EL SEVIER

Contents lists available at ScienceDirect

Experimental Neurology

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



Review

Hereditary spastic paraplegia: Clinical-genetic characteristics and evolving molecular mechanisms



Temistocle Lo Giudice ^{a,b}, Federica Lombardi ^a, Filippo Maria Santorelli ^c, Toshitaka Kawarai ^d, Antonio Orlacchio ^{a,b,*}

- a Laboratorio di Neurogenetica, Centro Europeo di Ricerca sul Cervello (CERC) Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Santa Lucia, Rome, Italy
- ^b Dipartimento di Medicina dei Sistemi, Università di Roma "Tor Vergata", Rome, Italy
- ^c Unità Operativa Complessa di Medicina Molecolare, Neurogenetica e Malattie Neurodegenerative, IRCCS Stella Maris, Pisa, Italy
- d Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medicine, University of Tokushima, Tokushima, Japan

ARTICLE INFO

Article history: Received 26 April 2014 Revised 7 June 2014 Accepted 12 June 2014 Available online 20 June 2014

Keywords: Hereditary spastic paraplegia Molecular genetics Neurodegenerative mechanisms Neurology Phenotype

ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurological disorders characterized by pathophysiologic hallmark of length-dependent distal axonal degeneration of the corticospinal tracts. The prominent features of this pathological condition are progressive spasticity and weakness of the lower limbs. To date, 72 spastic gait disease-loci and 55 spastic paraplegia genes (*SPGs*) have been identified. All modes of inheritance (autosomal dominant, autosomal recessive, and X-linked) have been described. Recently, a late onset spastic gait disorder with maternal trait of inheritance has been reported, as well as mutations in genes not yet classified as spastic gait disease. Several cellular processes are involved in its pathogenesis, such as membrane and axonal transport, endoplasmic reticulum membrane modeling and shaping, mitochondrial function, DNA repair, autophagy, and abnormalities in lipid metabolism and myelination processes. Moreover, recent evidences have been found about the impairment of endosome membrane trafficking in vesicle formation and about the involvement of oxidative stress and mtDNA polymorphisms in the onset of the disease. Interactome networks have been postulated by bioinformatics and biological analyses of spastic paraplegia genes, which would contribute to the development of new therapeutic approaches.

© 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Contents

oduction	519
etic classification of HSP	520
ADHSP	520
SPG3A	520
SPG4	
SPG6	521
SPG8	
SPG10	521
SPG12	521
SPG13	521

Abbreviations: AAA, ATPases associated with diverse cellular activities; AD, autosomal dominant; AEPs, auditory evoked potentials; AP, adaptor protein complex; AR, autosomal recessive; BiP, binding immunoglobulin protein; BMP, bone morphogenetic protein; CMT, Charcot-Marie-Tooth disease; DCVs, dense core vesicles; DTI, diffusion tensor imaging; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; ERAD, ER-associated degradation; ESCRT, endosomal sorting complex required for transport; HSP, hereditary spastic paraplegia; JALS, juvenile amyotrophic lateral sclerosis; MEPs, motor evoked potentials; MIT, microtubule interacting and transport (domain); NBIA, neurodegeneration with brain iron accumulation; RHD, reticulon homology domain; UPR, unfolded protein response; SCA, spinocerebellar ataxias; SEPs, sensory evoked potentials; SMA, spinal muscolar atrophy; SPG, spastic paraplegia gene; TCC, thin corpus callosum; VEPs, visual evoked potentials; WASH, Wiskott-Aldrich syndrome protein and scar homolog (complex); WMIs, white matter lesions; XL, X-linked.

E-mail address: a.orlacchio@hsantalucia.it (A. Orlacchio).

^{*} Corresponding author at: Laboratorio di Neurogenetica, Centro Europeo di Ricerca sul Cervello (CERC) - Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Santa Lucia, 64 Via del Fosso di Fiorano, Rome 00143, Italy. Fax: +39 06 50170 3312.

