2 ± 1.1 (n = 130)	3.3 ± 1.2 (n = 93)	0.46
Disease progression index (function/disease duration), mean ± SD (n = 221)	0.4 ± 0.4 (n = 128)	0.4 ± 0.5 (n = 93)	0.74
Women/men, % (n)	41/59 (58/83)	47/53 (47/53)	0.42
Cerebellar ataxia, % (n)	66 (87/132)	58 (56/97)	0.2
Cerebellar dysarthria, % (n)	36 (51/131)	36 (35/93)	0.7
Brisk reflexes, % (n)	76 (96/126)	92 (80/87)	0.003
Babinski sign, % (n)	71 (89/125)	77 (66/86)	0.4
Pyramidal syndrome, % (n)	86 (116/134)	97 (93/96)	0.01
Pes cavus, % (n)	17 (22/129)	30 (28/92)	0.02
Parkinsonism, % (n)	4 (5/131)	5 (5/94)	0.74
Dystonia, % (n)	4 (5/134)	2 (2/94)	0.70
Muscle wasting, % (n)	19 (25/133)	13 (12/92)	0.27
Abnormal vibration at ankles, % (n)	47 (62/133)	46 (43/93)	1
Ophthalmoplegia, % (n)	15 (18/122)	16 (14/85)	0.84
Ptosis, % (n)	3 (3/103)	6 (5/78)	0.29
Diminished visual acuity, % (n)	6 (6/108)	24 (22/93)	<0.001
Dysphagia, % (n)	15 (17/111)	11 (8/74)	0.51
Sphincter, % (n)	38 (49/129)	53 (48/90)	0.02
Mental retardation, % (n)	2 (3/134)	3 (3/95)	0.69
Cognitive impairment, % (n)	7 (10/134)	7 (7/95)	1

Abbreviation: SARA = Scale for the Assessment and Rating of Ataxia.

that allowed us to study the largest *SPG7* cohort available to date. Clinical features matched previous work that defined *SPG7* as a relevant cause of late-onset spastic ataxia.[5,6,18,22,23] Lower limb spasticity or cerebellar ataxia, both affecting gait stability, was present at onset, making it difficult to consider *SPG7* as primarily an HSP or an ataxia gene.[24] We were able to show that, among patients with a disease duration >20 years, 88% had pyramidal syndrome and 72% had cerebellar ataxia. The predominance of pyramidal signs and symptoms was significantly associated with the presence of homozygous LOF variants rather than missense variants, suggesting that the loss of paraplegin function drives spasticity. We could speculate that LOF of paraplegin still allows AFG3L2 to form functional oligomeric m-AAA protease. This could compensate for loss of paraplegin in the cerebellum because of the high AFG3L2 cerebellar expression, while in the spinal cord, AFG3L2 is poorly expressed. Missense variants, on the other hand, may form dysfunctional heteromeric complexes with AFG3L2 in the cerebellum and may disturb AFG3L2 function. Nonsense variants on both alleles predisposed patients to a more severe and complicated phenotype, with more frequent ophthalmologic involvement. Diminished visual acuity occurred in 31% of patients carrying homozygous LOF variants. Paraplegin is one of the metallopeptidases involved in the OPA1 cleavage, a protein that regulates mitochondrial fission/fusion processes and mitochondrial cristae structure.[25] The impaired balance of the different forms of OPA1 could be more severe in the presence of LOF variants, leading to optic atrophy even in the absence of OPA1 mutations.[26] Furthermore, we confirm that the Ala510Val variant is the most common variant in patients (58.5%), showing a minor allele frequency of 0.5% in public databases, in agreement

