Journal of the Neurological Sciences 277 (2009) 22–25

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Spastic paraplegia with thinning of the corpus callosum and white matter abnormalities: Further mutations and relative frequency in *ZFYVE26/SPG15* in the Italian population

Paola S. Denora [a,b,c,1], Maria Muglia [e,f,1], Carlo Casali [g,1], Jérémy Truchetto [a,c], Gabriella Silvestri [h,i], Demetrio Messina [e], Amir Boukrhis [b,c,d], Angela Magariello [e], Anna Modoni [h], Marcella Masciullo [h], Alessandro Malandrini [j], Maurizio Morelli [e], Maria Fulvia de Leva [k], Marcello Villanova [l], Elisabetta Giugni [m], Luigi Citrigno [e], Teresa Rizza [a], Antonio Federico [j], Alberto Pierallini [m], Aldo Quattrone [e,f], Alessandro Filla [k], Alexis Brice [b,d], Giovanni Stevanin [b,c,d,*], Filippo M. Santorelli [a,*]

[a] *Molecular Medicine & Neurology, IRCCS Bambino Gesù Hospital, Rome, Italy*
[b] *INSERM, UMR_S679 Neurologie & Thérapeutique Expérimentale, France*
[c] *UPMC Univ Paris 06, UMR_S679, France*
[d] *AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Paris, France*
[e] *Institute of Neurological Sciences, National Research Council, Mangone (Cosenza), Italy*
[f] *Institute of Neurology, University "Magna Graecia", Catanzaro, Italy*
[g] *Department of Neurology and ORL, University of Rome La Sapienza-Polo Pontino, Latina, Italy*
[h] *Department of Neuroscience, Catholic University of Rome, Italy*
[i] *IRCCS Don Carlo Gnocchi Foundation, Rome*
[j] *Department of Neurosciences, University of Siena, Italy*
[k] *Department of Neurological Sciences, Federico II University, Naples*
[l] *Villa Nigrisoli Hospital, Bologna, Italy*
[m] *Unit of Neuroradiology, IRCCS-San Raffaele Pisana, Rome, Italy*

ARTICLE INFO

Article history:
Received 7 August 2008
Received in revised form 23 September 2008
Accepted 25 September 2008
Available online 13 December 2008

Keywords:
Spastic paraplegia
HSP
ZFYVE26
SPG15
TCC

ABSTRACT

Spastic paraplegia with thinning of the corpus callosum (ARHSP-TCC) is a relatively frequent form of complicated hereditary spastic paraplegia in which mental retardation and muscle stiffness at onset are followed by slowly progressive paraparesis and cognitive deterioration. Although genetically heterogeneous, ARHSP-TCC is frequently associated with mutations in the *SPG11* gene, on chromosome 15q. However, it is becoming evident that ARHSP-TCC can also be the clinical presentation of mutations in *ZFYVE26 (SPG15)*, as shown by the recent identification of eight families with a variable phenotype. Here, we present an additional Italian ARHSP-TCC patient harboring two new, probably loss-of-function mutations in *ZFYVE26*. This finding, together with the report of a mutation in another Italian family, provides confirmation that *ZFYVE26* is the second gene responsible for ARHSP-TCC in the Italian population.

1. Introduction

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous Mendelian disorder characterized by weakness, spasticity, and loss of the vibratory sense in the lower limbs [1]. Both pure and complicated forms are recognized depending on whether the spastic paraplegia occurs in isolation or is combined with additional neurological or extraneurological features. Collectively, HSPs account for a large proportion of the motor and cognitive handicaps seen in children and young adults [2]. Whereas considerable advances have been made in understanding of the autosomal dominant types of HSP, which account for approximately 70–80% of cases, less is known about the autosomal recessive forms (ARHSP), which appear to be relatively less common and clinically more complex [3].