	 	521
SPG31	 	521
SPG33	 	521
SPG42	 	521
SPG72	 	525
ARHSP	 	525
	 	525
SPG7		525
SPG11	 	525
SPG15	 	525
SPG18	 	526
SPG20	 	526
SPG21	 	526
SPG26	 	526
SPG28	 	526
SPG30	 	526
SPG35	 	526
SPG39	 	526
SPG43	 	527
SPG44	 	527
SPG46	 	527
SPG47, SPG50-SPG52	 	527
SPG48	 	527
SPG49	 	527
SPG53	 	527
SPG54	 	527
SPG55	 	528
SPG56	 	528
SPG57	 	528
SPC58-SPG72	 	528
XLHSP	 	528
SPG1	 	528
SPG2	 	528
SPG22	 	528
Unassigned SPGs	 	528
GAD1 gene	 	528
<i>Cct</i> 5 gene		528
OD40		528
OPA3 gene	 	
BICD2, MAG, and LYST genes	 	529
BICD2, MAG, and LYST genes	 	529
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes	 	529 529
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules	 	529
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis	 · · · · · · · · · · · · · · · · · · ·	529 529
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport	 	529 529 529
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis	· · · · · · · · · · · · · · · · · · ·	529 529 529 530
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair		529 529 529 530 530
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair		529 529 529 530 530 530
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism		529 529 529 530 530 530 530
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination		529 529 529 530 530 530 530 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy	 	529 529 529 530 530 530 530 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation	 	529 529 529 530 530 530 531 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis	 	529 529 529 530 530 530 531 531 531 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping	 	529 529 529 530 530 530 531 531 531 531 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping Diagnosis	 · ·	529 529 529 530 530 530 531 531 531 531 531 531
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping Diagnosis Treatment	 	529 529 529 530 530 530 531 531 531 531 531 532 532
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping Diagnosis Treatment Potential therapies	 	529 529 529 530 530 530 531 531 531 531 531 532 532
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping Diagnosis Treatment Potential therapies Food for thought	 · · · · · · · · · · · · · · · · · · ·	529 529 529 530 530 530 531 531 531 531 531 532 532 532
BICD2, MAG, and LYST genes HSP with maternal inheritance Other phenotypes Functional modules Oxidative stress in HSP pathogenesis Dysfunction of axonal transport Abnormal lipid metabolism Abnormal DNA repair Dysregulation of myelination Autophagy Axon development Endosome membrane trafficking and vesicle formation Abnormal cellular signaling in protein morphogenesis Abnormal membrane traffic and organelle shaping Diagnosis Treatment Potential therapies	 	529 529 529 530 530 530 531 531 531 531 531 532 532

Introduction

Hereditary spastic paraplegias (HSPs) constitute a heterogeneous group of neurodegenerative diseases characterized by genetic mutations that cause distal neuropathy of the longest corticospinal tract axons (Harding, 1993); ascending fibers (column of Goll and spinocerebellar tracts) are also often involved (reviewed in Blackstone, 2012; Deluca et al., 2004; reviewed in Orlacchio et al., 2006). As a result of corticospinal dysfunction, progressive weakness and spasticity, extensor plantar responses, and

hyperreflexia of deep tendon reflexes in lower limbs are common clinical features in pure forms. *Iliopsoas*, *quadriceps femoris*, and *tibialis anterior* are the muscles most affected by spasticity and weakness. Hypertonic bladder and lower limb sensory disturbances (generally mild, regarding vibration and joint position sense) may be present in pure forms too.

Other manifestations may occur in complicated forms, including above all cognitive impairment, cerebellar atrophy, polyneuropathy, thin *corpus callosum* (TCC), epilepsy, skeletal abnormalities, amyotrophy, and optic atrophy.

Download English Version:

https://daneshyari.com/en/article/6017584

Download Persian Version:

https://daneshyari.com/article/6017584

<u>Daneshyari.com</u>