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A novel variant in the spatacsin gene causing SPG11 in a Malian family

Guida Landouré[1,2,3], **Kékouta Dembélé**[2], **Lassana Cissé**[2], **Salimata Diarra**[1,3], **Oumar Samassékou**[1], **Abdoulaye Bocoum**[1], **Abdoulaye Yalcouyé**[1], **Moussa Traoré**[1,2,†], **Kenneth H. Fischbeck**[3], **Cheick O. Guinto**[1,2], **The H3Africa Consortium**

[1]Faculté de Médecine et d'Odontostomatologie, USTTB, Bamako, Mali

[2]Service de Neurologie, Centre Hospitalier Universitaire du Point "G", Bamako, Mali

[3]Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD

Dear Editor,

Hereditary spastic paraplegia (HSP) is a group of heterogeneous neurodegenerative disorders presenting with spasticity and mild weakness in lower limbs in their pure form or associated with other neurological or non-neurologica features in their complex form [1]. Cases of HSP have been widely reported worldwide, presenting with all inheritance patterns. However, while dominant HSPs are prevalent in northern Europe and North America, recessive cases are mostly seen in North Africa, the Middle East, and Mediterranean regions [1,2]. Spastic paraplegia type 11 (SPG11) is caused by mutations in the spatacsin gene, and present both in pure and complex forms [3,4]. The hallmarks of the disease are spasticity, cognitive decline, and lower motor neuron degeneration associated with thin corpus callosum (TCC). SPG11 is the most common autosomal recessive SPG, with a few families reported in North Africa [5]; however, no case has been reported in sub-Saharan Africa.

This study was approved by our institutional ethics committee, and participants gave their written consent before enrolment. We present here a 32-year-old female from a consanguineous family (Fig. 1A), presenting with progressive weakness and walking difficulty since age 12, as well as recurrent generalized tonicoclonic seizures that resolved later after treatment. Her gait became progressively impaired, resulting in her becoming wheelchair-bound, with involvement of the upper limbs. She also had dysarthria, progressive memory decline, and episodes of delirium. Neurological examination showed cognitive impairment, weakness in all four limbs (0/5 in legs and 4/5 in arms), joint contractures, brisk reflexes, bilateral plantar extensor response, dysarthria and only slight peroneal atrophy. There was no sensory loss. No other family member had similar symptoms. A brain MRI showed a thin corpus callosum, periventricular leukodystrophy, and cerebral and cerebellar atrophy (Fig. 1B and 1C). SPG Next-generation DNA sequencing panel (58 genes, *SPG4*

Corresponding author: Guida Landouré, Faculté de Médecine et d'Odontostomatologie, USTTB, Bamako, Mali, BP: 1805, Tel: +22376363468, Fax: +22320229658, guida@icermali.org.

†In memory

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deletion, and *mtDNA*) was ordered from a CLIA-certified laboratory (Medical Neurogenetics, Atlanta, GA) and exon 27 of the spatacsin gene (RefSeq: NM_025137.4) failed to amplify. Furthermore, series of long range PCR and sequencing reactions were performed and revealed a homozygous deletion of an approximately 709 base pairs at position c.4636-297_4743+304del that includes this exon. PCR amplification using primers covering the deleted region showed one band in the patient's lane but her parents had two bands (one at the patient level and an upper band) while two siblings and five unrelated controls had the upper band only, confirming the homozygous deletion (Fig. 2A). This deletion was not previously reported and was not seen in SNP databases including gnomAD and ExAC, and exon 27 is well conserved among a wide range of species including mammals, birds and fish (Fig. 2B). In addition, this exon is located in an important Ncoils domain of the spatacsin protein spanning exons 27 and 28, strengthening the argument that its loss could probably be disrupting the protein and cause the disease in the family studied here.

The patient we report here had clinical and MRI features of a classical SPG11, with a teenage onset of symptoms, mental retardation, and TCC in addition to generalized brain atrophy. Moderate to severe lower motor neuron degeneration usually occurs in SPG11 around 20 years after disease onset [5]; however, the patient reported here had only slight peroneal atrophy and pes cavus after 20 years of disease duration. Several cases with atypical presentations have been described, but to our knowledge, epilepsy has not been reported. This symptom could represent an extension of the SPG11 phenotype due to the severe brain damage seen in this patient with a novel genotype or most likely be a chance association because epilepsy has a high prevalence in Mali [6]. This phenotypic heterogeneity could be due to the fact that SPGs in general, and SPG11 in particular, have high intra- and interfamily variability; however, Africa may have its own specific phenotypes due to the lack of standard care that can lead to early complications or other genetic or environmental factors. The patient passed away at age 35 after a complication of an infectious disease.

Although other SPG subtypes have been reported in sub-Saharan Africa [7-9], the case reported here appears to be the first description of SPG11 in sub-Saharan Africa.

Despite the progress made in characterizing many genetic disorders, there is still a need to study populations with diverse genetic backgrounds to further our knowledge in the phenotype-genotype correlation of these diseases for their better management. The increasing access of African populations to genetic analysis will make it possible to screen more SPG families to establish their genetic basis and uncover more novel genetic variants or potential genetic modifiers. This will likely improve our understanding of the disease mechanism which may also open roads for new therapeutic approaches.