Spastic paraplegia with thinning of the corpus callosum (ARHSP-TCC) [MIM 604360] is an autosomal recessive neurological disorder in which the cardinal pathologic features of upper motor neuron degeneration and cognitive deterioration are combined with characteristic brain MRI features, namely a "beaked" anterior corpus callosum and frequent

* Corresponding authors. Santorelli, is to be contacted at IRCCS Bambino Gesù – Piazza S. Onofrio, 4 – 00165 Rome, Italy. Tel.: +390668592105; fax: +390668592024. Stevanin, INSERM UMR_S679, Groupe Hospitalier Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France.
E-mail addresses: giovanni.stevanin@upmc.fr (G. Stevanin), fms3@na.flashnet.it, filippo3364@gmail.com (F.M. Santorelli).
[1] These authors contributed equally to this work.

0022-510X/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.jns.2008.09.039

white matter abnormalities (WMAs)[4]. Molecular studies have recently shown that mutations in *SPG11* (MIM 610844) account for most ARHSP-TCC cases [5] and occur with a particularly high frequency in the Mediterranean area [6]. We recently identified mutations in *ZFYVE26* (*SPG15*), encoding spastizin [7], in eight families in which 22 patients displayed variable combinations of spastic paraplegia, mental impairment, distal amyotrophy and pigmented maculopathy, sometimes matching the clinical presentation of Kjellin syndrome (MIM 270700). The presence of TCC, often associated with WMAs, in half of the kindred prompted us to investigate the relative frequency of mutations in *ZFYVE26* in Italian patients with ARHSP-TCC. We herein report an additional patient harboring two mutations predicting loss-of-function of stastizin.

2. Case report

Patients in this study were enrolled when they satisfied the following clinical and neuroradiological criteria: a) HSP+mental retardation/cognitive impairment+TCC on MRI (n=13); b) HSP and TCC without mental retardation/cognitive impairment (n=6); c) HSP with mental retardation/cognitive impairment for whom MRI was not available (n=4). A total of 23 Italian index patients (15 men and 8 women) with compatible phenotypes were studied. Six cases were born of consanguineous parents or had at least one sib affected by a similar disorder, whereas 17 patients were apparently sporadic. Median age at onset was 16±4 years, the presenting symptom being leg stiffness in 10 patients and learning difficulties at primary school in eleven. Brain MRI studies also detected WMAs in 14 cases (60%). Neurophysiological studies showed reduced compound motor action potentials and slowed nerve conduction velocities (NCVs) of the tibial nerve and diminished sensory nerve action potential and decreased NCVs of the sural nerve in 16 patients (69%). Involvement of the *SPG11* locus or gene on chromosome 15q had been excluded in all the cases, either by linkage analysis or direct gene sequencing [6].

ZFYVE26 (SPG15) mutations were detected in a single patient, whose early course has been described elsewhere [4]. This 33-year-old Italian woman (case F15-AR), born to healthy unrelated parents, began to experience difficult walking at around 21 years of age, since when her gait disturbances, accompanied by mild-to-moderate mental impairment (mainly shown by a low I.Q., <58), attention deficit and "childish" behavior, have progressed insidiously. A recent neurological examination showed marked spastic paraparesis, with deep tendon reflexes that were enhanced in the arms but weak in the legs, and bilateral Babinski sign. Pure tone audiometry and vestibular examination showed a moderate sensory hearing impairment (>45 dB for high frequencies); brainstem auditory evoked responses were not recorded. Case F15-AR can still walk unaided. Retinal degeneration was found on examination of the ocular fundus. Careful follow up over the past year has disclosed the full phenotype, with MRI showing TCC, WMAs and atrophy of the fronto-temporo-insular cortical regions and brainstem (Fig. 1). Two younger sisters (aged 29 and 25 years) are normal.