Table 3 Clinical presentation at first visit grouped by disease duration

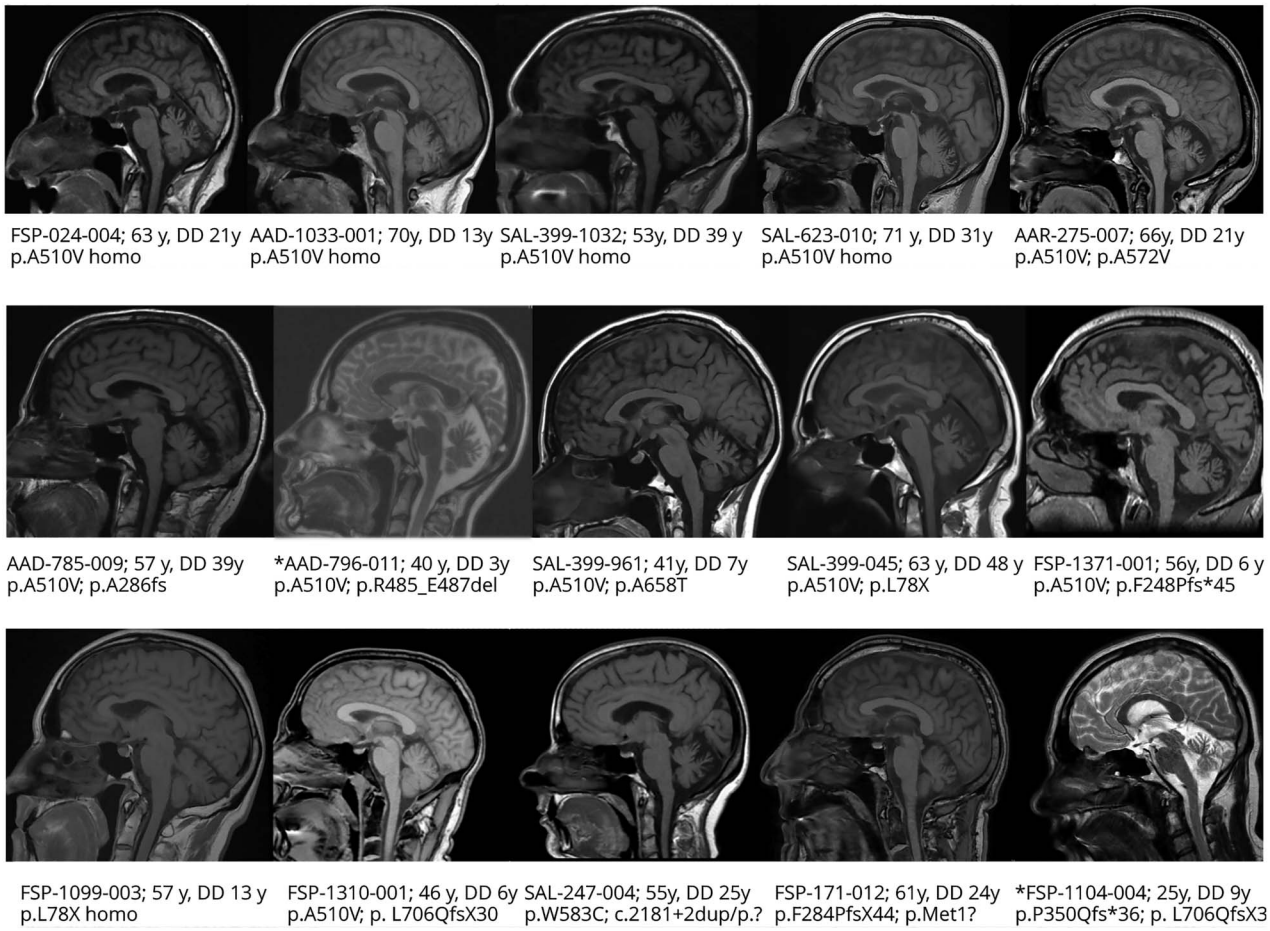
	Disease duration, y			
	<10 (n = 93)	10–19 (n = 79)	≥20 (n = 6 2)	*p* Value
SARA score, mean ± SD	7.9 ± 3.6 (n = 20)	11.3 ± 7.7 (n = 16)	12.7 ± 5.5 (n = 19)	0.03[a]
Disability stage (maximum value 7), mean ± SD (n = 221)	2.6 ± 0.8 (n = 88)	3.5 ± 1.1 (n = 75)	3.9 ± 1.2 (n = 58)	<0.0001[b]
Disease progression index (function/disease duration), mean ± SD (n = 221)	0.74 ± 0.6 (n = 88)	0.26 ± 0.09 (n = 75)	0.13 ± 0.04 (n = 58)	<0.0001[b]
Cerebellar ataxia, % (n)	56 (50/89)	64 (49/76)	72 (43/60)	0.16
Cerebellar dysarthria, % (n)	29 (26/89)	36 (27/74)	55 (33/60)	0.01
Brisk reflexes, % (n)	80 (70/87)	91 (59/65)	77 (44/57)	0.09
Babinski sign, % (n)	73 (63/86)	73 (48/66)	76 (42/55)	0.91
Pyramidal syndrome, % (n)	91 (84/92)	93 (70/75)	88 (51/58)	0.58
Pes cavus, % (n)	27 (24/88)	18 (13/71)	19 (11/57)	0.35
Parkinsonism, % (n)	7 (6/90)	4 (3/73)	2 (1/58)	0.42
Dystonia, % (n)	1 (1/91)	3 (2/74)	7 (4/59)	0.15
Muscle wasting, % (n)	10 (9/90)	11 (8/74)	32 (18/57)	0.001
Abnormal vibration at ankles, % (n)	33 (30/90)	55 (40/73)	53 (31/58)	0.008
Ophthalmoplegia, % (n)	11 (9/82)	13 (9/70)	27 (14/52)	0.04
Ptosis, % (n)	3 (2/70)	3 (2/63)	9 (4/46)	0.31
Diminished visual acuity, % (n)	11 (9/81)	10 (7/67)	24 (12/51)	0.09
Dysphagia, % (n)	12 (9/72)	11 (7/63)	19 (9/48)	0.53
Sphincter dysfunction, % (n)	33 (28/84)	48 (35/73)	56 (33/59)	0.02
Cognitive impairment, % (n)	7 (6/90)	8 (6/76)	8 (5/59)	0.90