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References

[1]. Harding AE, Hereditary spastic paraplegias, Semin. Neurol 13 (1993) 333–336. [PubMed: 8146482]

[2]. Erichsen AK, Koht J, Stray-Pedersen A, Abdelnoor M, Tallaksen CM, Prevalence of hereditary ataxia and spastic paraplegia in southeast Norway: a population-based study, Brain 132 (2009) 1577–1588. [PubMed: 19339254]

[3]. Guidubaldi A, Piano C, Santorelli FM, et al., Novel mutations in SPG11 cause hereditary spastic paraplegia associated with early-onset levodopa-responsive parkinsonism, Mov. Disord 26 (2011) 553–556. [PubMed: 21381113]

[4]. Daoud H, Zhou S, Noreau A, et al., Exome sequencing reveals SPG11 mutations causing juvenile ALS, Neurobiol. Aging 33 (839) (2012) e5–e9.

[5]. Stevanin G, Azzedine H, Denora P, et al., Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration, Brain 131 (2008) 772–784. [PubMed: 18079167]

[6]. Farnarier G, Vaz T, Diop S, Doumbo O, Epilepsy risk factors of epilepsy in Mali. An epidemiological study in an area of endemic onchocerciasis, Epilepsies 11 (1999) 222.

[7]. Landouré G, Zhu P-P, Lourenço CM, et al., Hereditary spastic paraplegia type 43 (SPG43) is caused by mutation in C19orf12, Hum. Mutat 34 (2013) 1357–1360. [PubMed: 23857908]

[8]. Guinto CO, Diarra S, Diallo S, et al., A novel mutation in KIF5A in a Malian family with spastic paraplegia and sensory loss, Ann. Clin. Transl. Neurol 4 (2017) 272–275. [PubMed: 28382308]

[9]. Landouré G, Dembélé K, Cissé L, Samassékou O, Diarra S, Bocoum A, Dembélé ME, Fischbeck KH, Guinto CO, from The H3Africa Consortium, Hereditary spastic paraplegia type 35 in a family from Mali, Am. J. Med. Genet. A 179 (7) (2019) 1122–1125. [PubMed: 31087769]

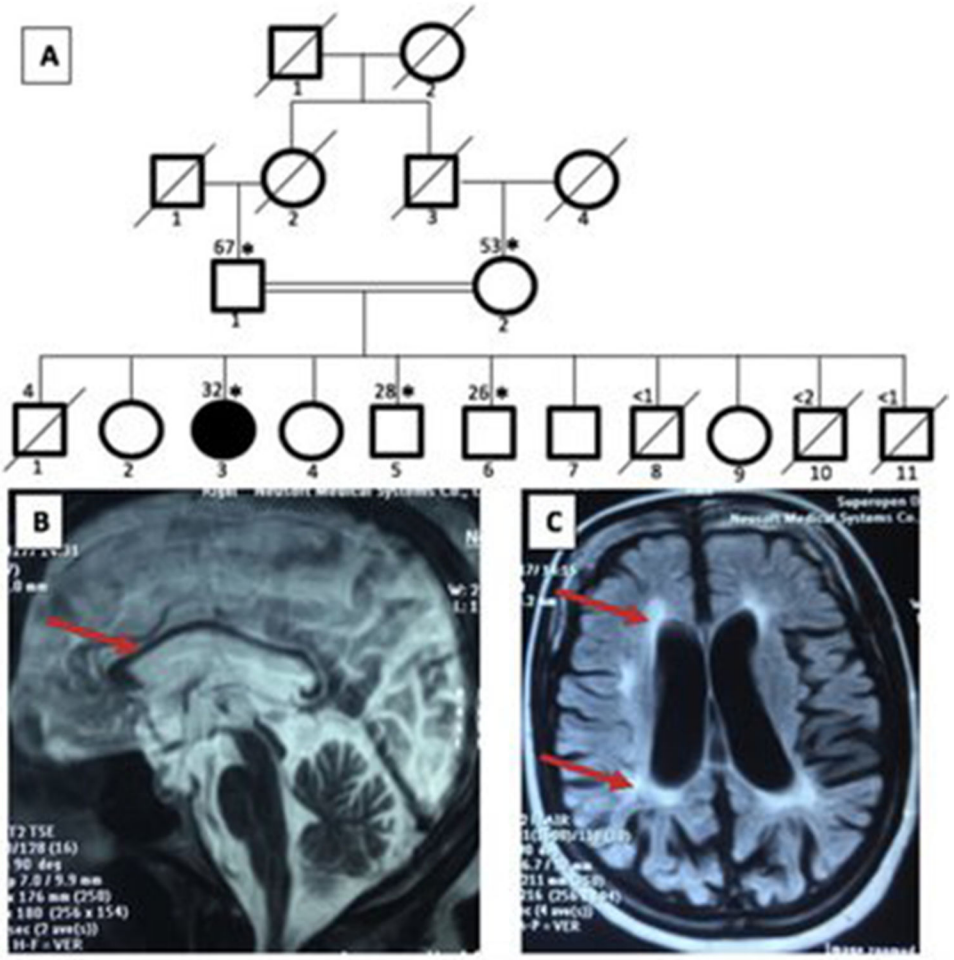

Figure 1:

Phenotypic features. **A)** Pedigree showing the consanguinity between parents. Brain MRI showing **B)** thin corpus callosum in T2 TSE signal and **C)** periventricular leukodystrophy in T2 FLAIR signal (red arrows).

Figure 2:

Genetic results. A) Gel electrophoresis of PCR amplification of a DNA fragment using primers flanking the deleted region covering the exon 27 of the spatacsin gene. Note that there is only one band in the patient (P) lane (meaning that she is homozygous for the deletion) while there are two bands (one upper and lower) in parents' (M and F) lanes (meaning that they are heterozygous for the deletion), and only one upper band in siblings (S1 and S2) and controls' (C1-C4) lanes (meaning that there are homozygous for the normal allele). B) Deletion in the patient and conservation of the exon 27 of the spatacsin gene in different species (in red are conserved residues from human).