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LETTER TO THE EDITORS

Exome sequencing reveals a novel homozygous mutation in ACP33 gene in the first Italian family with SPG21

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Dear Sirs,

SPG21, also known as Mast Syndrome (MIM 248900), is an ultra-rare autosomal recessive complicated form of hereditary spastic paraparesis (HSP) characterized by slowly progressive spasticity with dementia, occurring with high frequency in the Old Order Amish [1]. After the first Amish family, a single Japanese family with two affected members was reported [2]. Here we describe an Italian family with a single affected member carrying a novel homozygous single base deletion in the acidic cluster protein 33, *ACP33* gene (SPG21) and presenting with a phenotype characterized by cognitive decline prevailing on the spastic paraparesis component.

Difficulties at school and motor problems were noted in the patient since childhood. By the early 20s, mental function declined with progressive speech limitation, as well as evidence of clear executive dysfunctions and subtle personality disturbances. At neurological examination at 39 years of age, a spastic paraparesis was evident, with clear pyramidal signs apart from extensor plantar response. Extrapyramidal features like lack of facial expression, apathy, segmental dystonic torticollis and paucity of arm swing during gait were noted. The incoordination was minimal.

Over a 2 year follow-up the motor abilities were identical, whereas cognitive decline mildly progressed with muteness, mental and behavioral rigidity with irritability and attitudes among the oppositional and renunciation, and a wide social closure. Brain MRI revealed thin corpus callosum and non-specific periventricular white matter hyperintensities (Fig. 1a, b).The patient had previously been tested for mutations in few common forms of HSP (SPG4, SPG7, SPG11, SPG15) with negative results. After informed consent, the proband of this family (Fig. 1c) together with the unaffected mother and sister underwent whole exome sequencing performed at the Illumina NextSeq 500 platform). Variants not present at single-nucleotide polymorphism databases and fitting a recessive model were prioritized for further analysis. A novel homozygous single base deletion c.118delC, was identified in the *ACP33* gene (SPG21) (Fig. 1d) in the proband and confirmed by Sanger sequencing. The proband's mother and sister were both carriers, while the father was not available for analysis. However, based on family reports the father was healthy. The single base deletion leads to early truncation of the ACP33/maspardin protein (308 aa), p.R40EfsTer27 at the N-terminal of the alpha–beta hydrolase domain (20-269 aa) (Fig. 1e).This is the only functional domain of maspardin with a protein–protein interaction activity [3, 4]. A role for maspardin in normal and EGF-induced growth and maturation of primary cortical neurons in SPG21$^{-/-}$ mice was demonstrated [5, 6].