We analyzed, by direct sequencing, the coding region and the exon–intron boundaries of *ZFYVE26* using reported PCR conditions [7] and the BigDye 3.1 Chemistry on an ABI3730 automatic sequencer (Applied Biosystems, Foster City, CA). We also examined 837-bp upstream of the first ATG and 476-bp downstream of the termination codon (primers available upon request). Direct gene analysis detected two novel heterozygous mutations, c.1792delG in exon 11 and the c.6940A>T variant in exon 37, predicting p.D599fsX613 and p.K2314X protein changes, respectively (Fig. 2). The mother and one healthy sister carried the c.1792delG mutation in the heterozygous state whereas the father harbored the heterozygous c.6940A>T change. The new variants were

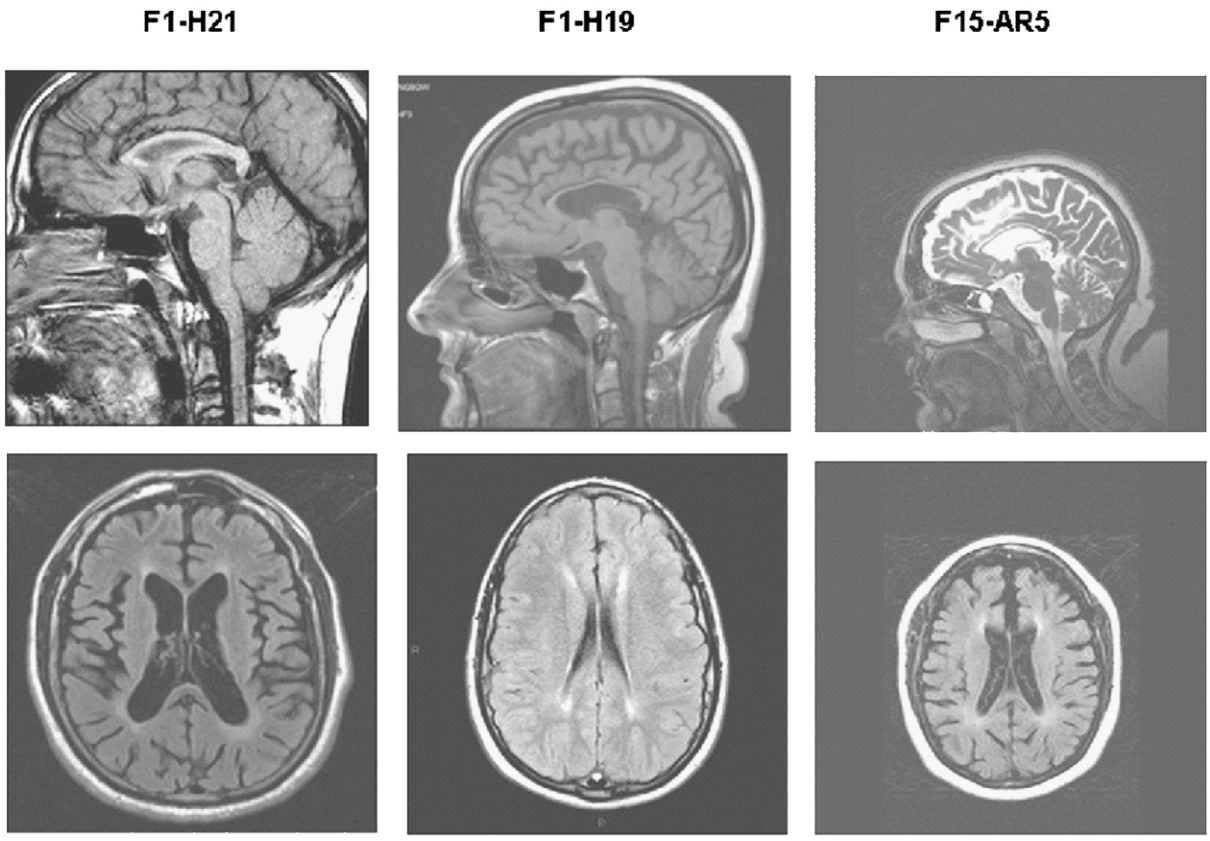

Fig. 1. Brain MRI (sagittal and axial sections) in Italian patients harboring mutations in the *ZFYVE26 (SPG15)* gene. Images in two patients (H19 and H21) identified in family F1-761 [4,7], and in patient F15-AR5 showed thinning of the rostral corpus callosum, leukoencephalopathy, and fronto-temporo cortical atrophy. These features have worsened over the past 5-years, since we first reported ARHSP-TCC cases in the Italian population [4].