Abbreviation: SARA = Scale for the Assessment and Rating of Ataxia.
p Value: analysis of variance for quantitative data and Fisher exact test for qualitative variables.
[a] Significant difference for the SARA score between the first group (evolution <10 years) and the third group (evolution ≥20 years) (post hoc comparisons).
[b] Significant difference for the stage of disability between the first group (evolution <10 years) and the second group (evolution 10–19 years) and between the first and third groups (evolution ≥20 years) (post hoc comparisons).

with other reports.[7,15,17,23,27] This variant was associated with a delayed onset of disease and a less complicated phenotype, that is, fewer pyramidal signs. This finding is similar to that for the Canadian population, for which Ala510Val was the most frequent variant and cerebellar features, including ataxia, were more pronounced than spasticity.[27] In contrast to the recent report on the English cohort,[23] we did not find a significant difference in age at onset of the disease between Ala510Val homozygous and Ala510Val compound heterozygous patients. Because Ala510Val variants represented 73% of the missense variant group, the cerebellar phenotype is biased toward 1 single variant. A link between predominant cerebellar presentation and null alleles has been reported,[18] but this difference could be explained by a possible recruitment bias.

We were able to study the progression in 30 patients with cerebellar *SPG7*, because the mean annual progression of SARA score was 1.0 ± 1.4. Compared to autosomal-dominant spinocerebellar ataxias (SCAs), which show an annual SARA progression of 2.1 for SCA1, 1.5 for SCA2, 1.6 for SCA3, and 0.8 for SCA6,[28] *SPG7* is comparable to SCA6 evolution. As for SCAs, *SPG7* is not restricted to cerebellar features, and the SARA score may not reflect the entirety of the disease progression.[29] The slow evolution is also reflected by the fact that patients with *SPG7* were still able to walk with a cane after 20 years of the disease, which is, for example, not the case for patients with SCA1.[30] Obviously, SARA does not quantify spasticity, and the lack of the Spastic Paraplegia Rating Scale scores[31] limits our estimation of overall disease progression because scoring was not done for the patients in this study, explained only partially by the presence of the cerebellar phenotype. The clinical picture became increasingly complex, with an increased frequency of cerebellar dysarthria, sphincter dysfunction, deep sensory loss, and muscle wasting over the years. Horizontal eye gaze limitation, a possible sign of mitochondriopathy, significantly increased in frequency during disease progression. Intriguingly, this was uncoupled from

Figure 3 Brain MRIs of patients with *SPG7* carrying different variants



Sagittal T1-weighted and T2-weighted (indicated by asterisk) brain MRIs showing different degrees of cerebellar atrophy. Age at brain MRI, disease duration (DD), and variants are reported for each patient, and no evident correlation with the degree of atrophy can be seen.