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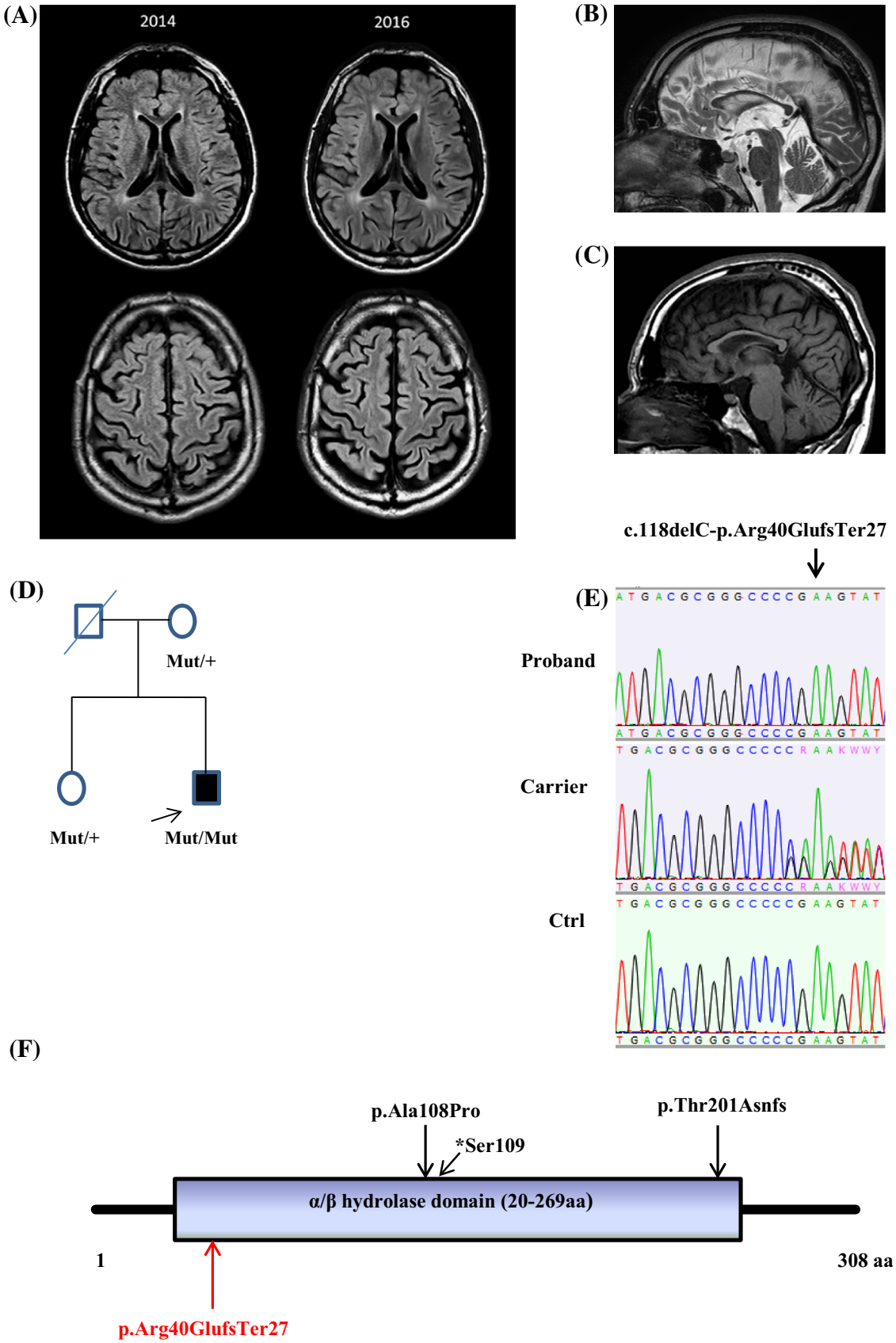
(A)
2014
2016
(B)
(C)
c.118delC-p.Arg40GlufsTer27
(D)
Mut/+
Mut/+
Mut/Mut
(E)
Proband
Carrier
Ctrl
(F)
p.Ala108Pro
*Ser109
p.Thr201Asnfs
α/β hydrolase domain (20-269aa)
1
308 aa
p.Arg40GlufsTer27

◀**Fig. 1** **a** Proband brain MRI. Axial T2 FLAIR images obtained in two brain MRI scans—1.5 and 3 T, respectively—2 years apart. Minimal progression of ventricular enlargement and widened sulci at the fronto-parietal convexity is displayed. **b** Sagittal T2-weighted image of the corpus callosum. **c** Sagittal T1-weighted image of the corpus callosum. **d** Pedigree of the family. **e** Electropherogram of the mutated sequence in the proband and in the carriers. **f** A schematic representation of the maspardin protein with the alpha–beta hydrolase domain (*grey bar*), the known mutations above and the novel one identified in the present work shown below. Within the domain, Serine 109 is the residue known to mediate maspardin interaction with CD4 protein

The homozygous p.R40EfsTer27 mutation leads to a putative truncated protein of only 40 aminoacid residues lacking the interaction domain, therefore, to a likely complete loss of protein function. It has been previously postulated that in absence of maspardin, one of the interactors, ALDH16A1, cannot localize properly. Loss of maspardin, probably mimicks loss of ALDH16A1 function which was hypothesized to be associated with a particular vulnerability of the upper motor neurons [4]. In line with that, mutations in another aldehyde dehydrogenase, ALDH18A1 lead to different HSP subtypes, SPG9A and SPG9B [7, 8]. The loss of the detoxifying enzyme, ALDH6A1 specifically expressed in mice in cerebral cortex may correlate well with the prominent cognitive profile of the SPG21 patient here described.

