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C9orf72 Repeat Expansions as Genetic Modifiers for Depression in Spinocerebellar Ataxias

The genetic interactions between pathological repeat expansions have been of major interests in neurodegenerative disorders. Recently, pathogenic *C9orf72* repeat expansions, a main genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia, and pathogenic *ATXN2* repeat expansions, the causative gene for spinocerebellar ataxia (SCA) type 2, are reported to coexist in a single family with ataxia.[1] Therefore, this observation raises an interesting possibility that *C9orf72* repeat expansions could be genetic modifiers in CAG-repeat SCAs and might influence the disease progression.

Therefore, we studied 277 patients with SCA1, 2, 3, and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias cohort,[2] and we determined the *C9orf72* repeat length as previously described.[3] The Scale for Assessment and Rating of Ataxia and the 9-item Patient Health Questionnaire were used to measure the severity of ataxia and depression, respectively. We studied the rate of ataxia and depression progression using generalized estimating equation to test whether the intermediate repeats of *C9orf72* were associated with ataxia or depression progression in SCAs. As described previously, full repeat expansions of *C9orf72* were defined as ≥ 31 hexanucleotide repeats, whereas intermediate repeat expansions were 8-30.[3-5]

We identified 7 patients (3 of 51 SCA1, 2 of 58 SCA2, 1 of 109 SCA3, 1 of 59 SCA6) with pathogenic *C9orf72* repeat expansions. None of the 7 cases had motor neuron disease, but they had various degrees of motor neuron signs (Table 1). When compared with the cognitively normal control population (the original paper cites 1039 Europeans and 620 African Americans),[5] the frequencies of expanded *C9orf72* repeats in our cohort were significantly higher in SCA1, 2, and 6, but not in SCA3 (Supplemental Table 1). Of SCA patients, 40% carry intermediate *C9orf72* repeat expansions, and the demographic and clinical features of SCA patients with normal and intermediate alleles of *C9orf72* are shown in Supplemental Table 2. Intermediate *C9orf72* repeat expansions did not influence the rate of ataxia progression but were associated with different rates of depressive symptom progression in SCA1, 3, and 6 (SCA1, $\beta = -1.90$, $P < .005$; SCA3, $\beta = 3.48$, $P < .001$; SCA6, $\beta = -1.72$, $P < .05$; Supplemental Table 3).

In the present study, we identified patients of SCA1, 2, 3, and 6 who also carried pathogenic *C9orf72* repeat expansions. Intermediate *C9orf72* repeat expansions might influence the nonmotor symptom (ie, depression) progression in SCAs. Our study highlights the genetic interactions between repeat expansions.

The presence of CAG repeat expansions could interfere with the DNA repair process,[6] which may destabilize *C9orf72* repeat expansions and explain the coexistence of *C9orf72* repeat expansions and expanded CAG repeats. Because cerebellar pathology could be found in *C9orf72*-linked amyotrophic lateral sclerosis, the presence of *C9orf72* repeat expansions might affect polyglutamine aggregates preferentially in the cerebellum or brain stem structures implicated in depression.

In conclusion, our study provides supporting evidence that repeat expansions of *C9orf72* may be genetic modifiers in SCAs and perhaps ataxia patients in general.[7] Therefore, the interplay of repeat expansions in 2 different loci may lead to diverse clinical phenotypes in degenerative cerebellar ataxia. ■

Karla P. Figueroa, MS,[1†] Shi-Rui Gan, MD, PhD,[2,3†] Susan Perlman, MD,[4] George Wilmot, MD, PhD,[5] Christopher M. Gomez, MD, PhD,[6] Jeremy Schmahmann, MD,[7] Henry Paulson, MD, PhD,[8] Vikram G. Shakkottai, MD, PhD,[8] Sarah H. Ying, MD,[9] Theresa Zesiewicz, MD,[10] Khalaf Bushara, MD,[11] Michael Geschwind, MD, PhD,[12] Guangbin Xia, MD,[13] S. H. Subramony, MD,[13] Tetsuo Ashizawa, MD,[14] Stefan M. Pulst, MD,[1*] and Sheng-Han Kuo, MD[3*]

[1]*Department of Neurology, University of Utah, Salt Lake City, Utah, USA*
[2]*Department of Neurology and Institute of Neurology, First Affiliated Hospital, Fujian Medical University, Fuzhou, China*
[3]*Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA*
[4]*Department of Neurology, University of California Los Angeles, Los Angeles, California, USA*

*__Corresponding author__: Dr. Stefan M. Pulst, 175 North Medical Drive East, Salt Lake City, UT 84132; stefan.pulst@hsc.utah.edu.
Dr. Sheng-Han Kuo, 650 West 168th Street, Room 305, New York, NY 10032; sk3295@columbia.edu

Karla P. Figueroa and Shi-Rui Gan contributed equally to this work.

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TABLE 1. Demographic and clinical features of 7 SCA patients with full *C9orf72* repeat expansions

Patient number	SCA type	CAG repeats number (small/large)	*C9orf72* repeats	Gender	Age of onset	SARA	Mental status	Motor neuron deficits				
								Fasciculation	Weakness	Reflexes of extremities	Plantar reflex	Spasticity
1	1	30/44	5/>30	Woman	38	10.5	MoCA 25/30	Present	None	Hyperreflexia in biceps, patellar, and Achilles	Extensor	Mild in lower and upper limbs
2	1	30/42	10/>30	Woman	45	0.5	MoCA 30/30	Present	None	Hyperreflexia in biceps, patellar, and Achilles	Flexor	Not evaluated
3	1	30/42	10/>30	Woman	52	8.5	MoCA 25/30	Present	None	Hyperreflexia in biceps, patellar, and Achilles	Flexor	Mild in lower limbs
4	2	22/39	6/>30	Man	35	24	Not evaluated	None	None	Areflexia in biceps, patellar, and Achilles	Extensor	Moderate in lower limbs, mild in upper limbs
5	2	22/39	2/>30	Woman	40	24.5	Poor in serial 7s	Mild in tongue/face and 4 limbs	Mild in 4 limbs	Areflexia in biceps, patellar, and Achilles	Flexor	None
6	3	28/70	2/>30	Woman	48	30.5	Not evaluated	Moderate in tongue and face	Mild in 4 limbs	Areflexia in biceps, hyperreflexia in patellar and Achilles	Extensor	Moderate in 4 limbs
7	6	11/23	8/>30	Man	59	12.5	Not evaluated	None	None	None	None	None

SCA, spinocerebellar ataxias; SARA, Scale for Ataxia Rating and Assessment; serial 7s, Serial Sevens Subtraction Test.

[5]*Department of Neurology, Emory University, Atlanta, Georgia, USA*
[6]*Department of Neurology, University of Chicago, Chicago, Illinois, USA*
[7]*Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA*
[8]*Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA*
[9]*Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA*
[10]*Department of Neurology, University of South Florida, Tampa, Florida, USA*
[11]*Department of Neurology, University of Minnesota, Minneapolis, Minnesota, USA*
[12]*Department of Neurology, University of California San Francisco, San Francisco, California, USA*
[13]*Department of Neurology, University of New Mexico, Albuquerque, USA*
[14]*Houston Methodist Research Institute, Houston, Texas, USA*

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website