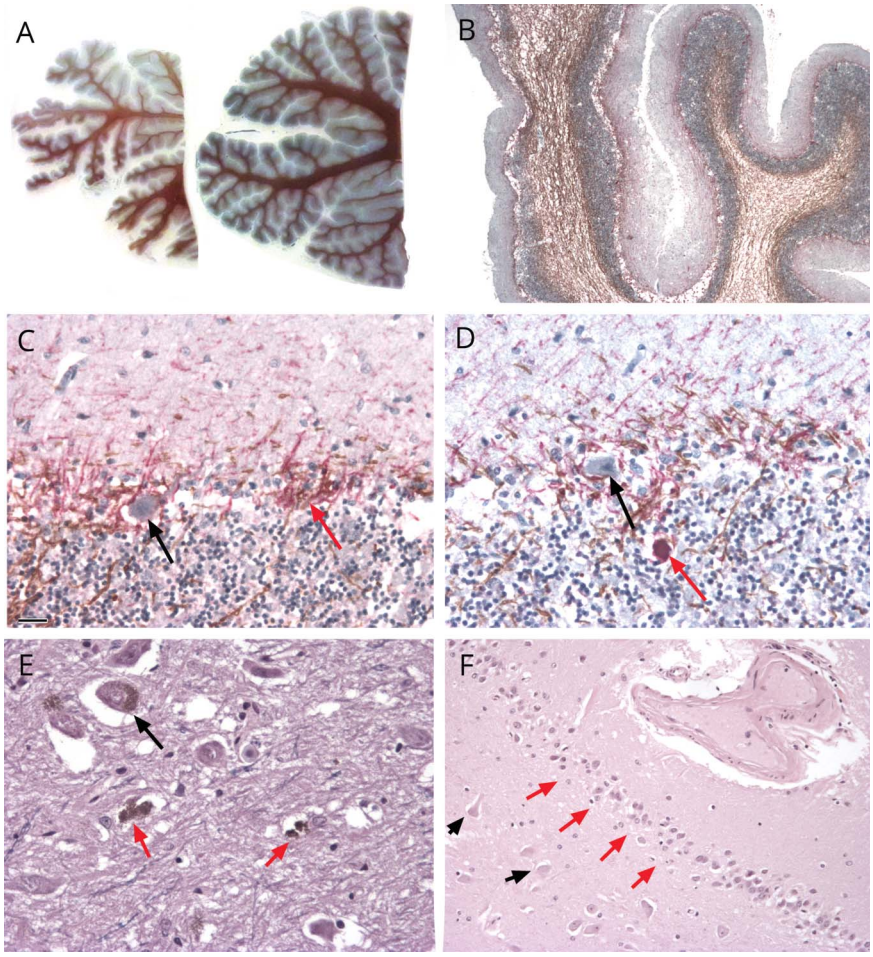
optic atrophy, which appeared to be present from disease onset, without decreased visual acuity for most patients.[6]

The presence of cerebellar atrophy by MRI was consistently associated with *SPG7*, but its degree did not correlate with severity of cerebellar signs (figure 3). When available, for a small subgroup of patients, nerve conduction studies confirmed the presence of axonal sensorimotor neuropathy.

All index patients carried 2 variants, of which 6% were of apparently dominant transmission, as already suggested by others.[6,15,18,32] The p.Arg485_Glu487del variant (the second most common mutation present in 9.3% of our cohort) was the most frequent in this group (3 families, 4 patients), and its link to dominant transmission has already been suggested.[18] Segregation has been confirmed and reported for only 2 autosomal-dominant families.[6] The p.Leu78* variant[15] was not found in our patients. The other variants detected in the dominant group were p.A286fs*, p.E320*, p.G349fs*, p.P350Qfs*36, p.A510V, p.A658T, p.N739fs*, p.P750L, and c.861+2dup(p.?). The possibility that variants in other HSP or SCA genes are also present cannot be ruled out in the affected heterozygous relatives, but we previously excluded the presence of a second variant in SCA28 in a subgroup of patients with *SPG7* because of the interaction of its gene product with paraplegin.[6] The potential dominant transmission in *SPG7*, the possibility to present neurologic signs when carrying only 1 variant (as for parents in autosomal-dominant families), and the high frequency of the A510V variant make genetic counseling challenging.