This is the first description of an Italian case of SPG21. The phenotype is partly overlapping to the one of the first Amish patients reported, especially regarding the childhood onset. The Japanese SPG21 patients instead displayed a strikingly late disease onset and the typical clinical signs of Mast syndrome such as bulbar, extrapyramidal and cerebellar signs were not present [2]. The clinical pattern and radiological findings of the Italian patient here described, suggest a pattern of neurodegeneration more widespread than that of the corticospinal tracts. Indeed, thin corpus callosum is always associated with either mental retardation and/or cognitive decline. Moreover, by tractography-based correlation analysis, we have already demonstrated [9] that also involvement of interhemispheric, limbic, cortico-cortical and cerebellar WM tracts result in cognitive impairment in HSP. Concerning our patient, the peculiar phenotype displayed further increases the clinical heterogeneity of SPG21 subtype. This aspect also needs to be considered to address the genetic testing within the heterogeneous genetic landscape of hereditary spastic paraparesis.

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Compliance with ethical standards

Conflicts of interest All authors declare not to have any conflict of interest with the study and manuscript.

Ethical standard The study was conducted according to the ethical standards stated in the declaration of Helsinki.

Informed consent Patients and patient's family were informed about the intention to publish the study and provided a written informed consent.

References

1. Simpson MA, Cross H, Proukakis C, Pryde A, Hershberger R, Chatonnet A, Patton MA, Crosby AH (2003) Maspardin is mutated in mast syndrome, a complicated form of hereditary spastic paraplegia associated with dementia. Am J Hum Genet 73:1147–1156
2. Ishiura H, Takahashi Y, Hayashi T, Saito K, Furuya H, Watanabe M, Murata M, Suzuki M, Sugiura A, Sawai S, Shibuya K, Ueda N, Ichikawa Y, Kanazawa I, Goto J, Tsuji S (2014) Molecular epidemiology and clinical spectrum of hereditary spastic paraplegia in the Japanese population based on comprehensive mutational analyses. J Hum Genet 59:163–172. doi:10.1038/jhg.2013.139
3. Zeitlmann L, Sirim P, Kremmer E, Kolanus W (2001) Cloning of ACP33 as a novel intracellular ligand of CD4. J Biol Chem 276:9123–9132 **(PubMed PMID: 11113139)**
4. Hanna MC, Blackstone C (2009) Interaction of the SPG21 protein ACP33/maspardin with the aldehyde dehydrogenase ALDH16A1. Neurogenetics 10(3):217–228. doi:10.1007/s10048-009-0172-6 **(PubMed PMID: 19184135)**
5. Soderblom C, Stadler J, Jupille H, Blackstone C, Shupliakov O, Hanna MC (2010) Targeted disruption of the Mast syndrome gene SPG21 in mice impairs hind limb function and alters axon branching in cultured cortical neurons. Neurogenetics 11:369–378. doi:10.1007/s10048-010-0252-7
6. Davenport A, Bivona A, Latson W, Lemanski LF, Cheriyath V (2016) Loss of maspardin attenuates the growth and maturation of mouse cortical neurons. Neurodegener Dis 16:260–272. doi:10.1159/000443666
7. Panza E, Escamilla-Honrubia JM, Marco-Marín C, Gougeard N, De Michele G, Morra VB, Liguori R, Salviati L, Donati MA, Cusano R, Pippucci T, Ravazzolo R, Németh AH, Smithson S, Davies S, Hurst JA, Bordo D, Rubio V, Seri M (2016) ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. Brain 139(Pt 1):e3. doi:10.1093/brain/awv247
8. Coutelier M, Goizet C, Durr A, Habarou F, Morais S, Dionne-Laporte A, Tao F, Konop J, Stoll M, Charles P, Jacoupy M, Matusiak R, Alonso I, Tallaksen C, Mairey M, Kennerson M, Gaussen M, Schule R, Janin M, Morice-Picard F, Durand CM, Depienne C, Calvas P, Coutinho P, Saudubray JM, Rouleau G, Brice A, Nicholson G, Darios F, Loureiro JL, Zuchner S, Ottolenghi C, Mochel F, Stevanin G (2015) Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain 138(Pt 8):2191–2205. doi:10.1093/brain/awv143
9. Agosta F, Scarlato M, Spinelli EG, Canu E, Benedetti S, Bassi MT, Casali C, Sessa M, Copetti M, Pagani E, Comi G, Ferrari M, Falini A, Filippi M (2015) Hereditary spastic paraplegia: beyond clinical phenotypes toward a unified pattern of central nervous system damage. Radiology 276:207–218. doi:10.1148/radiol.14141715