The neuropathologic data from our postmortem study showed clear involvement of the cerebellum, with the loss of Purkinje cells and gliosis in the dentate nucleus. Despite the conserved number of Betz cells, the pyramidal tract diameter appeared to be reduced at the level of the medulla oblongata. This shows that axonopathy is the hallmark of HSPs. Until now, only 3 postmortem studies have been performed in *SPG7*: 1 patient carrying a homozygous p.Arg470Gln variants,[18] 1 patient homozygous for the p.Ala510Val variant,[20] and our case carrying p.Trp583Cys and c.2181+2dup(p.?). For the second patient, the authors mentioned the presence of

Figure 4 Cerebellum of patient AAR-247-004 with *SPG7*



(A) Macroscopic aspect of the cerebellum. Sagittal section of the cerebellar vermis on the left and of the hemisphere on the right. Note the contrast between the severe atrophy of the vermis and the relatively preserved size of the hemisphere. (B) A closer view of a folium of the vermis showing pallor of the album and an almost complete loss of Purkinje cells. (C) Preserved Purkinje cell marked with a black arrow, and loss of a Purkinje cell shown by an empty basket (red arrow). (D) Preserved Purkinje cell marked by a black arrow, and a torpedo, evidence of axonal alteration, marked by a red arrow. (E) Substantia nigra pars compacta with the presence of extracellular pigments as an evidence of moderate neuronal loss (red arrows). The black arrow shows 1 normal, pigmented neuron. (F) Hippocampus with a thin dentate gyrus marked by red arrows and 2 neurons (CA4 sector) indicated by black arrows. (A–D) Double labeling (histochemistry) of myelin (myelin basic protein in brown) and axons (neurofilament in red). Scale bar: (A) 5 mm, (B) 2 mm, and (C and D) 50 μm. (E and F) Hematoxylin & eosin stain with additional Luxol for myelin in panel E. Scale bar: 100 μm.

tau pathology, which we did not find in our patient, possibly explained by the different variants and the greater age (i.e., 70 years for their patient vs 56 years for our patient).

This study assembled an unprecedented cohort of patients with *SPG7*, showing cerebellar ataxia to be the most notable element after the pyramidal syndrome. Genetic counseling will remain difficult in families with seemingly dominant transmission and requires functional experiments to be developed or the identification of biomarker(s) to prove variant pathogenicity.

Author contributions

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Acknowledgment

The authors acknowledge Jean-Philippe Azulay, MD, PhD; Patrick Calvas, MD, PhD; Guilhem Sole, MD; Stephan Klebe, MD; Susanne Otto, MD; Ali Benomar, MD; Cyril Goizet, MD, PhD; Jerome De Seze, MD, PhD; Pascale Labouret, MD; Pierre Labauge, MD, PhD; Anna Castrioto, MD, PhD; and the ICM DNA bank.

Study funding

The study received funding from the Agence Nationale de la Recherche (SPATAX-QUEST, to G.S.), the Connaitre les Syndromes Cérébelleux Association (to G.S.), Verum Foundation (to A.D. and G.S.), and SPATAX Hospital Clinical Research Program (PHRC) (to A.D.). M.S., A.D., G.S., B.P.C.v.d.W., P.D.J., and M.A. are supported by the European Union's Horizon 2020 Research and Innovation Program under the ERA-NET Cofund action No. 643578 (BMBF 01GM1607 to M.S. and ANR-15-RAR3-011-03 to G.S.), under the frame of the E-Rare-3 network PREPARE. Research reported in this publication was supported by the National Institute of Neurologic Disorders and Stroke and the NIH under award 5R01NS072248 (R.S.), E-RARE JTC grants NEUROLIPID (BMBF, 01 GM1408B to R.S.), European Union (grant F5-2012-305121 NEUROMICS to L.S., grant PIOF-GA-2012-326681 HSP/CMT genetics to R.S.; grant 779257 Solve-RD from the Horizon 2020 Research and Innovation Programme to R.S.), the Spastic Paraplegia Foundation (to R.S.), and the German Center for Neurodegenerative Diseases. J.B. is supported by a Senior Clinical Researcher mandate of the Research Fund - Flanders (FWO) under grant agreement 1805016N. M.T.B. is supported by Italian Ministry of Health under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases grant NEUROLIPID, and Italian Ministry of Health (RC 2016–2018).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* October 14, 2018. Accepted in final form January 31, 2019.

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